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An Update on the CS Standard Analyses and Code Sharing Working Group

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ABSTRACT

The Standard Analyses and Code Sharing Computational Science (CS) Working Group is providing recommendations for analyses, tables, figures, and listings for data that are common across therapeutic areas (laboratory measurements, vital signs, electrocardiograms, adverse events, demographics, medications, disposition, hepatotoxicity, pharmacokinetics). The working group has published seven white papers, and has also created an online platform for sharing code. Crowd-sourcing code development will enable consistent interpretation of methods and substantial savings in resourcing across the industry. This presentation will provide an update on these efforts.

INTRODUCTION

The Computational Science Collaboration represents a formal agreement between the Pharmaceutical User Software Exchange (PhUSE) and the FDA. Its mission statement is "To provide an open, transparent, and collaborative forum in a non-competitive environment in which Academia, Regulators, Industry, and Technology providers can address computational science needs in support of product development and regulatory review, ultimately bringing safe and effective products to those who need them." Products created by the CS Working Groups are intended to bridge the gaps between industry standards, such as those developed by the Clinical Data Interchange Standards Consortium (CDISC), and the needs of regulatory agencies. CDISC standards do not address analyses and data displays, so the Standard Analyses and Code Sharing Working Group was formed to fill in that hole.

COMPUTATIONAL SCIENCE WORKING GROUPS

At this time, six CS Working Groups have been chartered by the PhUSE Board of Directors. The groups cover issues regarding data transparency, optimizing the use of data standards, emerging trends and technologies, nonclinical topics, educating for the future, and the focus of this paper, standard analyses and code sharing. The working groups are further subdivided into teams of volunteers from both industry and regulatory agencies, who are working on various types of deliverables.

STANDARD ANALYSES AND CODE SHARING

Considerable progress has been made in recent years with respect to standardization; however, most of that has come in the areas of data collection and storage. The CDISC Analysis Data Model (ADaM) intentionally avoids advocating specific forms of analyses for given types of data. As a result, the Standard Analyses and Code Sharing Working Group was formed to recommend standards for analysis and display of commonly-collected information and to develop code to support those standards. Figure 1 is a diagram showing how the Working Group fits into the clinical data flow process:

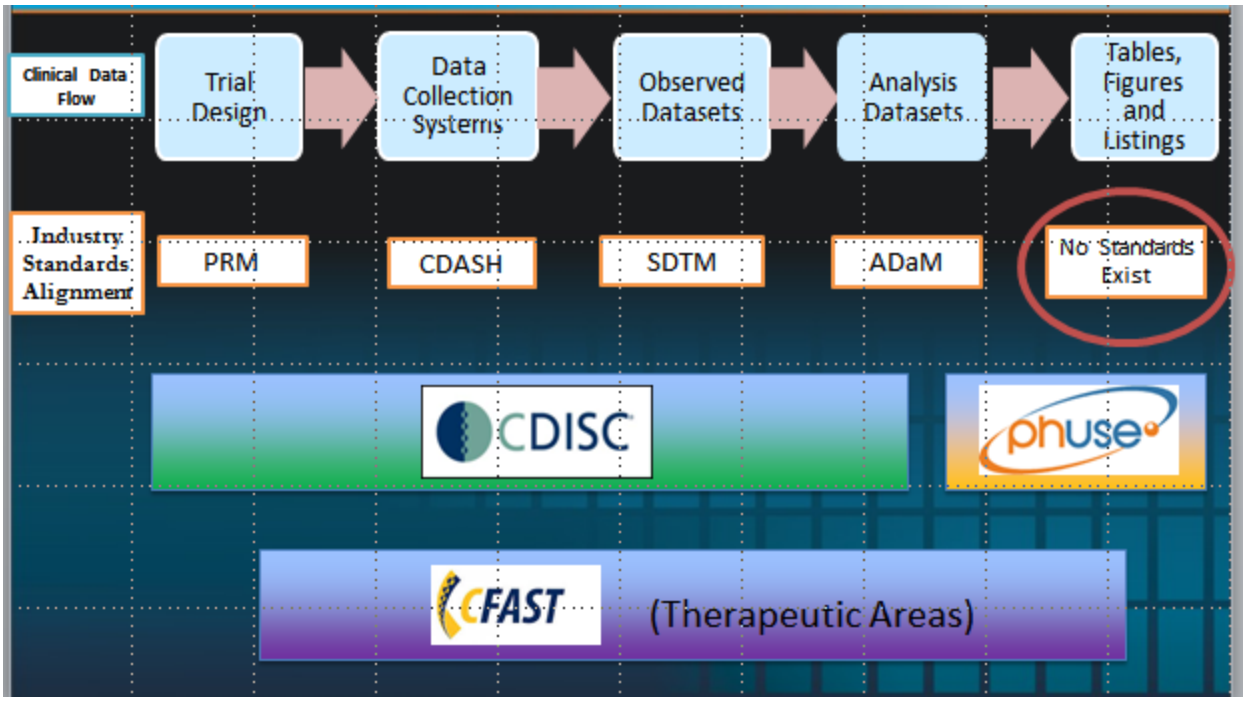

Figure 1. Current Industry Data Standards

The Working Group is further subdivided into four focus areas:

- Analysis and Display White Papers, led by Mary Nilsson
- Communication, Promotion and Education, led by Jared Slain and Wendy Dobson
- Test Data Factory, led by Peter Schaefer
- Script Repository, consisting of 4 sub-projects

WORKING GROUP FOCUS AREAS

Ten white papers are at various stages of development, including seven that have been finalized. The latest white paper to be published covers analyses and displays for adverse events, while previously published white papers address vital signs, ECG and labs central tendencies (2013); non-compartmental pharmacokinetics (2014); vital signs, ECG and labs outliers and shifts (2015); thorough QT/QTc studies (2016); and screenshots of the displays created using programs contributed by the FDA (2017). In addition, version 2 of the demographics, disposition and medications white paper was released in 2018. The white papers are all available on the PhUSE website, http://www.phuse.eu; click on "Working Group Deliverables" under the Resources tab.

Work is currently ongoing on white papers covering treatment-emergent adverse event definitions, hepatotoxicity, questionnaires, and events of special interest, with a goal of publishing one or more by the end of 2018.

The Test Data Factory project has updated the SDTM datasets in the CDISC pilot to comply with SDTM Model v1.4 and SDTM IG v3.2, and is currently working on updating the CDISC pilot ADaM datasets to comply with ADaM IG v1.1.

SCRIPT REPOSITORY

The code repository contains a wealth of scripts (code) that have been written by PhUSE members or donated by other organizations. Development is supported by four projects:

- Script Discovery and Acquisition, led by Rebeka Revis and Alfredo Rojas
- Repository Content and Delivery, led by Gustav Bernard and Andrew Miskell
- Repository Governance and Infrastructure, led by Hanming Tu and Mike Carniello
- Script Metadata for Sharing, led by Hanming Tu

The Script Discovery project has selected the MIT license to cover distribution of the scripts, developed a qualification process and a user-friendly front end, and created a place in the repository for storing code developed by other groups, such as scripts provided by FDA reviewers and Spotfire templates used for safety reviews. They have also conducted six Scriptathons in the past few years, which have produced scripts at various stages of development to take CDISC pilot ADaM data, and produce data displays shown in the Central Tendency white paper.

The Repository Content and Delivery project is working on finishing the scripts developed at the Scriptathons.

The Repository Governance and Infrastructure project has set up the repository where the scripts are stored and is developing rules and processes for qualifying the scripts for use.

The Script Metadata for Sharing project is creating machine- and human-readable metadata describing the scripts stored in the repository, including user documentation.

Figure 2 shows a schematic of the script repository:

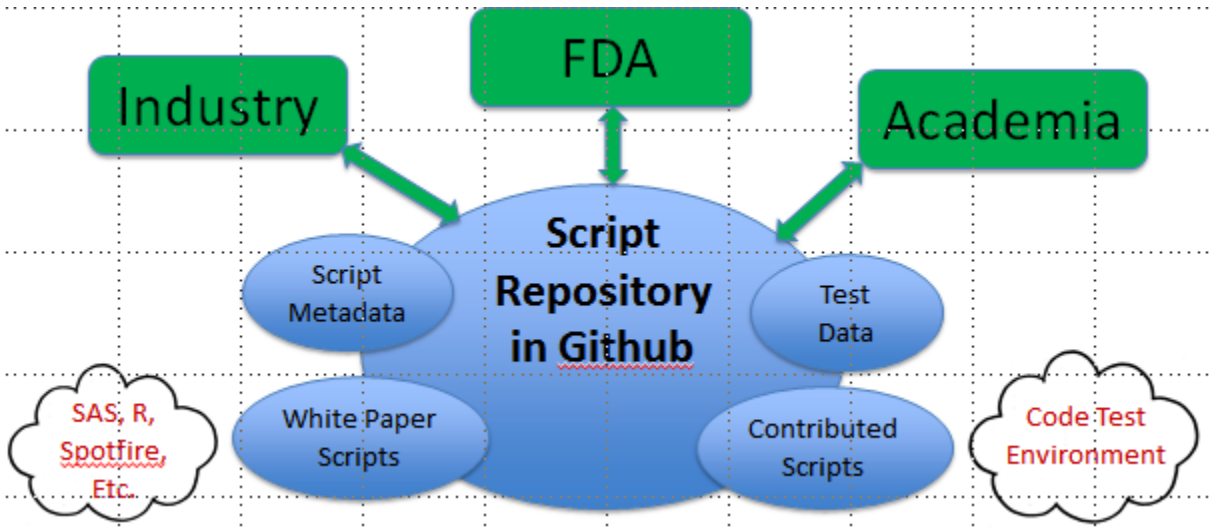

Figure 2. Script Repository Structure

NEXT STEPS

All of the projects have goals to accomplish by the end of the year. The Repository Content and Delivery team is working to increase the usability, acceptability and quality of the scripts currently stored in the repository, and is developing additional scripts to produce the data displays described in the other white papers. The Script Metadata for Sharing project is finalizing the structure of the standard metadata which will be created for each script in the repository. The Test Data Factory project will be starting production of simulated test data, which can be used for testing the scripts. The White Papers group is targeting publication of one or more additional white papers by the end of the year. And finally, the

Communications, Promotion and Education team is developing training material aimed to improve safety analytics expertise by understanding the purpose and rationale for the recommendations in the analysis and display white papers, as well as instructions for the use of the repository and its scripts.

HOW CAN YOU HELP?

More project team members are needed. We have set some ambitious goals for 2018, but our projects are staffed by volunteers, and the demands of their day jobs take priority over Working Group tasks.

We especially need people to review our work. The white papers should be reviewed by statisticians, medical writers, clinicians, and other clinical study stakeholders to ensure they address the needs of those communities, and accurately reflect current scientific and statistical thinking. Please forward the white papers to such groups within your companies, so we can get a broad variety of viewpoints in the document reviews.

Participate in reusable code development. If there are programs in your projects that produce data displays similar to those in the white papers, consider removing any proprietary information, and donating it to the code repository. Also keep your eyes open for existing scripts that could use a public home.

Finally, advertise! Advertise! Advertise! Spread the word that these white papers have been created to address common data display requirements in clinical studies, and consider using them in your Statistical Analysis Plans (SAPs).

To sign up for a Working Group, go to the PhUSE Wiki (www.phusewiki.org), and click on the "Join a Working Group Now" link. Then search for the name of the group you wish to join. Wiki pages for each of the projects are also available at www.phusewiki.org.

CONCLUSION

The Standard Analyses and Code Sharing Working Group is working on developing recommendations for analysis and display of commonly-collected clinical study data, and then collecting or creating scripts to meet those standards. Crowd-sourcing that code development will enable consistent interpretation of methods and substantial savings in resources across the industry. .

REFERENCES

Pharmaceutical User Software Exchange. Accessed August 22, 2018. http://www.phuse.eu.

PhUSE Wiki. Accessed August 22, 2018. http://www.phusewiki.org.

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