PhUSE

Nonclinical Topics Working Group

Investigating Endpoint Modeling:

Nonclinical Biomarker Modeling

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Notice of Current Edition

This edition of the Nonclinical Biomarker Modeling is the current edition, which supersedes and rescinds all previous editions of the Nonclinical Biomarker Modeling.

Additions and/or Revisions

The Additions and/or Revisions table references both content and format changes to the document as well as any updates made after distribution.

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Overview: Purpose

The Investigating Endpoint Modeling PhUSE Project Team (IEM Team) embarked on an investigation in 2015-2016 to determine suitable ways to model endpoints that are not modeled in the SEND Implementation Guide (SENDIG V.3.0), and developed a methodology for the inclusion of data such as biomarker, anti-drug antibody (ADA) and immunophenotyping results. This paper describes the recommended methodology.

Problem Statement

A common challenge in the full implementation and use of the Standard for Exchange of Nonclinical Data (SEND) is uncertainty over how to handle the incorporation of endpoints that are not currently modeled in the SENDIG. In 2015, the IEM Team was chartered to examine several broad types of unmodeled endpoints and to provide recommendations on best practices for the inclusion of these endpoints. The IEM Team determined that the best approach to ensuring a consistent methodology was to author a white paper outlining best practices for the inclusion of endpoints that are not modeled in the SENDIG such as biomarker, anti-drug antibody (ADA) and immunophenotyping.

Background and Scope

The IEM Team is comprised of individuals from the pharmaceutical industry including pharmaceutical companies, contract research organizations, contract service companies, software vendors, and the FDA. The original charter for the IEM Team specifically mentioned anti-drug antibody (ADA), biomarkers, and immunophenotyping. The group recognized that ADA and immunophenotyping represent two broad categories of endpoints that are conceptually distinct but reported similarly as quantitative or semi-quantitative concentration-based findings. Alternatively, a biomarker is generally a role assigned to a particular finding or measurement and, therefore, covers a much broader arena of potential endpoints. As a result, there was a need to first identify the broad data type categories of findings that, for purposes of a given study, could be assigned to a biomarker role. The group met biweekly to examine examples of these endpoints in order to gain an understanding of the endpoints and to consider what methodologies could be employed to include these endpoints in a SEND dataset.

Investigating Endpoint Modeling Evaluation Phase

1. Biomarkers

The first challenge for the project team was to determine what constitutes a biomarker. Definitions of the term “biomarker" and examples of biomarker data were collected and reviewed from a wide variety of sources. Sources included, but were not limited to:

- FDA Guidance for Industry: Use of Histology in Biomarker Qualification Studies
- CDISC Therapeutic Area Data Standards User Guide for Asthma
- CDISC Virology Therapeutic Area Data Standards User Guide
- SDTM Implementation Guide, 3.1.4
- Various Internet searches
- Information the project team gathered from their affiliated organizations

As mentioned above, the final step of the evaluation was to have the project team members gather examples of biomarkers currently in use and being considered for future use from their respective organizations. Because the IEM Team is a part of PhUSE Nonclinical Topics Working Group, emphasis was placed on gathering information for biomarkers commonly understood and used within the nonclinical space. The compiled examples were reviewed by the entire team.

The compiled examples allowed the project team to develop a comprehensive understanding of biomarkers including how the term biomarker is used, data collection methods, reporting formats, scientific interpretation, and the endpoints associated with biomarkers. In turn, these attributes helped the project team to gain an understanding of the supporting metadata needed to interpret a submitted biomarker result.

Based on this information, the project team agreed to the following definition:

> *Biomarkers are anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of specific disease states, medical conditions, or other biological characteristics. Biomarker data are detectable and measurable by a variety of methods including physical examination, microscopic examinations, laboratory assays, and medical imaging.*

This definition is somewhat more constrained than the FDA definition, which additionally encompasses clinical disease etiology, progression, and prognosis:

> *A biological marker or biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. A biomarker can define a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of a normal or abnormal biologic function. Biomarkers include measurements that suggest the etiology of, the susceptibility to, the prognosis of, or the progression of disease; measurements related to the mechanism of response to treatments; and actual clinical responses to therapeutic interventions. (From "Guidance for Industry - Use of Histology in Biomarker Qualification Studies")*

The project team concluded that in the nonclinical environment, biomarkers have been broadly applied to describe:

- Structural features from the molecular to the anatomic level (e.g., genetic composition, receptor expression patterns, cell surface antigen expression patterns, radiographic appearances, morphometric measurements, images)
- Biochemical measurements (e.g., blood levels of electrolytes, enzyme activity levels, diagnostic antigen levels, mRNA expression patterns, plasma microRNA concentration)
- Physiologic organ system function (e.g., creatinine clearance, pulmonary function tests, cardiac ejection fraction, electrocardiography)

With respect to classifying biomarkers in a manner that assists in determining how to populate them into SEND datasets, the IEM Team determined that biomarker was a role that was assigned to an endpoint, rather than an endpoint. In some cases, an endpoint assigned the role of biomarker is unique and not currently modeled in SEND. In other cases, an endpoint assigned the role of biomarker is already modeled in SEND. The study protocol and/or study report often highlight the special designation of an endpoint as a biomarker.

2. Anti-Drug Antibody (ADA) and Immunophenotyping Data

From the foregoing discussion of biomarkers, the team determined that ADA and immunophenotyping data are simply special topic-related cases of the more general concept encompassing the term 'biomarker.' While ADA fits neatly into the biochemical measurements category as a nonstandard clinical chemistry test and while immunophenotyping data are currently primarily concerned with enumerating subclasses of blood cells defined by antigen expression patterns (thereby being a

nonstandard hematology test), a deeper challenge may exist around the need for accompanying method-related metadata.

Because, in many cases, data for atypical endpoints are generated using nonstandard assay systems, it is likely that, even when a quantitative or semi-quantitative result can easily be populated into a SEND dataset, the result may not be easy to interpret without additional information specifying precisely how the result was obtained. As a result, although the endpoint data itself might easily be accommodated technically into an existing SEND domain model (e.g., the LB domain), the sponsor should also consider the scientific "fitness for use" of the reported data to determine whether supplementary information needs to accompany the dataset.

ADA and immunophenotyping data are likely to fall into this more complex reporting paradigm. Currently, there is no predefined SEND domain to capture method-related details, although the need for one is being discussed. With these caveats in mind, for the purpose of this white paper, ADA and immunophenotyping data can be considered to be special cases of biomarkers to be treated in like manner according to the team's recommendations for handling the reporting of results.

Recommendations

From the beginning, the IEM Team felt that a key principle to providing sound guidance would be to encourage use of existing domains whenever possible.

Not every potential study type has been modeled in SEND yet, therefore encountering unmodeled endpoints is not an unusual experience. Before incorporating additional data, it is important to carefully consider the data to determine what endpoints and metadata are needed for accurate scientific interpretation.

Fortunately, the structures of the existing SEND domains are extremely flexible and can often handle the endpoint and associated metadata. An existing SEND domain should be utilized whenever possible. Predefined SEND domains have been thoroughly defined, tested, and verified to ensure the domain contains all of the variables needed to scientifically interpret data and conforms to standard reporting practices and validation checking tools.

If the endpoint and metadata cannot be incorporated into an existing SEND domain, the SENDIG allows for the addition of SDTM variables to an existing SEND domain or, beginning with SENDIG 3.1, the creation of a custom domain. A custom domain must conform to the predefined set of SDTM variables.

Care must be taken when creating a custom domain so as not to inadvertently omit variables needed to fully report or interpret the data

The IEM Team has developed methodology to assist in the determination of whether or not a custom domain is required for the incorporation of these additional endpoints (See Appendix 1.)

In keeping with the proposed process of incorporating data into an existing SEND domain whenever possible , the recommendation is that structural cytology, histology, and anatomy tests, including those where special stains are employed, typically would be reported in the Microscopic Findings (MI) or Organ Measurements (OM) domains. Results from gross observations (i.e., those seen with the unaided eye, generally at the time of necropsy) are reported in the Macroscopic Findings (MA) domain. The SEND MI domain typically utilizes "Microscopic Examination" as the test name; however, the MITEST codelist is extensible and additional tests may be added over time. The domain also contains a noncontrolled test method variable (MIMETHOD). It does not presently support inclusion of images. Numerical measurements (e.g., morphometrics) should be represented by including the existing SDTM variable --STRESN.

Data around the absorption and metabolism of test-article-related analytes (e.g., parent compound, drug metabolite concentrations) are reported in the Pharmacokinetics Concentrations (PC) and Pharmacokinetics Parameters (PP) domains.

In contrast, biochemical measurements reported as analyte mass concentrations or enzyme activities in activity-unit concentrations, as well as enumerations of classes and subclasses of formed blood elements are most often reported in the Laboratory Test Results (LB) domain. The LB domain is also an appropriate place to represent externally administered diagnostic substances that are the basis of a test used to establish normal or abnormal biological function.

Physiologic organ system function tests are generally represented in domains that have specifically been modeled to handle them by organ system. Functional tests conducted as part of a set of specific organ-function tests (e.g., safety pharmacology battery) may be more appropriately grouped together in one of the domains specifically modeled for the organ system. (For example, heart rate, QT interval, and blood pressure measurements (all cardiovascular-related endpoints) are populated into either the Cardiovascular Test Results (CV) or ECG Test Results (EG) domains, depending on the nature of the test. Similarly, respiratory function tests are generally populated into the Respiratory Test Results (RE) domain, and nervous system function tests are populated into the Nervous System Test Results (NV) domain.

Oftentimes, a role of 'biomarker' may be assigned to one or more endpoints in a study without considering whether the endpoint is a routinely measured parameter (e.g., glucose concentration to monitor the therapeutic activity of a glucose-lowering therapy) or an atypical endpoint (i.e., not generally a part of a standard safety test battery). Currently, there are no SEND variables to specifically indicate within the dataset that an endpoint is being used as a special, for-cause biomarker in the study (note that this role is different from the general understanding that all measured or evaluated endpoints in a toxicology study are, in fact, safety-related biomarkers). At the present time, it is common practice to highlight the special designation of an endpoint (whether routinely measured in standard toxicology studies or not) as a 'for-cause' biomarker in the study protocol and/or within the text of the study report. The IEM Team recommends that the designation of an endpoint as a biomarker be indicated in the SEND dataset, define file, and/or Study Data Reviewer's Guide. One method to accomplish this within the dataset is to populate the term "BIOMARKER" into the Subcategory (--SCAT) variable. An alternate method is to include the information as a Supplemental Qualifier.***

Decision Methodology

The methodology that the project team used to determine whether to use an existing domain or create a custom domain for modeling biomarker data is documented in Appendix 1. This evaluation and decision process can also be applied to other unique, nonstandard endpoints.

Additional endpoints can be incorporated using one of three methods:

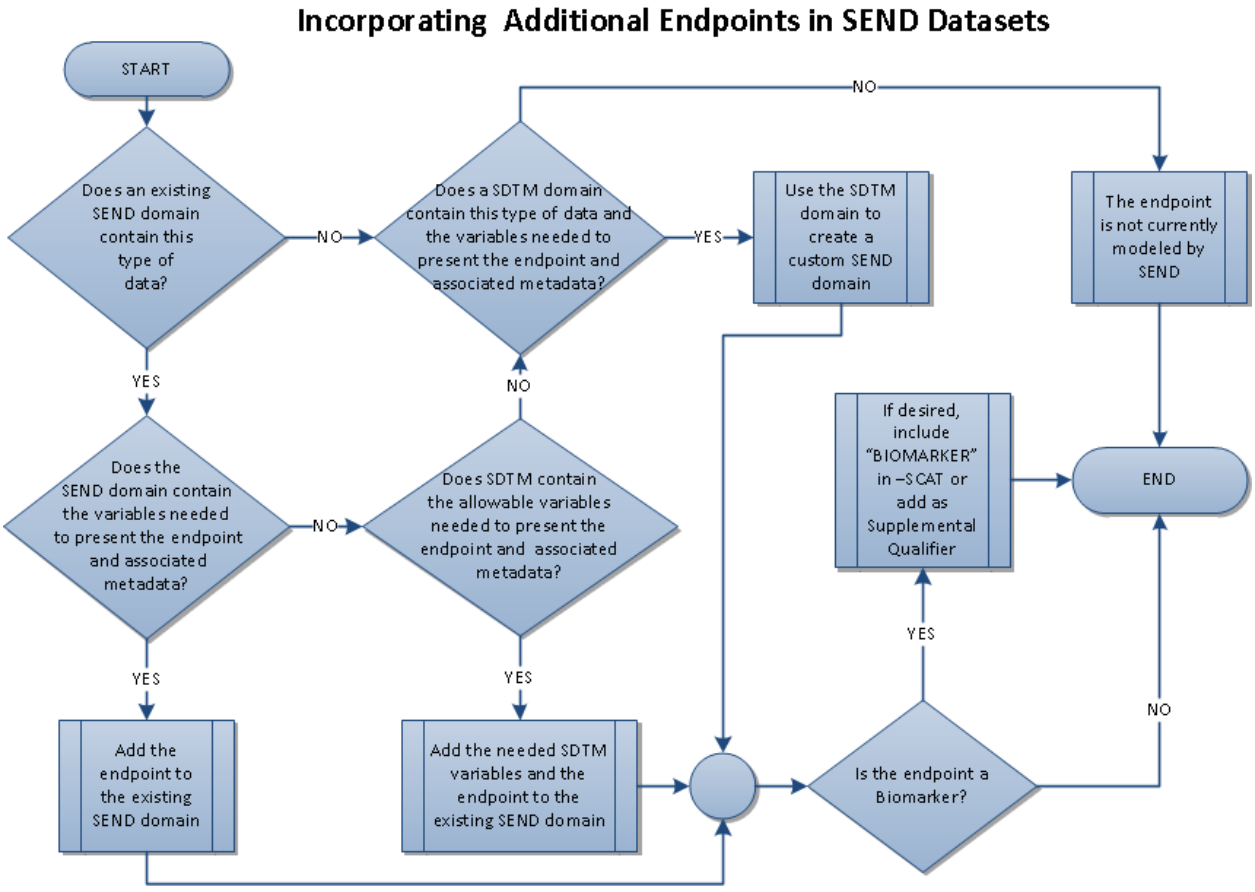
1. The endpoint and associated metadata are added to an existing SEND domain.
2. Additional allowable SDTM variables are added to an existing SEND domain to accommodate the addition of the endpoint and associated metadata.
3. The endpoint and associated metadata are added to an existing SDTMIG domain.

If the endpoint and associated metadata cannot be incorporated using one of the three methods listed above, the endpoint should be considered to be outside the current scope of SEND and not incorporated.

Conclusions

Based on the evaluation conducted by the working group, the IEM Team is of the opinion that data for biomarker tests are to be populated in the topic-related domains to which they pertain. It is likely that, at some point in the future SEND will supplement the standard with a laboratory method details domain to accommodate assay metadata needed to interpret some of the nonstandard endpoints used as biomarkers and will further define new domains for topics related to specialized procedures, as it has done for Microscopic Findings, ECG, and organ function tests. For example, although SDTM is attempting to model immunophenotyping tests into the Laboratory Test Results (LB) domain, we anticipate challenges to the ultimate success of this approach (at least without adding additional variables to the domain). As an alternative, it may be worthwhile to suggest that SEND consider developing an Immunophenotyping domain, especially as the approach becomes extended to encompass more than subclassifying blood cells.

Appendix 1 – Decision Flowchart



Footnotes

[1] Note that these domains (CV, RE, and NV, respectively) are not part of Version 3.0 of the SENDIG. CV and RE will be introduced in Version 3.1, which is currently pending publication, and NV will be introduced for public comment in the near future.

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