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Using an MDR to Manage Lab Test Specifications

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ABSTRACT

Many companies manage lab test definitions today in spreadsheets. With the coming FDA requirements to use LOINC codes in lab data for regulatory submissions, it will be necessary to align lab metadata so that each lab test definition can be explicitly defined and mapped to LOINC codes where applicable. A lab test definition managed in an MDR can relate the LOINC codes and dimensions to the CDISC LB Domain variables as well as any company or lab test specific attributes. The MDR can be used to govern the lab tests centrally and provide an organization with a single and accessible source of truth. In addition, the MDR can also provide governance, traceability and help maintain versions and variants of lab test definitions.

This paper will address the issues with lab test definitions and how an MDR can provide a managed process for maintaining lab metadata.

INTRODUCTION

The use of clinical laboratory testing is a key part of a successful clinical trial. A clinical trial may make use of different lab testing organizations such as central labs, that run a bulk of clinical trial laboratory tests, local labs, situated close to the investigator site, and specialty labs that can run novel, or special, lab tests for a given trial. Since the first useful lab test in 1920, the number of analytes has grown exponentially. This growth in lab tests will continue as clinical trials continue to use genomic and other new types of testing for use in clinical trial analytics and to provide targeted and personalized medicines and therapeutics. It is important for a sponsor to specify the lab tests needed for a clinical trial. It is equally important that the lab vendors to understand the specific attributes required for each test so that the correct tests are performed under the correct conditions. Managing the lab test specifications and data are critical to ensure proper analyses of the lab test results.

The introduction of the requirement to include the LOINC code is a step towards harmonizing healthcare practice and clinical research. LOINC codes are routinely used in healthcare practice for ordering and billing. Usage of LOINC codes in research can also benefit regulators and sponsors alike when analyzing cross product or drug class signals. Addition of LOING in the SDTM LB Domain results will also add additional burden in the maintenance of a company's lab test specifications. Many lab tests do not have a similar LOINC code or multiple LOINC codes could match depending on the lab test attributes and the specificity of the LOINC code. The LOINC code and relating LOINC dimensions to lab tests are more attributes and relationships to manage in the lab test specifications.

Many pharma, biotech and CRO's are currently managing these important specifications as excel spreadsheets, or in a bespoke application with a relational database table. Some may employ LIMS systems that may provide LOINC support but do not provide mapping to CDISC attributes. These methods can be manually intensive and subject to poor quality. Managing the lab test specification in a metadata repository (MDR) is a way to handle the complexity of the lab test specifications, create the capability to adapt to changing lab tests or new lab test not yet conceived and can be the governed and approved single source of truth for laboratory specifications. The MDR can provide programmatic access to lab specifications for internal study teams as well as laboratory vendors.

LAB METADATA

When lab test results are sent to a sponsor from a lab, there is usually a lab test name, a lab test code and the unit of measure. While the dataset has the lab test code, test name and units, that is not usually enough to uniquely identify the actual lab test that was performed. There could be missing information such as the test category, specimen type, the test method, unit conversion factors. For a programmer, this information may be found in the protocol or other documentation to properly identify the meaning and context of this lab data in order to produce the LB Domain.

Unique ID	CDISC Test Name	CDISC Test Code	Units	Specimen Material Name	Category	Method	SI Units
LAB ID	LBTEST	LBTESTCD	UNIT	LBSPEC	LBCAT	METHOD	SIU
10006	Alanine Aminotransferase	ALT	U/L	SERUM	CHEMISTRY	FLOW CYTOMETRY	U/L
10007	Glucose	GLUC	mg/dL	PLASMA	CHEMISTRY	ENZYMATIC CollectionLORIMETRY	mmol/L
10008	Glucose	GLUC	mg/dL	URINE	URINALYSIS	DIPSTICK	mmol/L

Table 1: Incomplete Specification of Lab Tests

CURRENT METHODS OF ORGANIZING LAB TEST SPECIFICATIONS

Many pharma, biotech and CRO companies have a multitude of sources of lab tests and can also have many ways to identify them. Clinical study teams use central and/or local labs augmented by specialty labs and many times, a lab test performed during a clinical trial is not uniquely identified and key information about the test is missing. Incorrect or insufficient specification of the lab tests may increase the risk of poor-quality data and analyses with potential integrity issues.

In some companies, there may be several lists of lab tests maintained by multiple groups. There can also be multiple lab codes from multiple systems and no single source of the truth to specify and identify a lab test and if a study used that lab test. A larger company may have a dedicated organization, a lab standards group, within the company to manage lab test specifications, while smaller companies have just one person or outsource lab definitions to the lab providers To avoid getting undefined or unknown lab data back from a local or central lab, the lab standards group may create and maintain and govern a list of lab tests that it shares with its vendors. Some of these groups may start with the list of lab tests from the CDISC set of lab tests and then amend with additional company information. The lab test list grows and changes and makeshift governance processes are set up out of necessity to try to keep some order.

ACCESSIBILITY AND GOVERNANCE ISSUES

Once a centralized list of lab tests is created, it is sometimes stored in a shared space where teams can access it. There may still be some discrepancies and it may also not be kept up to date. Study teams, programming and biostatistics can then use it as a reference for interpreting lab datasets. But, once a spreadsheet is downloaded, the study team is now working with a copy or snapshot of the standards and not the latest. If the standards change, the study team may not go back and update. Or the team may update the spreadsheet with information that does not get back into the main standards spreadsheet.

Using a spreadsheet and sharing it works, but once the spreadsheet is downloaded, there is no control over it. What happens when a study team needs a lab test that is not on the list of lab tests? Does the team just update their copy of the lab specification? Or, how would a study team know if the lab test exists in a list of hundreds? How do you add a new lab test to the list? Who determines what goes on the list? How is the list maintained and data approved? How can a study team determine if the lab test does not exist? How can the study team compare lab test datasets received from a central or local lab to the specification? As you can see, many questions arise after creating the list of lab test specifications. And, if there are many clinical trials run by a sponsor, there could be many lab tests required, and new lab test requests could come in often. If the study is in a relatively new area such as cell biology or genomics, the test specifications or the attributes of the test may not yet exist and are completely new. A study team would need a place to search for lab test specifications that the trial can use and would need standards support and guidance

There would need to be business processes developed to add a new lab test to the list. There would also need to be some business process set up to request a new or changed lab test, some way to review and approve the test, a way to add/modify the current specification to create a new version and then a way to notify the requestor of the added lab test. In addition, you may also need to notify any user of the lab specification that there is a change and identify the changes. These kinds of processes get handled with emails and phone calls with no audit trail or record of the decision making.

LOINC REQUIREMENT

Although there is not an urgent need in 2019 to include LOINC codes in the LB Domain in a submission, it will be required in 2020. Planning for a 2020 implementation would need to start in 2019. In the guidance by the CDISC LOINC Working Group in November 2017[1], the recommendation was to continue to use the CDISC Lab model but to include the LOINC code if it applies. Sponsor companies will need to require the lab test providers to provide the LOINC code with the lab tests and the sponsor will also want to maintain the relationship between the lab test

specification and the LOINC code. It will also be necessary to review/update LOINC codes or to go through some process to govern the addition of the LOINC code to the lab test standards.

LAB SPECIFICATIONS IN AN MDR

The FDA Study Data Technical Conformance Guide[2] states that it is important to standardize the definition of metadata, but it is also important to capture and represent relationships between data elements in a standard way. Lab test specifications are metadata. The lab test name LBTEST and the lab test code (LBTESTCD) are controlled terminology and provide some idea to programmer what that test is. However, the additional attributes, which can also be controlled terminology provide that additional definition and meaning of the lab test. The sum of all the attributes and their relationships to each other provide a full context and meaning for each test. An MDR is the place to manage lab test attributes and their relationships to each other to provide a true and complete source of the lab test definition.

LB DOMAIN

An important artifact created for submission is the LB Domain. The LB Domain contains the lab results related to a clinical trial. Clinical trial teams take the lab data from the vendors and merge the information together into an LB domain. There could be lab tests from several vendors that need to be accounted for in this process. To create the LB Domain, the programmer will use the trial datasets and definitions. The lab test specification can aid with compliance checks and ensure that all lab tests in the LB domain are correctly specified. Some data in the LB domain, such as LBSTAT (completion status), LBEASND (Reason Test Not Done) does not need to be managed by the MDR. These variables are dependent on the trial execution and would not be described by standards. However, there are several variables in the LB Domain that should be managed in an MDR. There are variables that could also be managed in the MDR such as Reference Ranges. A reference range for a lab test would need to be in the context of the trial and this would add complexity to managing the specifications. But a lab model in an MDR could be extended to include reference ranges

Field Name	Reqd	SAS Variable Name	Max Len	Datatype	Explanation	Suggested Codelist
Lab Test Name	No	LBTEST	100	Text	The name of the test performed as defined by the data provider.	(none)
Lab Test ID	Yes	LBTESTCD	20	Text	The ID of the test performed as defined by the data provider.	(none)
Original Result units	Expected	LBORRESU				
Specimen Material Name	No	LBSPEC	40	Text	The name of the specimen material (e.g. "Blood", "Urine" etc.).	HL7 V 2.4 Specimen Source Code Table 0070
LOINC Code	No	LBLOINC	10	Code	The LOINC code ID for the test performed.	LOINC
LOINC Code List ID	No	LOINCCD	40	Text	If utilized, the code list identifier and version number for the LOINC code.	
Conventional Units	No	CNVU	20	Text or Coded	Conventional result units at laboratory.	HL7 Common ISO derived units and ISO+ extensions
Conventional Reference Range Low	No	CNVNRLO	40	Text	Conventional lower limit of reference range.	(none)
Conventional Reference Range High	No	CNVNRHI	40	Text	Conventional upper limit of reference range.	(none)
SI Units	No	SIU	20	Text or Coded	SI result units at laboratory.	HL7 Common ISO derived units and ISO+ extensions
SI Reference Range Low	No	SINRLO	40	Text	SI lower limit of reference range.	(none)
SI Reference Range High	No	SINRHI	40	Text	SI upper limit of reference range.	(none)

Battery ID	Yes	BATTRID	20	Text	The ID of the battery or panel to which the test belongs. If a Battery ID does not exist, use the Test ID from the next level.	(none)
Battery Name	No	BATTRNAM	40	Text	The name of battery or panel to which the test belongs.	(none)

Table 2: LB Domain Variables that could be maintained as metadata in an MDR

THE LAB MODEL

Within an MDR the lab test specifications are more than lists. Each of the attributes of the lab test are individual objects and these objects with relationships to other objects. Modeling the lab test specification is an important part of creating a flexible and extensible way to manage lab test specifications.

DECOMPOSING THE LAB SPECIFICATION

A lab test has many more attributes than a test code (LBTESTCD) and lab name (LBTEST) There are several attributes or properties that make a lab test uniquely identifiable. A lab test can be decomposed into a set of attributes that define the context of the test. Some of those attributes are part of controlled terminology such as LBTESTCD. And there would need to be company or protocol-specific lab tests to extend the terminology that are not yet defined from CDISC. A company may also want to retain some provenance of where the lab test came from, it's source. The source of the lab test could be from a legacy company specification or system, or it could be from a protocol, a specialty lab, a local lab or central lab provider. It may be helpful also to link the lab test to a lab test number from a central or local lab.

A unique lab test would have some sort of identifier that may be just a number, or a string with some meaning or naming convention. This identifier would have a common set of properties that when linked together, create a unique lab test record. The MDR can manage the individual codelists and relate the items in the codelist to each other to create a virtual unique record. To extend the model and add additional properties, would be to create new codelists and add new relationships without disturbing the original model and data.

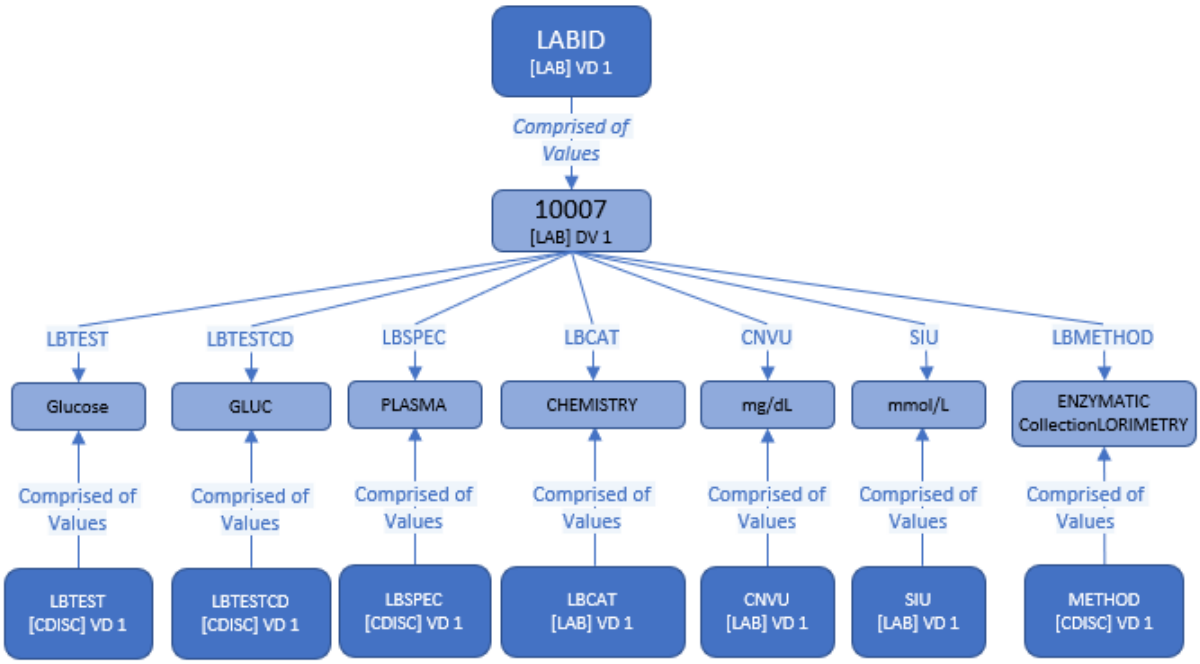

Figure 1: Depiction of the relationships in a Lab Specification

By creating a unique lab test record with these attributes, it will be clearer what LOINC code should be assigned. The guidance from CDISC's LOINC Working Group[1] compares LOINC dimensions (Component, Property, Time, System, Scale and Method) to the LB Domain variables. Knowing the attributes of the lab test and how they compare to LOINC dimensions can simplify assigning LOINC codes. Once the lab test is specified, the LOINC code becomes an attribute of the test. Impact to any future changes in LOINC codes could be identified quickly using the MDR lab model.

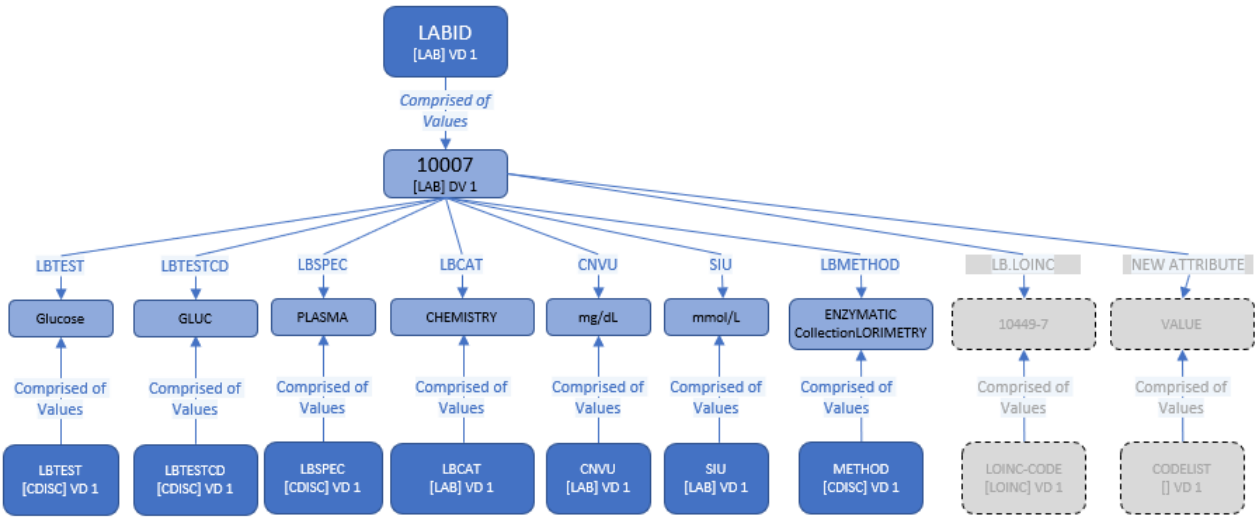

Figure 2: Depiction of adding new controlled terminology and relationships to the existing lab specification

ENVISIONING THE LAB MODEL

In the table below is an example list of lab tests. The red box around the LBTEST column would be represented in and MDR as a codelist, a set of controlled lab test names. Each lab test name would have its own metadata and properties. Each column in the table would then be an individual set of controlled terminology values.

The red box around the row with LABID=10007 would represent a unique lab test. Except that this row is not represented in the MDR as a database table or as it looks here like an Excel spreadsheet entry. Instead, an MDR would maintain the relationships between the terminology values of each codelist. By cutting across the table like this, the MDR creates a way to add new attributes and extend the lab test specification without affecting the previous lab test specifications.

Unique ID	CDISC Test Name	CDISC Test Code	Specimen	Category	Method	Conv Units	SI Units	LOINC Code
LABID	LBTEST	LBTESTCD	LBSPEC	LBCAT	METHOD	CNVU	SIU	LOINC**
10006	Alanine Aminotransferase	ALT	SERUM	CHEMISTRY	FLOW CYTOMETRY	U/L	U/L	16324-6
10007	Glucose	GLUC	PLASMA	CHEMISTRY	ENZYMATIC CollectionLORIMETRY	mg/dL	mmol/L	16903-7
10008	Glucose	GLUC	URINE	URINALYSIS	DIPSTICK	mg/dL	mmol/L	16913-6

Table 3: Example Lab Test Metadata **LOINC Code Mapping is an example and not verified

BENEFITS OF MDR-MANAGED LAB SPECIFICATION

By having a list of lab test specifications, there is at least a reference or definition of lab tests used in clinical trials. Having a uniquely defined set of lab tests can eliminate uncertainty during data analysis and can be a reference for study teams and lab test providers. In addition, having the lab test specifications in a single place makes them accessible and a good reference for all to use. Using an MDR to manage the lab specifications creates additional benefits including easier accessibility, improved governance, traceability

ACCESSIBILITY

Because an MDR has the lab specifications in a central database, the lab test specifications are now more easily accessible through a search using the MDR user interface. This eliminates the need to maintain multiple copies of spreadsheets in a shared location. Most MDR's have the capability to search and browse the lab test specifications. Determining if a lab test has already been defined is now reduced to a simple online search. Guidelines and other information can be stored with the lab test metadata including guidance documents for use of lab tests and test panels, suggestions for high/low reference ranges, units, unit conversions etc. All this information could be available online as well as available through automatic programming interfaces (API's) to enable automated data analysis programming.

GOVERNANCE/CONTROL

An MDR can provide a central place to manage specifications but can also provide governance and control of your lab test specifications. By creating request and content creation workflows, the lab standards group can manage change requests, provide automated notifications to requestors and route questions/input to subject matter experts. The lab standards group can control not only the lab test names, but also the values that are used in the attributes. For example, the Category and Method and Specimen naming convention can be managed as separate codelists and the group can ensure that only these controlled terminologies are used. This can increase the quality of the lab test data by controlling the specification. In addition, there can be a reduction in email exchanges and requests because the requests would be centrally managed. Requestors could look at online status of requests.

The lab standards group can also reject new lab test requests and recommend lab tests that are already defined.

TRACEABILITY

By using a governance process and controlling the lab specification metadata within the MDR, the lab standards group can use the MDR to show traceability. The governance process and the MDR audit trail can show all changes to the lab test, including who requested the change and when. An MDR can also link the specific lab test to individual studies that use the lab test, thus showing traceability to company lab test specifications. The MDR can also update and maintain versions of lab test specifications. The version changes would be automatically added to an audit trail and provenance of the lab test changes would be captured as well.

IMPACT ANALYSIS

Some MDR's have the functionality to show impact analysis. An impact analysis identifies where changes in metadata affect other standards or metadata. Changes to a controlled terminology or to any lab test attribute can impact the data collection and analysis of current and future trials. By running an impact analysis, the lab standards group can determine the effect of a change to the lab standards and reduce business risk and make better decisions in implementing lab data standards. This would enable the standards group to provide guidance to clinical trial teams that are just starting up or in mid-trial and need to determine if any changes to lab tests are required.

CONFORMANCE CHECKING

Even though lab standards are specified by a sponsor, there is still some quality checking that can and should be done when receiving lab data. When lab test data comes in from a laboratory, the sponsor will want to ensure that the data is conforming to the specified lab tests. Using the lab test specification in the MDR, a company can automate conformance checking of lab data to the specified lab tests. If there are discrepancies in the controlled terminology or if there is an unidentified or mislabeled lab test, these can be surfaced and corrected quickly.

EXTENSIBILITY

Getting together a list of lab tests and all the attributes of lab tests is a large task. But once it is completed, there will still be more lab tests to add and changes to make. In addition, there may also be additional attributes and new types of lab tests that will require a change to the lab model. The model used in an MDR would be a future-proof way to manage the lab data because the model is extensible. That is, the model can be adapted and added to without needing to rebuild and redo the entire lab specifications. The MDR lab model can add additional attributes, additional lab tests and relationships easily and with an audit trail, all changes and additions to the model can be changed. Versions of lab tests can be easily managed keeping the lab test specifications in order while planning and handling growth and change in the specifications at the same time.

CONCLUSION

It is very important for sponsor companies to manage the lab test standards and specifications it uses during a clinical trial. Use of excel spreadsheets and shared directories create a labor intensive and low-quality way to manage lab test specifications. In addition, governance processes that are email based do not provide a robust way to control lab metadata and notify users of the metadata of changes or of approval of new lab test specifications.

An MDR is the best way to handle the complexity of the lab test metadata, the controlled terminology and the changing nature of the attributes that define the tests. With the LOINC requirement pending in 2020, an MDR can also provide a technical solution to representing and relating your lab test specifications with the LOINC standard. Adapting an MDR-based lab standard management, sponsors, CRO's and lab providers can manage and adapt to the ever-changing clinical trials, lab tests, analysis and reporting.

REFERENCES

(1) "Recommendations for the Submission of LOINC® Codes in Regulatory Applications to the U.S. Food and Drug Administration", LOINC Working Group: U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), Clinical Data Interchange Standards Consortium (CDISC), and Regenstrief Institute., November 2017.

(2) Study Data Technical Conformance Guide, Technical Specifications Document, US Dept. of Health and Human Services, FDA, Center for Drug Evaluation and Research, October 2018)

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