Office of the Secretary Patient-Centered Outcome Research Trust Fund Project HP-19-011

SHIELD (Systemic Harmonization and Interoperability Enhancement for Laboratory Data) - Standardization of Lab Data to Enhance Patient-Centered Outcomes Research and Value-based Care

Final Report

U.S. Food and Drug Administration (FDA) Office of In Vitro Diagnostics (OIVD) within the Center for Devices and Radiological Health (CDRH)

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Contract # 75F40119C10164

1 OVERVIEW AND OBJECTIVES

The program's purpose and objectives are detailed below.

1.1 Purpose

Laboratory in vitro diagnostic (IVD) testing data makes up a sizable portion of Electronic Health Record systems (EHRs) and is highly utilized in decisions influencing patient care [1][2]. The absence of laboratory semantic interoperability for IVD data has been cited as a significant impediment to overall public healthcare. The erosion of accuracy for IVD test data due to interoperability failures can have patient safety consequences and impede timely access to and analysis of lab data on a nationwide scale [3]. Healthcare laboratory data exchange requires that laboratories reproducibly encode their test data using industry coding standards. For laboratory data, appropriate use of Logical Observation Identifiers Names and Codes (LOINC®) and Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT®) are essential to ensure tests and results are accurately and reliably described within EHRs, laboratory information systems (LIS), and public health reports.

1.2 Objectives

The objectives were to: (1) Assess the effectiveness of providing Logical Observation Identifiers Names and Codes (LOINC®)-to-In Vitro Diagnostic (LIVD) coding recommendations in a mapping file supplied on the Centers for Disease Control and

Prevention web site (LOINC In Vitro Diagnostic (LIVD) Test Code Mapping for SARS-CoV-2 Tests | CDC). Use of this file is required by the United States Department of Health and Human Services for SARS-CoV-2 reporting, in medical center laboratories. And (2) Assess the findings to help inform future United States Food and Drug Administration (FDA) policy on the use of real-world evidence in regulatory decisions.

The infrastructure intended for deployment within this project was developed/adopted by the SHIELD (Systemic Harmonization and Interoperability Enhancement for Laboratory Data) initiative. SHIELD is a collaborative of federal agencies and key stakeholder organizations that was assembled with a singular focus on improving the interoperability and utility of diagnostic test data.

The overarching objective of this work was to evaluate the use of industry standards and infrastructure that were agreed to by the SHIELD community multi-stakeholder initiative for piloting at Implementing Healthcare Institutions (IHI) prior to its consideration on a national scale. The infrastructure intended for implementation consists of the following:

- Semantic Standards
    - LOINC® [4]
    - SNOMED CT® [5]
    - UCUM (Unified Code for Units of Measure) [6]
    - UDI (Device Identifier component only) [7]
- Transmission/Mapping
    - LAW [8]
    - LIVD [9]
    - LIVD FHIR® profile [10]

Because every healthcare institution is different, not all parts of the aforementioned industry standards and infrastructure are possible or appropriate for all IHIs (e.g., institutions not leveraging Fast Healthcare Interoperability Resources (FHIR®) could not implement the LIVD FHIR® profile). The SHIELD evaluation team determined what was reasonable and appropriate for each individual IHI infrastructure to demonstrate interoperability for this study. The specific aims of this work were to:

- Aim 1: Identify and onboard active healthcare institutions as pilot sites for the assessment of SHIELD-harmonized standards.
- Aim 2: Collect laboratory test codes to be used in the assessment of implementation of SHIELD-harmonized standards.
- Aim 3: Evaluate the use of the industry standards and infrastructure at participating IHIs.

Key deliverables are as follows:

1. A report detailing the descriptive code sets used in laboratory production environments for IVD (In Vitro Diagnostics) tests, and a comparison of those code sets with those recommended for those same IVD tests by the Device Manufacturers' LIVD Catalogs (~100 LOINC codes per IHI).
2. A report detailing system interoperability assessed pre- and post- implementation laboratory use of the LIVD mapping file .

2 BACKGROUND – PROBLEMS ADDRESSED

Through this work, we sought to address the following problems: standardized collection of clinical data, collection of participant-provided information, linking clinical and other data for research, use of clinical data for research, and use of enhanced publicly funded data systems.

2.1 Standardized Collection of Standardized Clinical Data

IVD test results are often represented differently between different institutions, or even within an institution, impacting their utility in patient care, research, and public health use cases. This variation in IVD data results in a lack of interoperability and can increase patient safety risk. To assist, specifications have been developed, such as Laboratory Analytical Workflow (LAW) and LIVD. LAW—developed by the Integrating the Healthcare Enterprise (IHE) Laboratory Technical Committee—is the transport framework for exchanging data between IVD instruments and LIS using Health Level Seven (HL7) V2 messaging standards [5][6]. LIVD aligns the terminology codes for each specific IVD by vendor-defined codes so labs can report such codes properly; it was initially released as a spreadsheet and industry-developed JavaScript Object Notation (JSON) definition and will soon be represented using HL7 FHIR® constructs. FHIR® is the registered trademark of HL7 and is used with permission of HL7. Other standards are available but not widely implemented to properly exchange data through the continuum of care: inside the lab, between different labs, between providers and labs, between labs and public health institutions, and in access for research.

This project focused on implementing infrastructure that directly addresses laboratory data interoperability failures at their root by harmonizing how laboratory data informatics standards are practically applied within healthcare institutions through a sole authoritative source (i.e., LIVD). LIVD is a collaborative resource curated through efforts of IVD Vendors (through their contribution of vendor-defined codes) with participation from laboratory and other experts. These efforts to harmonize the application of standardized nomenclatures and streamline high-quality health information exchange help address the priorities within the 21st Century Cures Act [11] (Public Law 116–136, § 18115(a)) to improve electronic data interoperability, CMS (Centers for Medicare &

Medicaid Services) interim final rule (85 FR 54820) for hospitals reporting information regarding the public health emergency for COVID-19, and the CDRH priorities to build a National Evaluation System for Healthcare Technology (NEST).

This project will help ensure that the IVD descriptive information that feeds into all these processes is consistent and unambiguous. These semantic standards are key to this project by facilitating the storage, exchange, and pooling of results for clinical care, outcomes management, and research by providing a set of standard names and identifiers that can be used across heterogeneous computing environments.

2.2 Collection of Participant-Provided Information

By leveraging deidentified, semantically interoperable diagnostic information from patients, real-time data can be used to help drive innovative solutions to significant public health challenges.

2.3 Linking Clinical and other Data for Research

The loss or compromise of IVD test data due to interoperability failures can have deadly consequences [3]. IVDs are used by healthcare professionals to ‘ask’ a question of a clinical specimen to gain insight into a patient’s physiologic status (e.g., glucose levels, disease presence/absence, etc.), which helps guide clinical decisions and subsequent therapeutic actions. Semantic interoperability is a vital aspect to ensuring that the questions that IVD tests ask and the results from those tests are accurately and consistently described within electronic healthcare records (EHRs) so that it can be used by multiple data consumers.

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By empowering the entire healthcare ecosystem to use the same terminology to describe the same diagnostic observation the same way every time, critical public health information can be instantly transmitted and analyzed by those across the nation and world.

2.4 Use of Clinical Data for Research

Although digitized, IVD data is often represented differently between institutions (or even within an institution) leading to ambiguity and incapacitating its utility for research or other purposes.

This project intended to ‘pressure test’ the implementation of industry standards and infrastructure prior to roll-out on a national scale and showed significant gaps in reproducibility of real world data test representation and reporting. Electronic healthcare system interoperability was assessed pre- and post-implementation of the LIVD mapping file.

This effort is expected to also have a significant impact on the ability to use Real World Evidence (RWE) in regulatory decisions, realize real-time epidemiology, enhance clinical decision support, and enable research related to key diseases, including (but not limited to) opioid overdose, antimicrobial resistance, sepsis, cancer, renal failure and much more.

2.5 Use of Enhanced Publicly Funded Data Systems

The infrastructure intended for deployment within this project was developed/adopted by the SHIELD community. Bridging the gap between private and public stakeholders, SHIELD works in a collaborative consensus framework to adopt informatics standards and procedures to improve the interoperability of laboratory data. These efforts to harmonize the application of standardized nomenclatures and streamline high-quality health information exchange.

The results from our research and findings provided insights into the following questions:

1. How effective was providing LIVD code specification mappings to medical center labs?
    a. The existing specifications were not sufficient to promote interoperability. Medical centers vary in how they organize, categorize, and store LIS catalog information. This variation impacts data quality and interoperability [13].
    b. National implementation of LIVD and further efforts to promote laboratory interoperability will require a more comprehensive effort and continuing evaluation and quality control [13].
2. Can we use the findings to help inform future FDA policies on RWE regulatory decisions?
    a. Not currently. Further studies and quality control are needed.
3. What were the gaps between manufacturers and the medical center recommended LOINC codes for the same test?

    a. There was a 41% (136 codes) mismatch between IVD manufacturer LIVD files that matched LOINC codes used at the pilot sites medical centers [13]. This data shows a significant variation between how diagnostic test manufacturers and medical center laboratories use industry coding standards (i.e., LOINC) to represent the same information.
4. What were the similarities?
    a. There was a 59% (195 codes) match between IVD manufacturer LIVD files that matched LOINC codes used at the pilot sites medical centers [13].

3 METHODOLOGY

The team conducted a pilot site study with five medical centers' laboratories to better understand the problems with laboratory methodology. The following section outlines the setting, pilot site recruitment, data collection, and evaluation process of this study.

3.1 Setting

During a two-year span from September 2019 to September 2021, the pilot program was housed in five medical centers' laboratories across the United States. FDA's CDRH contracted with Deloitte Consulting who recruited participants and evaluated the data recorded through these five pilot sites. The study was designed to evaluate the implementation of the standardized LIVD file, and associated infrastructure in clinical laboratories. The study design was updated in 2020 to evaluate the use of the LIVD file by clinical laboratories during the rollout of the Coronavirus Aid, Relief, and Economic Security (CARES) Act reporting requirements for COVID-19. Due to the pandemic, the focus of the study changed to COVID-19 and associated conditions in 2020 [13].

3.2 Pilot Site Recruitment

Medical center laboratories' eligibility in the pilot was based on their willingness and ability to produce informatics and terminology data from their LIS and health IT systems. We started recruiting from a list of well-known institutions and accepted referrals from initial participants to generate additional candidates [13].

3.3 Data Collection

Each medical center was asked to extract about 100 LOINC® codes from their LIS for prioritized tests of interest focused on high-risk conditions and SARS-CoV-2. We coordinated with SHIELD stakeholders and the IVD Industry Connectivity Consortium (IICC) to request manufacturer LIVD catalogs containing the LOINC® codes per IVD

instrument per test from manufacturers [13] [14]. The IICC is a nonprofit organization that encourages adoption of unified industry coding standards with the aim of reducing the cost and variability of data exchange between IVD devices and information systems in clinical laboratories. [14]

3.4 Evaluation

We compared gaps and similarities between diagnostic test manufacturers' recommended LOINC® codes and the LOINC® codes used in medical center laboratories for the same tests. We identified medical center and manufacturer intersections where a medical center used a specific IVD that was present in the LIVD file sent to us by a particular manufacturer. We identified every record in the data submitted by the medical centers that did not have a match for the corresponding manufacturer LIVD file [13].

4 ACCOMPLISHMENTS BY FINAL DELIVERABLES

There were two key deliverables developed from the pilot site program: (1) a report detailing IVD descriptive code sets used in selected laboratory production environments compared with the recommended IVD coding recommended by the device manufacturers' LIVD Catalogs and (2) a report detailing interoperability assessed pre- and post- implementation of industry standards and infrastructure.

4.1 Report Detailing IVD Descriptive Code Sets used in Production Laboratory Environments compared with IVD Manufacturer Recommend Code Sets

A final report detailing descriptive code sets in production environments was published as part of an article in Journal of the American Medical Informatics Association (JAMIA). This section identifies the location of this information.

Deliverable Name	Description	Target Audience	Location
Final Descriptive Code Set Report – Manuscript Publication	Article in the Journal of the American Medical Informatics Association (JAMIA) measuring the interoperability of laboratory data as it moves between systems. The study	Health IT and clinical stakeholders across industry and government agencies.	**Publication Citation:** Cholan RA, Pappas G, Rehwoldt G, Sills AK, Korte ED, Appleton IK, Scott NM, Rubinstein WS, Brenner SA, Merrick R, Hadden WC, Campbell KE, Waters

	produced data on the significant variation (41%) between how diagnostic test manufacturers and medical center laboratories use industry coding standards (i.e., LOINC) to represent the same information. Efforts to promote interoperability will require a more comprehensive effort and continuing evaluation and quality control.		MS. Encoding laboratory testing data: case studies of the national implementation of HHS requirements and related standards in five laboratories. J Am Med Inform Assoc. 2022 Jul 12;29(8):1372-1380. doi: 10.1093/jamia/ocac072. PMID: 35639494; PMCID: PMC9277627.
Final Descriptive Code Set Report – PDF	See above	See above	**Attachment 1 – JAMIA Publication**
Final Descriptive Code Set Report – MS Word	See above	See above	**Attachment 2 – JAMIA Manuscript**

4.2 Report Detailing System Interoperability Assessed Pre- and Post- Implementation of SHIELD community recommended Standards and Infrastructure

A final report detailing system interoperability pre- and post- implementation of industry standards and infrastructure was presented at the American Medical Informatics Association (AMIA) Annual Symposium 2021. Two previous deliverables that contributed to this report are included: the first deliverable is a poster presented during the AMIA 2021 conference, and the second deliverable was an updated poster that highlights post-implementation analysis of industry standards.

Deliverable Name	Description	Target Audience	Location
Final Pre- and Post-Implementation Report – Conference Poster Publication	Poster presented at the American Medical Informatics Association (AMIA) Annual Symposium 2021 in which we (1) describe the laboratory coding information collected from the five pilot sites, (2) assess the extent to which LOINC (Logical Observation Identifiers Names and Codes) codes in the LIVD catalog files from IVD manufacturers compare to LOINC codes chosen in information systems in five pilot medical centers, (3) analyze the difference between pre-implementation site data (non-COVID test data) and post-implementation site data (COVID test data, due to the Health and Human Services (HHS) requirement for LIVD files for SARS-CoV-2 reporting to be made available to laboratories and (4) discuss lessons learned and implications for the SHIELD workgroup.	Health IT and clinical stakeholders across industry and government agencies.	**Publication Citation:** Rehwoldt G, Cholan RA, Sills AK, Appleton IK, Williams, T, Scott, N, Pappas G. Piloting FDA (Food and Drug Administration) SHIELD's LOINC to In Vitro Diagnostic (LIVD) Specification in Five Medical Centers: Implications for Interoperability. AMIA Annual Symposium Proc. 2021 Nov 1.

Final Pre- and Post-Implementation Report – Conference Poster Publication (2021 Presented Version)	See above	See above	**Attachment 3 – AMIA Poster Presentation 2021**
Final Pre- and Post-Implementation Report – Conference Poster Publication (2022 Final)	See above	See above	**Attachment 4 – Poster 2022 Pre and Post Implementation Report**

5 LESSONS LEARNED AND CONSIDERATIONS FOR FUTURE WORK

The five medical centers and three test manufacturers vary in how they organize, categorize, and store LIS catalog information. This variation impacts data quality and interoperability. Within and across pilot sites there is a lack of standardization for encoding test data.

The results of this body of work indicate that providing the LIVD mappings was not sufficient to support laboratory data interoperability. National implementation of LIVD and further efforts to promote laboratory interoperability will require a more comprehensive effort and continuing evaluation and quality control.

As medicine becomes more granular with precision medicine, we will need software that can standardize, represent, and have the capacity and efficiency to keep up with the volume and knowledge management these systems require [15]. This is the only cost-effective method as the number of human resources needed to keep up with the volume of data will not only be economically prohibitive, but also prone to human error.

The current terminology inconsistency and complexity has led to challenges encoding laboratory test results in a safe and effective interoperable manner [15]. Using another standard that represents LOINC using a robust methodology, such as SNOMED CT®, should be considered. Another approach is a SNOMED CT® extension of LOINC® that would utilize the strength of both terminologies, in particular inferencing and semantic equivalence [16]. However, even if a LOINC® extension of SNOMED CT is developed, there are many other terminologies that still need to be harmonized. Tools, such as HL7's Terminology Knowledge Architecture (Tinkar), may be used to create a harmonized representation of current terminologies, and is also an extensible architecture that in can accommodate future terminology needs as well.

A subsequent study with more rigid study protocols may be useful, so that all production environments could be compared equally, unambiguously, and consistently. For instance, the lack of LIVD use prior to assignment of LOINC codes to tests may not have provided sufficient user experience to gain familiarity and expertise to make more correct assignments.

LIVD tooling needs to be revamped with non-spreadsheet tools. The ecosystem could continue with FHIR development, knowledge management, and error monitoring to assure quality.

The COVID-19 LIVD file is curated by a SHIELD committee and hosted by the CDC (Centers for Disease Control and Prevention) for distribution. A potential limitation is whether SHIELD is representative of all stakeholders and interests. An independent validation of the COVID-19 LIVD file content could not only confirm internal validation, but also mitigate potential bias per best practice.

There is an opportunity to further pursue and build out the use cases for LIVD by engaging an increasing number of medical center laboratories and obtaining their feedback so that LIVD can be used in laboratory health IT environments. A formative evaluation of LIVD use cases should be an ongoing effort to demonstrate LIVD's value. This should be part of a comprehensive system of quality control built into the system.

Lastly, updating the format of LIVD can make it more accessible by providing tooling and including proper value sets for specimen type, results when qualitative, coded units of measures for quantitative results, and additional metadata. These updates could be incorporated via the creation of a repository of LIVD files from different manufacturers and may be considered in future studies.

The findings from this pilot study contributed to the creation of the SHIELD community Roadmap—a document created by a group of public and private collaborators whose common goal is to achieve laboratory data interoperability. This roadmap document provides greater understanding to what needs to be done to achieve end-to-end laboratory data interoperability and ultimately better healthcare technology

infrastructure. Issues of data inoperability span across the world, not just the nation, and this study's finding can act as a foundation for additional research and eventual development of a long-term solution that will propel the advancement of laboratory standardization to a global level.

6 REFERENCES

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