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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 content 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 7 project teams, all working on various aspects of collection and analysis of safety data:

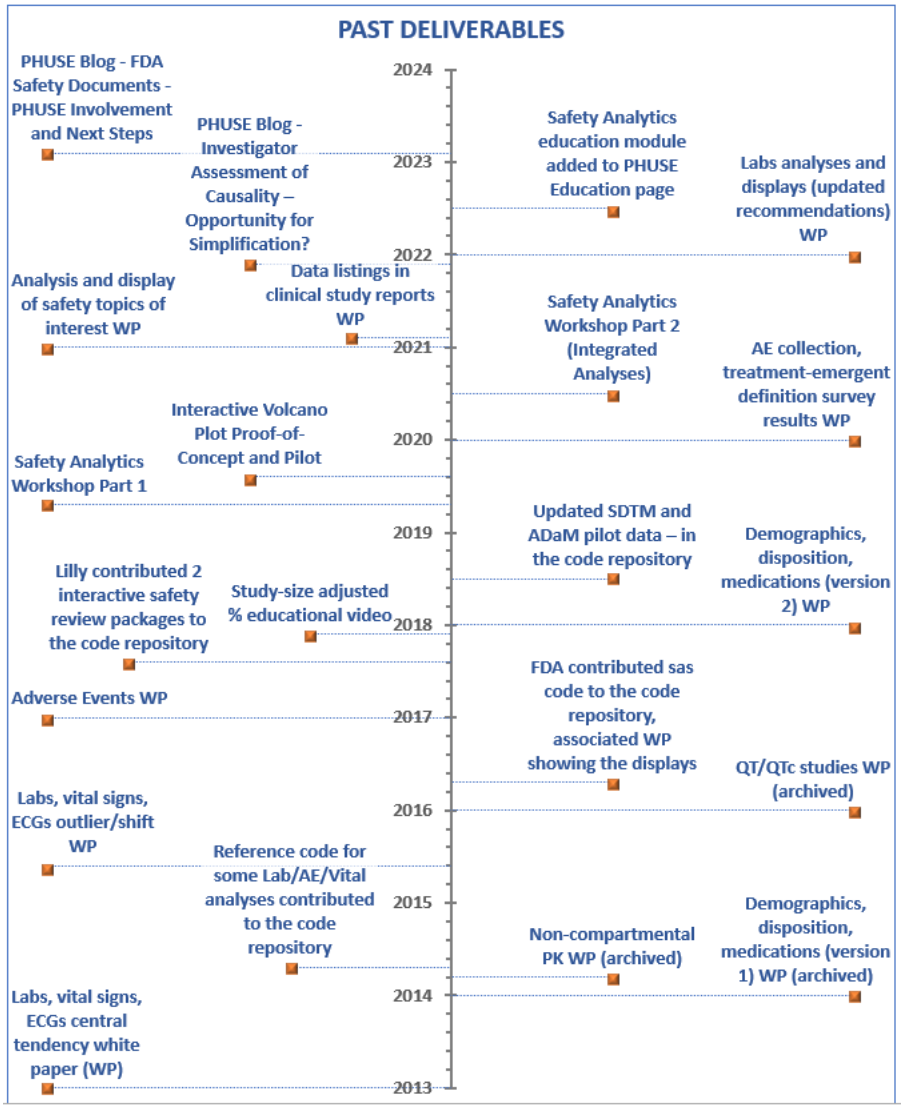
- Adverse Event Collection Recommendations
- Analysis & Displays for Hepatotoxicity
- Analysis & Displays for Laboratory Data
- Treatment Emergent Definition Recommendations
- Adverse Event Groupings in Safety (AEGiS)
- Interactive Displays for Laboratory Data
- Safety Analytics Education

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

The FDA and PHUSE collaboration began in 2012 as a platform for academia, regulators, industry, and technology providers to address computational science needs in support of regulatory review. The PHUSE Working Groups are 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. The Safety Analytics working group is one of eight working groups that are part of this collaboration.

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. The public review period for their draft white paper containing recommendations for adverse event collection instructions with a focus on Phase 2-4 clinical trials ended in February 2024, and they are currently addressing comments. 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 released a draft white paper for review by project team members and Working Group leads. The project team is led by Melvin Munsaka and Terry Walsh.

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. This project team has now closed, and work has shifted to the new project team developing recommendations for interactive displays for laboratory data.

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 has drafted a white paper with recommendations on treatment emergent definitions based on the survey results which will be available soon for public review; it is led by Bill Palo and Mary Nilsson.

ADVERSE EVENT GROUPINGS IN SAFETY (AEGiS)

The 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. 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 mid-2024.

INTERACTIVE DISPLAYS FOR LABORATORY DATA

The Interactive Displays for Laboratory Data team is developing a white paper concerning the use of interactive displays in the assessment of laboratory data during Phase II to III clinical trials. Their goal is to provide platform-agnostic recommendations about the features and options that should be considered for interactive displays of laboratory data. An initial call for volunteers was made during the PHUSE/FDA CSS 2023 conference in September, and the team is currently determining the scope of their efforts and scheduling demonstrations of existing applications. It is led by Charles Beasley and Christopher Smith.

SAFETY ANALYTICS EDUCATION

The Safety Analytics Education project team has developed a library 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. The project team also hosted a series of webinars in 2023 on Interdisciplinary Safety Evaluation for Decision Making, and a March 7, 2024 webinar on “Integrated Safety Analyses in Drug Marketing Applications: Avoiding Common Mistakes”. Additional webinars will be provided this year, including an SBIA webinar on “Statistical Considerations for Premarket Applications”, which is scheduled for May 16. The team is actively recruiting new members. This project team is led by Bill Palo and Christopher Smith.

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:

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

Please contact the PHUSE office at workinggroups@phuse.global if you are interested in working on or leading any of these projects (contact information is below). There are also PHUSE/CDISC ADaM sub-teams developing a standard approach for incorporating FDA Medical Query (FMQ) variables into ADaM, and creating a standard ADaM dataset to support one of the more complex lab tables in 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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