**CDISC Interchange 2018 - Paper**

# Delivering LOINC Codes in Future – Bridging Gaps within clinical lifecycle

Veena Nataraj, Diane Piper, Shire, Lexington MA

## ABSTRACT

Clinical study data is submitted to regulatory agencies and requires the use of standardized data for submission and analysis. In addition, the Food and Drug Administration (FDA) has expressed the need to use LOINC Codes when submitting the Laboratory data (central and local) by making this as a requirement in April 2018, which has been postponed to 2020 according to the current FDA Data Standards Catalog.

This presentation discusses the different stakeholders within the clinical lifecycle, gaps currently present, options if any to bridge this gap.

## INTRODUCTION

In a clinical trial, laboratory tests can be used to monitor the safety of the clinical subjects; demonstrate the efficacy of the investigational product and assess pharmacodynamics, pharmacokinetics and pharmacogenomics. Central and local laboratories perform traditional laboratory testing, while core and analytical laboratories conduct specialty testing. It is therefore possible that during the course of a clinical trial, the data could come from multiple types of laboratories where the reported test names, test results and units are based on the laboratory's conventions.

In 1994, a group of researchers met in Indianapolis at the Regenstrief Institute to begin the development of a system to assist in the exchange and pooling of laboratory test results, which they called the Laboratory Observation Identifiers Names and Codes (LOINC®) code system. In 1997, this system was renamed to Logical Observation Identifiers Names and Codes, to cover not only laboratory test results but also clinical observations. The LOINC codes are maintained in a database. There is a utility called Regenstrief LOINC Mapping Assistant (RELMA™) for searching this database, which can assist in the mapping of local test codes to LOINC codes. Both the LOINC database and RELMA are freely available from http://www.regenstrief.org/loinc/.

The Food and Drug Administration (FDA) will be requiring LOINC codes to be included with standardized clinical laboratory test results for all clinical studies staring from March 2020, so to align with the US National Health Information Technology interoperability initiatives. Standardized terminology and metadata helps to support the semantic interoperability between healthcare and regulated clinical research, which will ultimately benefit patient care and future medical research.

The LOINC can be represented for both laboratory and clinical observations for a clinical trial. The FDA requirement in the Study Data Standards Catalog for 2020 is specific to the laboratory data. For this paper, we will limit the focus to the challenges of using LOINC codes for clinical trial laboratory observations.

## STAKEHOLDERS IN CLINICAL LIFE CYCLE:

With the FDA's LOINC code requirement coming onto effect in early 2020, it is important for a Sponsor or a CRO to ensure that the selected laboratory service providers can provide LOINC codes with the desired laboratory test results. Each laboratory may be at a different maturity level with respect to LOINC code implementation and maintenance. The same may be true for SDTM capabilities.

Sponsors often outsource one or more aspects of their clinical trials to Contract Research Organizations (CROs) and auxiliary vendors such as central laboratories, imaging vendors and other service providers, in either a tactical or strategical manner.

The central laboratory model is the most widely used for the outsourcing of clinical laboratory services

especially for global clinical trials. Some CROs also offer central laboratory services. Most central laboratories work with third party specialty laboratories for specific tests, or where the specialty laboratory has an Intellectual Property (IP) patent on a particular technology. Alternatively, the Sponsor may contract directly with the specialty laboratory. Local laboratories are generally used when an immediate result is needed.

At the planning phase of a clinical trial, the need to engage a central, specialized or local laboratory is determined based on the requirements outlined in the study protocol and on operational considerations. During trial conduct, the results of the laboratory tests are sent to the investigative sites for medical review and clinical significance evaluation. They are also sent to Sponsor or CRO for review and any resulting data discrepancies are reconciled with the laboratory and sites. At trial close-out, the information collected from these laboratory vendors is incorporated into the analysis of the clinical trial. If this is performed by a CRO, it is then delivered to the Sponsor who in turn prepares it for submission in a submission ready format to a regulatory authority, such as the FDA.

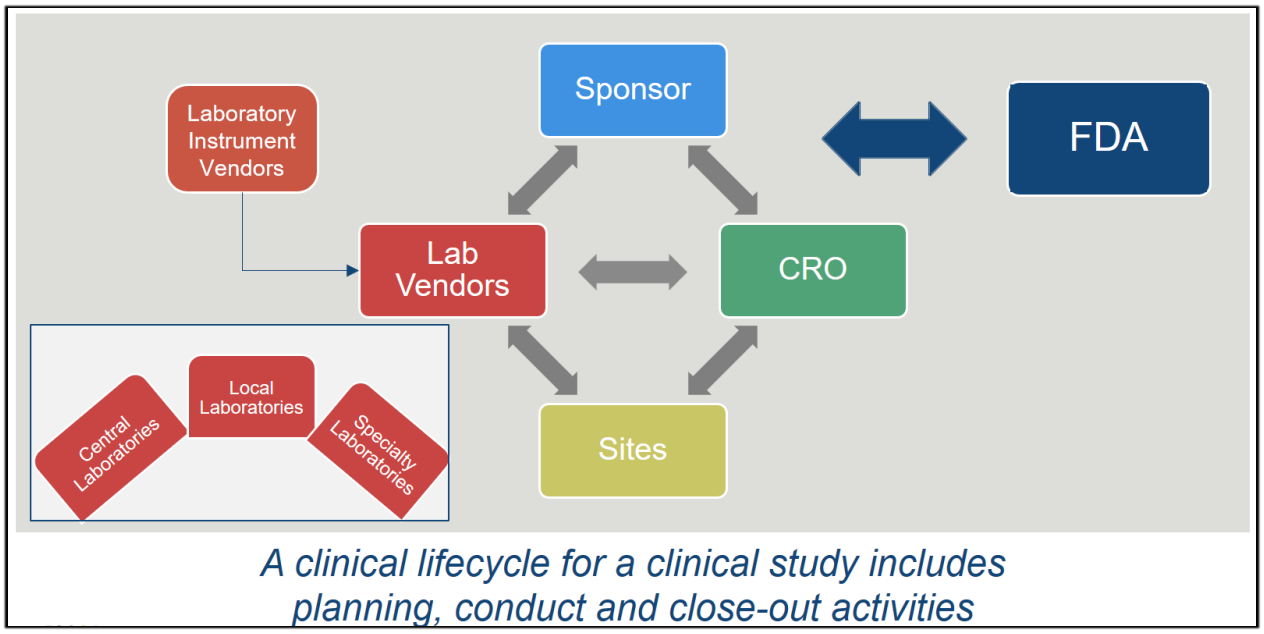



Fig-1: Stakeholder in a Clinical Lifecycle

## LOINC – LOGICAL OBSERVATION IDENTIFIERS NAMES AND CODES

LOINC is different from a number of other coding systems, such as Systemized Nomenclature in Medicine (SNOMED®), Medical Dictionary for Regulatory Activities (MedDRA™) which provides a mechanism to standardize and categorize the observations. LOINC has a set of identifiers names and codes that identifies the observation for which a result is collected. If we consider the observation as a question and the observation values as answers, LOINC provides codes for the questions and can be used for tests that are part of panels or packages for both clinical and laboratory observations.

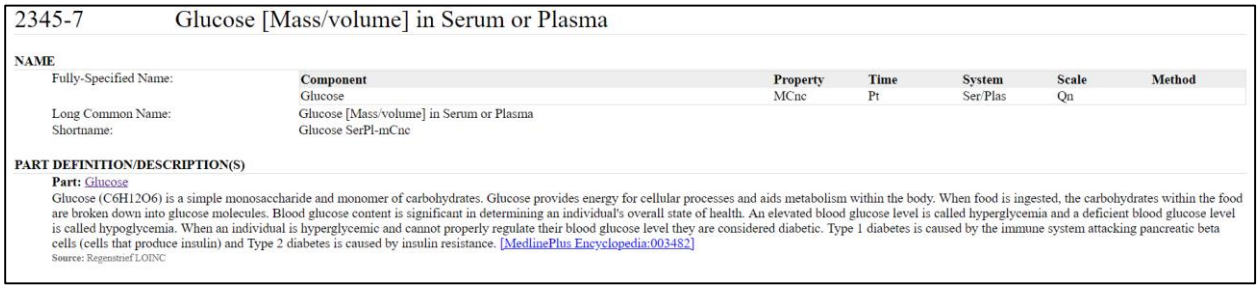
### LOINC CODE – WHAT IS IT AND WHY?

The LOINC Codes is a universal standard to identify health measurements and observations. The requirement for this type of a universal code becomes a necessity when different organizations want to exchange these measurements. Having a standard such as LOINC helps in supporting system interoperability of data (i.e., facilitating data to move seamlessly between systems).

LOINC terminology uses a number of attributes to uniquely identify a given laboratory test. For example, looking at Glucose, there is the analyte name and sample type, as well as parameters such as the unit, scale, method and timepoints which are also important to understand how the result was obtained by the laboratory. The LOINC code is determined based on this detailed information, and any variation in these

parameters results in a different code for the test. Method is included when the method distinction makes an important difference to the clinical interpretation of the result.

The LOINC representation of Glucose in Serum or Plasma is as follows:



2345-7 Glucose [Mass/volume] in Serum or Plasma

**NAME**

| | Component | Property | Time | System | Scale | Method |
|---|---|---|---|---|---|---|
| Fully-Specified Name: | Glucose | MCnc | Pt | Ser/Plas | Qn | |
| Long Common Name: | Glucose [Mass/volume] in Serum or Plasma | | | | | |
| Shortname: | Glucose SerPl-mCnc | | | | | |

**PART DEFINITION/DESCRIPTION(S)**

**Part:** Glucose

Glucose (C6H12O6) is a simple monosaccharide and monomer of carbohydrates. Glucose provides energy for cellular processes and aids metabolism within the body. When food is ingested, the carbohydrates within the food are broken down into glucose molecules. Blood glucose content is significant in determining an individual's overall state of health. An elevated blood glucose level is called hyperglycemia and a deficient blood glucose level is called hypoglycemia. When an individual is hyperglycemic and cannot properly regulate their blood glucose level they are considered diabetic. Type 1 diabetes is caused by the immune system attacking pancreatic beta cells (cells that produce insulin) and Type 2 diabetes is caused by insulin resistance. [MedlinePlus Encyclopedia:003482]

Source: Regenstrief LOINC

Fig-2: Example of the LOINC Code for Glucose

To contrast the above with a Glucose result obtained from urine sample, the attributes are:

2345-7: Glucose [Mass/volume] in Serum or Plasma

| Property | Time | System | Scale | Method |
|---|---|---|---|---|
| MCnc | Pt | Ser/Plas | Qn | |

5792-7: Glucose [Mass/Volume] in Urine by Test strip.

| Property | Time | System | Scale | Method |
|---|---|---|---|---|
| MCnc | Pt | Urine | Qn | Test strip |

The Property value of “MCnc” indicates the units would be in mg/dL. The Scale value of “Qn” indicates a Quantitative measurement; The System value of “Ser/Plas” indicates serum/plasma, while “Urine” indicates a test performed on a urine sample. These tests can be part of the other panel tests. A change to one attribute results in a different LOINC code. For example, the value in the property component identifies the unit of the result for the test conducted, and a value of “SCnc” identifies the unit as mmol/L.

## LOINC NAMES

Each LOINC has three sets of names. They are Fully Specified Names usually known as “FSN”, Long Common Name known as “LCN” and the Short Name. A Fully Specified Name is a 6-part name (Name:Property:Timing:Type of Sample:Scale:Method) and uses the scientific names and is not typically readable. The Long Common Name is a human readable name for the LOINC term. A Short Name is the 40-character limit name that is usually used within systems. The use case of what name to use depends on how this information is used. In reports, LCN can be used and for exchange of data systems can use FSN and Short Names.

Below are the examples for Glucose in Serum and Urine:

2345-7: Glucose [Mass/volume] in Serum or Plasma

| FSN | LCN | Short Name |
|---|---|---|
| Glucose:MCnc:Pt:Ser/Plas:Qn: | Glucose [Mass/volume] in Serum or Plasma | Glucose SerPl-mCnc |

5792-7: Glucose [Mass/Volume] in Urine by Test strip

| FSN | LCN | Short Name |
|---|---|---|
| Glucose:MCnc:Pt:Urine:Qn:Test strip | Glucose [Mass/volume] in Urine by Test Strip | Glucose Ur Strip-mCnc |

### LOINC VIS-À-VIS CDISC SDTM

In the Study Data Tabulation Model (SDTM) standard, laboratory results from a study are represented in the LB domain. The results are primarily identified through the use of CDISC controlled terminology associated with the LBTEST and LBTESTCD variables (e.g., LBTEST=Glucose, LBTESTCD=GLUC). Other SDTM variables support the representation of other attributes (qualifiers in SDTM nomenclature) associated with the test, such as specimen condition, specimen type, and method used to obtain the result. Using CDISC conventions, all of these attributes are required to uniquely and accurately identify a given test and its results. This can be challenging, and the variability of how these attributes are managed and implemented make it difficult to determine if a given test conducted in one study is comparable to a test in another study, even within studies conducted by a single Sponsor company, never mind across the industry.

In contrast, LOINC incorporates all of the SDTM attributes as well as others to properly and uniquely identify a test in a single term. The LBLOINC variable in SDTM is used to capture the LOINC term. Currently this variable is optional, so it is usually omitted from SDTM submissions. A LOINC is not a synonym for a laboratory test code or test name. Some elements of LOINC code align to SDTM LB concepts, for example “Component” aligns to the TEST/TESTCD. Of the 6-part LOINC Code, 4-parts aligns to the SDTM concepts. The 2 additional parts “Property” and the “Scale” are not directly represented in SDTM.

## AWARENESS AND CHALLENGES BASED ON THE CLINICAL STUDY EXPERIENCE

Clinical study protocols are increasingly more complex, and it is not unusual to be faced with laboratory data originating from multiple sources. Central laboratories tend to be the gold standard since they offer operational simplicity and improved data quality, as there is consistent testing methodology, kits and reagents across clinical studies, subjects and sites. If local laboratories are used then the preference, where feasible, is to submit the local laboratory samples to the central laboratory for processing to mitigate challenges with the management of normal/reference ranges and units. A few tests though may still need to be performed by local or specialty labs.

The laboratory test results can be transferred electronically as an external data file which is later merged with the clinical data at the time of SDTM development or integrated within the clinical trial database. This latter approach though tends to add complexity to the database design and set-up. Each laboratory may have different file formats. For some clinical trials the local laboratories test results may be entered directly into the clinical trial database. Setting-up a Data Transfer Agreement (DTA) with each laboratory and agreeing on the file format specifications at the beginning of a trial will help reduce issues.

Central laboratories tend to have their own file formats but are usually willing to work with the Sponsor or CRO to define data transfer specifications at the start of a study. Data can typically be provided as in comma separated values (CSV) or SAS format, and may or may not be aligned to SDTM. If aligned to SDTM, then it is preferred that the laboratory vendor sends the data to the organization (e.g., a CRO or the Sponsor) who is reviewing the SDTM mapping specifications for approval.

The laboratory test results are converted into an electronic standardized submission-ready format by representing them in the CDISC SDTM within the LB domain. The resources available from CDISC includes an SDTM Implementation Guide (SDTMIG) version 3.2, which provides an overview and describes how to represent this data, the CDISC Lab Model (CDISC-LAB) standard, along with a CDISC document on test and unit codelists (CDISC-LABCT) and the CDISC National Cancer Institute (NCI) Controlled Terminology, which is updated quarterly. Although CDISC-LAB model was last updated in 2003, there are many concepts that are still valid, while others may not be as relevant due to changes in the processes within the industry.

The process of converting the lab test results to SDTM is not without its own set of challenges. For example, Sponsors or CROs must map what they obtain from the labs to CDISC controlled terminology, which is an error prone process. In the SDTM LB domain, the LBCAT (category) variable is expected, while LBSPEC (Specimen) and LBMETHOD (Method of Test) are permissible. Further, the values in LBCAT are sponsor-defined (unique to each company) and lack any CDISC-specified controlled terminology. The Specimen and Method have CDISC controlled terminology, but the code list values are not always conceptually distinct or comprehensive. As a result, while a combination of these variables can be used to identify a test uniquely, there is no overarching conceptual model in how to do so.

Furthermore, the standardization of units, and the conversion of results to standard units, is often a significant challenge. As a starting point, it is important to map all units (both as collected in the original unit variable LBORRESU, and as standardized in the LBSTRESU variable) to CDISC terminology when possible. Currently the LB domain uses CDISC controlled terminology for units as represented in the UNIT codelist. There are instances when the units used in other systems such as electronic health records are based on the Unified Code for Units of Measurement (UCUM) standard. Currently there is no 1:1 relationship between the CDISC Controlled terms of units and UCUM. Until this is resolved, it will remain as a significant challenge for future data interoperability.

In addition to the standardized lab test results, the FDA wants LOINC codes to be included so that study and Sponsor comparisons can be performed. The LOINC information can be mapped to the LBLOINC variable in SDTM, and LOINC and other standardized variables in SDTM can be leveraged in down-stream processes, such as the generation of PARAMCD and PARAM in ADaM. Currently this variable is optional, so it is usually omitted from Sponsor SDTM submissions. As interoperability is a main goal of FDA and other organizations, this will be furthered by consistent expectations and usage of LOINC.

In 2017, the FDA convened a Committee, including FDA, NIH, CDISC, and Regenstrief Institute, to evaluate the use of terminology standards. Reporting to the Committee was a LOINC Working Group, which developed the following set of recommendations:

- LOINC codes should be submitted for human clinical studies only.
- Sponsors should include LOINC Codes for any test where a valid LOINC code exists including the most common laboratory tests utilized as standard of care.
- Sponsor should not attempt to derive LOINC codes if they are not provided by the laboratory.
- For laboratory tests where LOINC Code is not submitted, the reason for its omission should be noted in the Study Data Reviewers Guide (SDRG).
- The LOINC code specified in the LBLOINC variable in SDTM applies to the original result (LBORRES).
- When LOINC codes have a status of deprecated it should not be submitted.

For the laboratories the process of mapping their local codes/test catalogue to LOINC codes is a complex one because there is not always a one to one relationship between the tests run on the instruments and the existing LOINC codes. Most instrument and kit vendors are helping to address this issue by routinely providing laboratories with LOINC codes mappings for their tests. The FDA is encouraging in vitro diagnostic (IVD) test manufactures to provide LOINC codes.

## BEST PRACTICES AND FUTURE STEPS:

As the industry operationalizes LOINC implementation the following considerations should be taken into account:

- Laboratory test results must be standardized according to the CDISC SDTM and CDISC Controlled terminology.
- It is recommended that Sponsors and CROs have an understanding of the maturity level of their laboratory vendor's LOINC implementation, the validation process for LOINC mappings, how it is being maintained and which laboratory tests currently have LOINC codes.
- For specialized laboratories LOINC codes may not yet be available for new or complex laboratory tests. For such tests it is highly recommended that a new LOINC term be requested via the LOINC website.
- Protocols vary in the degree of preciseness of stating what is to be measured, for laboratory tests this could be addressed by including LOINC codes in the clinical trial protocol. Although this helps the downstream processes to create SDTM datasets, it is hard to keep track if the laboratories requests made by sites for subjects use the LOINC listed in the protocol.
- The Statement of Work with the laboratory vendors should include a statement that LOINC codes with be supplied with the test results. Alternatively, this need could be specified in the Data Transfer Agreement (DTA).
- When it is not possible for local laboratories to send LOINC or CDISC format, the tests and results can be sent to a central laboratory which can send results in CDISC format and contains LOINC codes.
- More experts in LOINC codes who understand CDISC and HL7 are needed.
- It is important for personnel at the Sponsor and CRO to understand concepts, in particular the LOINC code, LOINC Name, and their clinical relevance. More educate sessions on LOINC tailored to specify industry roles are needed.
- There needs to be a clear relationship between the controlled terms present in the variables of SDTM -LBTEST/LBTESTCD/LBMETHOD/LBSPEC to the LOINC Code and Name. This has to be maintained regularly and must be synchronized to the publishing cycles of CDISC CT and LOINC. To make this a reality, there needs to be a cross collaboration across industry, Standard Development Organizations and regulatory agencies.
- Volunteering in the CDISC Teams such as SDTM to discuss ideas about how to represent detailed LOINC information (6-part) in LB domain (SUPPQUAL versus change to the Domain structure)
- It would also help if CDISC defines Controlled Terms to Laboratory Category variables which will support the aggregation of data.
- Having a way to review the LOINC information to search and filter similar to CDISC Controlled Terminology would be useful. In addition, if there are APIs that are available so that other software systems can easily integrate so that automatic coding can be performed similar to other coding systems.

For ensuring the regulatory requirement is met, below are suggestions that may help:

- Sponsors, should develop a roadmap to ensure LOINC codes will be represented in data. This may require additional resources by either central laboratory vendors and SMEs who can support this process via a Statement of Work or a Data Transfer Agreement.
- If a Sponsor is to be responsible for mapping collected data to LOINC terminology, then it is critical that the necessary parameters (e.g., assay method) are captured from the beginning.

## CONCLUSION

Data and Terminology standards are helping to drive system interoperability thereby transforming clinical research and patient healthcare. This transformation is facilitating the emergence of personalized medicine and fostering a paradigm shift in clinical trials to a more patient-centric approach. The widespread adoption of these standards has been a prominent challenge over the past decade, along with the challenge of how to best connect the different clinical research and healthcare standards. The CDISC BRIDG model was developed to begin to address this connection.

Clinical laboratory data is a major source of data in both healthcare and clinical research. LOINC codes were originally developed to facilitate the exchange of laboratory test results from different laboratories and their aggregation. The FDA's 2020 requirement of Sponsors providing LOINC codes along with standardized laboratory test results for submissions (SDTM) raises the question of how best to build a bridge between the different standards.

This paper provided an overview of the operational considerations on the testing and reporting of laboratory data for a clinical trial, described LOINC codes, discussed the challenge of laboratories providing LOINC codes and of connecting LOINC with SDTM, as well as providing suggestions on how to address them. In the future as many Therapeutic Area standards have developed domains that represents a specialized subset of laboratory results, LOINC codes and LOINC names should be developed for such tests.

From an industry perspective there needs to be a continued cross collaboration between Pharma, Healthcare, Standard Development Organizations such as CDISC and the Regenstrief Institute, and Regulatory Agencies, to ensure a clear mapping between LOINC and CDISC CT. CDISC Controlled Terminology needs to include the representation for Laboratory Category and there needs to be a discussion about how to represent detailed LOINC information (6-part) in LB domain (SUPPQUAL versus change to the Domain structure).

## REFERENCES


1. Regenstrief Institute - https://www.regenstrief.org/
2. Connecting Health and Care for the Nation - https://www.healthit.gov/sites/default/files/hie-interoperability/nationwide-interoperability-roadmap-final-version-1.0.pdf
3. Clinical Data Interchange Standards Consortium (CDISC)- http://www.cdisc.org
4. Details of LOINC Code for Glucose in Urine: https://s.details.loinc.org/LOINC/5792-7.html?sections=Comprehensive
5. Details of LOINC Code for Glucose in Serum - https://s.details.loinc.org/LOINC/2345-7.html?sections=Comprehensive
6. CDISC SDTM Model 1.4 - https://www.cdisc.org/system/files/members/standard/foundational/sdtm/study_data_tabulation_model_v1_4.pdf
7. CDISC Study Data Tabulation Model Implementation Guide (SDTMIG) Version 3.2
8. FDA Data Standards Resources - https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
9. Which LOINC name should I use for what? - https://danielvreeman.com/loinc-name-use/
10. LOINC, a universal standard for identifying laboratory observations: a 5-year update - https://www.ncbi.nlm.nih.gov/pubmed/12651816
11. FDA Recommendation (2017): Recommendations for the Submission of LOINC® Codes in Regulatory Applications to the U.S. Food and Drug Administration- https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm586363.pdf

12. LOINC, a universal standard for identifying laboratory observations: a 5-year update - https://www.ncbi.nlm.nih.gov/pubmed/12651816
13. FDA Recommendation (2017): Recommendations for the Submission of LOINC® Codes in Regulatory Applications to the U.S. Food and Drug Administration - https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm586363.pdf
14. FDA Guidance (2018): Logical Observation Identifiers Names and Codes for *In Vitro* Diagnostic Tests - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM610636.pdf
15. LOINC in Regulated Clinical Research - https://loinc.org/files/meetings/2017-06-07/Handout%20-%20LOINC%20CDISC%20Presentation%20-%20Lauren%20Becnel.pdf
16. An Alternative CDISC-Submission Domain for Laboratory Data (LB) for use in Electronic Health Record Data - https://www.ejbi.org/scholarly-articles/an-alternative-cdiscsubmission-domain-for-laboratorydata-lb-for-use-with-electronic-health-record-data.pdf

## ACKNOWLEDGMENTS

We would like to acknowledge to Shire and CRO Governance teams, Laboratory vendors who provided a framework to establish data standards within Shire and for their continued support.

## CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

| | |
|---|---|
| Veena Nataraj<br>Shire<br>vnataraj@shire.com<br>www.shire.com | Diane Piper<br>Shire<br>dpiper@shire.com<br>www.shire.com |