PharmaSUG 2014 - Paper DS17

Update: Development of White Papers and Standard Scripts for Analysis and Programming

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ABSTRACT

A PhUSE Computational Science Symposium (CSS) Working Group is creating white papers outlining safety, demographics, disposition and medications analysis and reporting for clinical trials and regulatory submissions. An online platform for sharing code has also been created, making these standards easy to implement. This paper provides an update as of April 2014 on the progress made in these efforts.

INTRODUCTION

Industry standards have evolved over time for data collection (CDASH), observed data (SDTM), and analysis datasets (ADaM). Creating a consistent set of analyses and reports, at least for safety, is the natural next step in this remarkable journey. Members of a PhUSE CSS Working Group are creating white papers outlining recommendations for safety analysis and reporting for clinical trial study reports and integrated safety-related submission documents. Development of standard tables and figures with associated analyses will lead to improved product life-cycle evaluation by ensuring reviewers receive optimal analyses for the evaluation of patient safety. More importantly, having an organized process for shared learning of improved methodologies can lead to earlier safety signal detection and better characterization of the safety profile of the products. Additionally, a platform for sharing code to implement the recommendations has been created and is ready, making the standards easy to use. Crowd sourcing for code development will enable consistent interpretation of methods and substantial savings in resourcing across the industry. This paper describes the progress on these efforts and how people can participate in the creation and use of cross-industry analysis and reporting standards.

WORKING GROUP DESCRIPTION

The goal of the Working Group is to produce recommendations and establish a platform for the collaborative development of specialized programs to be used as analytical tools for clinical trial research, reporting, and analysis. This platform includes:

- Identification of areas that can benefit from a standard set of analyses
- Development of recommendations for analyses, tables and figures within a topic area
- Creation of a process and guidelines for documentation and management of scripts
- Incorporation of data standards whenever feasible

The Working Group is led by a team of representatives from both industry and the FDA. Mary Nilsson is the industry co-lead, with Hanming Tu as the project manager and Mike Carniello as the lead of the standard scripts project; Steve Wilson and Mat Soukup are the current FDA liaisons. There are two main areas of focus - the creation of white papers outlining recommendations for analysis and reporting of different types of safety data, and the development of scripts (programs) for generating the data displays shown in the white papers.

WHITE PAPERS

The following white papers have been drafted, or are in progress (more current information on their status will be presented at the conference, as work is still ongoing):

1. Analyses and Displays Associated with Measures of Central Tendency – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Summary Documents *(finalized in October 2013, and used for requirements in the Scriptathon held at the March 2014 Computational Science Symposium conference)*
2. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Summary Documents *(draft sent for public comment in February 2014, comments are being addressed)*

3. Analyses and Displays Associated with Adverse Events – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(first draft targeted for public comment in May 2014)*
4. Analyses and Displays Associated with Demographics, Disposition, and Medications – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(second draft targeted for public comment in April 2014)*
5. Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(first draft targeted for public comment in May 2014)*
6. Analyses and Displays Associated with Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials *(finalized in March 2014)*
7. Analyses and Displays Associated with QT Studies *(team lead identified, call for volunteers went out in March 2014)*

The scope of the white papers includes information that would normally be included in a Statistical Analysis Plan, plus any associated table, listing and figure shells, and detailed information that might be required for performing the analysis. However, actual implementation details, such as page layouts, margin requirements and variables to be used will not be addressed. Recommendations for difficult or potentially controversial decisions related to analyses or displays will be provided where possible; when a decision cannot be reached, a description of the issues that have been considered will be included.

Our goal is to have all of these white papers completed, or at least near completion, by the end of 2014, and available for public download from the publications section of the PhUSE website (http://www.phuse.eu/publications.aspx). Drafts can be viewed in the CSS Working Groups section of the PhUSE Wiki (http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08). These white papers will also be presented at several industry conferences during the upcoming year.

SCRIPT REPOSITORY

The script repository project will establish the basic structure and management of the Google Code repository to be used for development and storage of the PhUSE standard scripts. Google Code provides a scalable, reliable, and fast collaborative development environment for developing and sharing standard scripts and documents for data transformations and analyses. The goals of this project are to:

- define the folder structure and name conventions
- define roles and responsibilities for each role
- define tasks and duties
- define the process of tracking issues
- define required metadata and recommended programming style for scripts
- provide test data and validation documentation

The script repository is intended to be language-independent, but with a primary focus on SAS and R, as those are currently the two main languages used for reporting and analysis within the industry.

Several scripts have already been developed; a complete index is available on the PhUSE Wiki, at http://www.phusewiki.org/wiki/index.php?title=Standard_Script_Inventory. The MIT license governing the development and distribution of open source code was chosen, in order to make all scripts freely available for use. The PhUSE script repository can be accessed at http://code.phuse.com , and instructions for using the repository can be found at http://www.phusewiki.org/wiki/index.php?title=User_Guide_for_Standard_Script_Repository.

A Scriptathon was held at the March 2014 CSS conference, using requirements created for data displays outlined in the Measures of Central Tendencies, Outliers and Shifts, and Non-Compartmental Pharmacokinetics white papers as a starting point for the creation of scripts to generate those displays. Data from the updated CDISC ADaM pilot was used for programming, with additional datasets created to handle multiple baseline definitions required by the Outliers and Shifts displays, and de-identified PK datasets for the Pharmacokinetics displays. Twenty people participated in the event, some remotely; eight SAS and R scripts were drafted, and have been added to the */scriptathon2014/scripts* folder in the Source section of the repository.

We are encouraging people to submit additional scripts, along with their ideas for others that should be written, with a goal of building a repository that people can borrow from for their own projects. In addition, there are plans for developing templates and metadata for documenting scripts, along with steps for qualifying scripts for use.

CONCLUSION

This paper is intended to serve as an update as of April 2014 on the progress made by the Standard Scripts Working Group in developing white papers outlining recommendations for analysis and reporting of various types of clinical trial safety data, and the creation of scripts for generating the data displays described in the white papers. As part of this effort, a Google Code repository has been created, and the Working Group is actively seeking contributions to the code library. If you would like to get involved in these efforts, please see the PhUSE Wiki for instructions on contacting the Working Group leadership team.

REFERENCES

Standard Scripts Project 3 (Code Repository)- http://www.phusewiki.org/wiki/index.php?title=WG5_Project_03

Standard Scripts Project 8 (White Papers)- http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08

ACKNOWLEDGMENTS

Many thanks to all of the members of the Standard Scripts Working Group who reviewed this paper.

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