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PHUSE Safety Analytics Working Group – Overview and Deliverables Update

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ABSTRACT

The PHUSE Safety Analytics Working Group, a cross-disciplinary cross-industry collaboration, is working to improve the strategy and implementation of clinical trial safety assessments for medical research, leading to better data interpretations and increased efficiency in clinical drug development and review processes. The Working Group has produced numerous deliverables (Conference Posters and Presentations, White Papers, Publications, Blogs, etc.,) over the past 10 years and has many ongoing projects. This presentation will provide an overview of the Working Group and its associated project teams, and share an update of the teams' progress, key deliverables for awareness and a summary of ongoing projects.

INTRODUCTION

The PHUSE Safety Analytics Working Group currently consists of the following 8 project teams, all working on various aspects of collection and analysis of safety data:

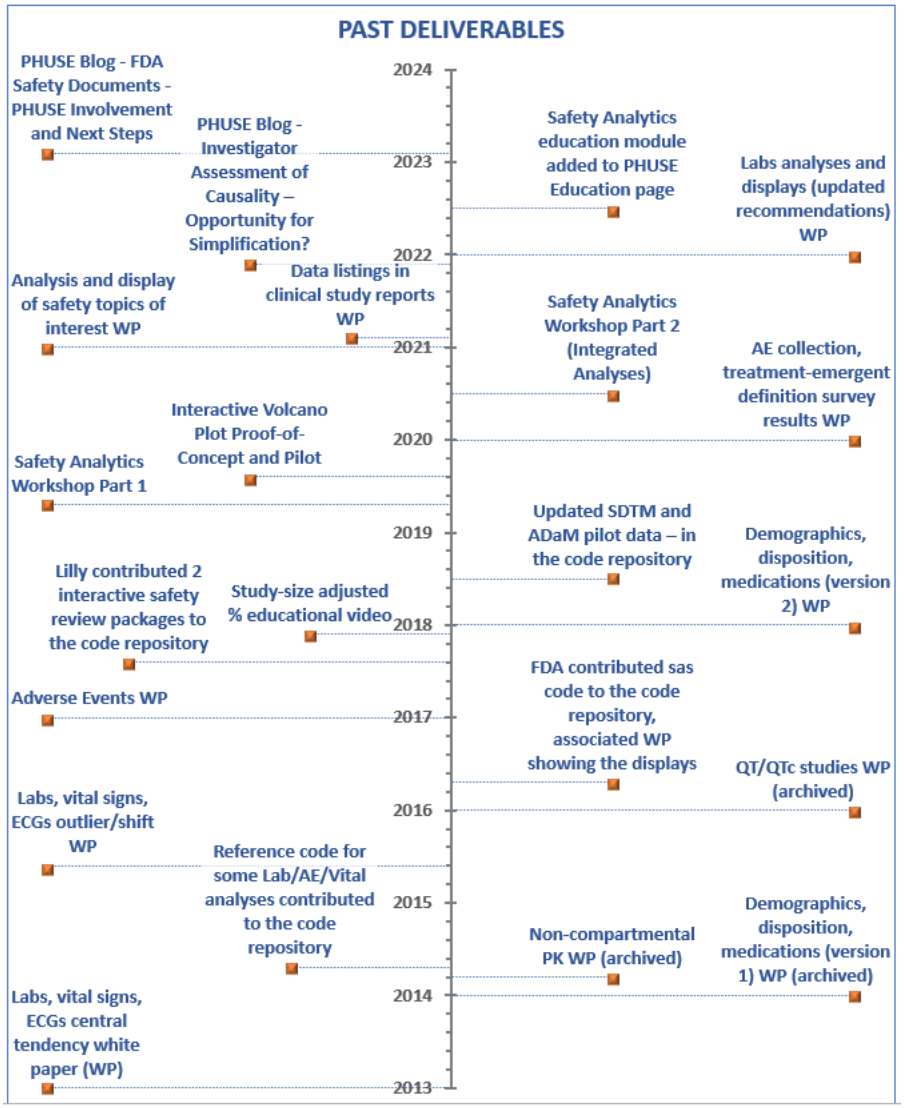
- Adverse Event Collection Recommendations
- Analysis & Displays for Hepatotoxicity
- Analysis & Displays for Laboratory Data
- Listings for Clinical Study Reports
- Treatment Emergent Definition Recommendations
- Adverse Event Groupings in Safety (AEGiS)
- Comments on FDA's Safety Tables and Figures Integrated Guide
- Safety Analytics Education

These teams consist of representatives from both industry and regulatory agencies, and are developing deliverables outlining best practices within their topic areas. This paper provides an update on the project activities and status. We encourage feedback and we are accepting additional volunteers.

BACKGROUND

FDA and PHUSE collaboration on safety analytics topics began in 2012 as a platform for academia, regulators, industry, and technology providers to address computational science needs in support of regulatory review. The Safety Analytics Working Group is supported by PHUSE, the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) with a goal of providing resources that improve preparation and analysis of regulatory data and associated documentation.

Here is a list of the publications released by the Safety Analytics Working Group since its inception:



ADVERSE EVENT COLLECTION AND RECOMMENDATIONS

The Adverse Event Collection and Recommendations project team focuses on developing best practices for collecting data about adverse events (AEs) so that AE data may be combined and reviewed across studies, compounds and even companies without losing important information. One topic they are addressing is the value, or lack of value, of investigator-determined causality, which they presented during the April 2022 PHUSE Webinar Wednesday, as well as in the December 13, 2021 PHUSE Blog. They are currently working on a white paper containing recommendations for adverse event collection instructions, with a focus on Phase 2-4 clinical trials. The project team is led by Aimee Basile and Mary Nilsson.

ANALYSIS & DISPLAYS FOR HEPATOTOXICITY

The Analysis and Displays for Hepatotoxicity project team is developing a white paper with recommendations for analyses and displays associated with hepatotoxicity, focusing on Phase 2-4 clinical trials and integrated submission documents. The team is taking a two-stage approach (Stage 1 and Stage 2) to the effort in developing the white paper. Stage 1 analyses are performed for all drugs. Stage 2 analyses on the other hand are performed depending on the findings in the Stage 1 analyses, along with

the results of pre-clinical and toxicology studies and the results of Phase 1 studies that might not have been predicted by the pre-clinical and toxicology studies. The two-staged approach in essence generalizes to any safety topics of interest where there are suggestions of the need for more in-depth analyses (deep-dive) based on evolving and expanding database and emerging scientific and medical knowledge. Stage 2 analyses might be performed following appropriate medical discernment. Additionally, Stage-2 analyses might require novel designs and planning. The team has completed the first draft of Stage 1 recommendations and is targeting finalization of this draft in Q2 2023. The project team is led by Terry Walsh and Melvin Munsaka.

ANALYSIS & DISPLAYS FOR LABORATORY DATA

The Analysis and Displays for Laboratory Data project team published a white paper with updated recommendations for analyses and displays for laboratory data, with a focus on Phase 2-4 clinical trials and integrated submission documents, in June 2022. This is the first version of the white paper specifically for laboratory analyte measurements. Two previous white papers (PHUSE 2014, PHUSE 2015) included recommendations for laboratory analyte measurements and are precursors to this white paper, but this white paper provides additional information instead of superseding the previous white papers. The project team will be considering additional deliverables, and will be led by Charles Beasley and Chris Smith.

LISTINGS FOR CLINICAL STUDY REPORTS

The Listings for Clinical Study Reports project team published a white paper in December 2021 outlining strategies that companies can implement to enable review of clinical study data without resorting to the traditional pile of “data-dump” listings, and spent 2021 and 2022 communicating their message at various conferences, such as the 2021 CDISC Interchange, 2022 PHUSE US Connect and PharmaSUG 2022. They also published a viewpoint article in the January 2023 issue of *Pharmaceutical Statistics.* The project team is led by Mercy Navarro and Nancy Brucken.

TREATMENT EMERGENT DEFINITION RECOMMENDATIONS

The Treatment Emergent Definition Recommendations project team created a survey to elicit thoughts on how treatment emergence should be defined, and received responses from a variety of disciplines (Biostatistics, Statistical Programming, Clinical, Pharmacovigilance, etc.) at pharmaceutical companies, CROs, and regulatory agencies. The project team is now creating a white paper with recommendations on treatment emergent definitions based on the survey results; it is led by Bill Palo and Mary Nilsson.

ADVERSE EVENT GROUPINGS IN SAFETY (AEGiS)

The new AEGis project team is creating a white paper with recommendations on when to choose an FDA Medical Query versus a MedDRA SMQ versus creating a custom grouping, interpreting groupings in different settings (e.g., AESI vs. signal detection), how groupings can be maintained, and recommendations for developing efficient & standardized processes for implementing use of AE groupings. Additionally, ways to leverage new technologies in this process will be discussed. This project team is well under way, and is led by Mac Gordon and Peg Fletcher, with plans to issue a white paper for review in late 2023.

COMMENTS ON FDA’S SAFETY TABLES AND FIGURES INTEGRATED GUIDE

Another new project team, the group providing comments on the FDA’s draft Safety Tables and Figures Integrated Guide consolidated responses from the PHUSE community and sent them on to the FDA during the public review period in late 2022. The project team also published a PHUSE Blog posting in January 2023, “FDA Safety Documents - PHUSE Involvement and Next Steps”. This effort has been led by Mary Nilsson, Greg Ball and Mac Gordon.

SAFETY ANALYTICS EDUCATION

The Safety Analytics Education project team has developed a repository of fundamental safety references that they have found helpful in their careers. The intended audience is someone new to patient safety analyses in clinical trials and cross-functional colleagues. This project team is led by Bill Palo.

POTENTIAL FUTURE PROJECTS

The Safety Analytics Working Group has identified a number of potential future projects that would be beneficial to the industry as a whole.

Here is a partial list of what has been proposed so far:

Estimands for safety	Safety population definition recommendation
Specifications for interactive safety review tools	Preparing for the FDA Type C meeting on integrated safety plans
Adverse event analyses and displays (version 2)	Notable criteria, narratives
Vital signs analyses and displays (version 2)	Combining studies for integrated analyses
ECG analyses and displays (version 2)	Analysis of genomic and biomarkers
Disposition collection recommendations	Writing statistical results for safety
Improving lab data quality	Analyses and displays of adjudicated data
Defining gender-specific MedDRA preferred terms	Safety in rare disease
Plain language summaries	Analyses for Clin Pharm studies
Safety update recommendations	

Please contact Mary Nilsson or Greg Ball if you are interested in working on or leading any of these projects (contact information is below). In addition, a PHUSE/CDISC ADaM sub-team has been proposed to develop a standard approach for incorporating FDA Medical Query (FMQ) variables into ADaM, as well as the addition of any variables needed to support the FDA's draft Safety Tables and Figures Integrated Guide.

CONCLUSION

As you can see, the Safety Analytics Working Group project teams have accomplished a considerable amount over the past year, but we still have more work to do. Additional volunteers for the current project teams are welcome, and the Working Group also encourages proposals for new projects that fit under the Safety Analytics umbrella.

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