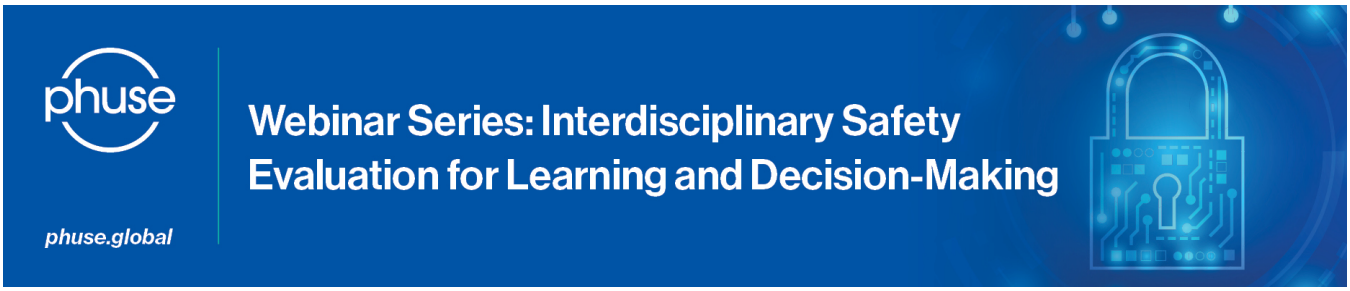
Safety Analytics Webinar Series: Overall Safety Assessment – AE Groupings for Assessment of Safety Topics of Interest



Catch up Here!

This Webinar took place 14 September 2023. Catch up by viewing the recording or reading the slides.

Webinar Series: Interdisciplinary Safety Evaluation for Learning and Decisionmaking

Sponsors and the FDA have been working together to improve approaches for assessing accumulating safety data, with progressively more cross-functional teams for planning and coordinating program-level safety assessments and more guidance on aggregate safety assessments.

To meet the spirit of the IND safety reporting final rule, sponsors have developed processes and procedures to evaluate, assess and act on accumulating safety information during development on an ongoing basis.

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Webinar 3: Overall Safety Assessment – AE Groupings for Assessment of Safety Topics of Interest

Summary:

The topic of this third webinar in the series was Adverse Event Groupings for Assessment of Safety Topics of Interest. Scott Proestel (Acting Associate Director of Biomedical Informatics and Regulatory Review Science at the FDA) provided an overview of the FDA Medical Queries (FMQs) project, which was developed by FDA staff to improve clinical trial safety signal detection by grouping similar adverse events based on a common set of ground rules.

This was followed by presentations by Mac Gordon and Peg Fletcher, the Co-Leads of the PHUSE Adverse Event Groupings in Safety (AEGiS) Project team, part of the Safety Analytics Working Group. The AEGiS Project team is tasked with discussing the importance of improving safety assessment utilising AE groupings (e.g. FMQs, SMQs, custom, semi-custom) and providing recommendations for best practices when implementing the process. A draft version of the team's white paper is expected in 4Q23 for community review.

During the webinar, the audience was asked about the challenges they have faced with grouping adverse events. The most common responses related to issues with reaching agreement on custom groupings and the effort required with each upversioning of MedDRA:

Challenges	Number of Responses
Difficulty reaching agreement on custom groupings	6
Effort of upversioning MedDRA	5
Insufficient knowledge or experience with groupings	2
Validation, documentation and maintenance of groupings	1
Regulatory agencies need more experience with groupings	1
Need to reach agreement on which groupings to use	1

The audience also asked the following questions during the webinar:

Question	Answer
How are FMQs different from or similar to SMQs?	While FMQs and SMQs both consist of groupings of AEs intended for safety signal detection, there are a number of differences between the strategies. An underlying principle for FMQs is to capture every instance of a given medical concept, regardless of the presumed likelihood that the event could be caused by a drug. However, SMQs sometimes exclude AE terms based on the etiology contained within the terms. In addition, SMQs were created by multiple groups that were able to create their own rules regarding how to group terms, while FMQs were created based on a common set of Ground Rules. An additional difference is that SMQs are designed to be used with data using a specific version of MedDRA, while the FMQs are cumulative and the current FMQ version is intended to be able to be used on all prior versions of MedDRA from version 7.0 on. FMQs also include terms from other terminologies and terms that have previously been submitted to the FDA by companies.
Will there be online browser capability to run data in FMQs similar to MedDRA SMQ analysis in their web browser?	Although an FMQ browser has been developed for internal FDA use, it has not yet been decided whether this browser will be distributed publicly versus simply providing new spreadsheets for each FMQ version update.
Can FMQs contain PTs from different SOCs?	Yes, FMQs can contain PTs from different SOCs, as well as former PTs, terms that were never PTs, and even misspelled terms that have previously been submitted to the FDA.
FMQs and FMQ tables have been discussed in the context of labelling and aggregate safety analysis review /investigations, but would you also consider the FMQ table to be appropriate in other documents such as the CSR, the IB and/or aggregate reports (e.g. DSUR, PSUR, PBRER)?	While it is up to sponsors and other stakeholders to decide how and whether to incorporate FMQs into their safety evaluation practices, we believe that such groupings may be appropriate for any documents that are intended to evaluate the safety of medical products.
Can we expect FMQ versions to be released in step with MedDRA versions?	At a minimum, a new FMQ version will be released following each major MedDRA version update in March. Our goal is to be able to produce this update typically within three months of each major MedDRA version release. It is possible that additional minor FMQ updates may be released as needed.
For categorising FMQs, is it best to use verbatim AETERM or the standardised MedDRA terms (AEDECOD)?	Our recommendation would be to use coded terms whenever possible. Verbatims could be used if needed; however, they would need to be mapped to FMQ terms, as appropriate.
Could you please provide the details of the working group on ADaM datasets?	There's a CDISC ADaM sub-team that has been created to facilitate the implementation of tables and figures using FMQs. The sub-team plans to communicate a recommendation for either a new ADaM dataset or new ADaM variables soon.
Will FMQs eventually replace SMQs?	We don't know, although we agree that it would be preferable to eventually have a single common grouping strategy that is used internationally.
Will FMQ spreadsheets have version control?	Each FMQ update will have a version number and a separate listing of the changes that have been made.
Is there any plan to align with other regulatory agencies to prevent sponsors having to create different definitions of events for different regulatory agencies if other countries don't agree with FMQ definitions?	While this idea has been discussed and we are in favour of such an effort, there is no current plan that we are aware of for international alignment on AE groupings.

Presenter	Bio

Greg Ball, *ASAP Process Consulting*

Greg Ball served in the Navy and taught High School maths and physics before earning his master's in statistics from Purdue and his PhD in Biostatistics from the University of Texas. His research on blinded safety monitoring procedures is being developed in collaboration with statistical and clinical scientists at several pharmaceutical companies (including AbbVie and Merck). With Mary Nilsson, Greg co-leads the PHUSE Safety Analytics Working Group. Greg established, with Bill Wang, the ASA Biopharm Safety Monitoring working group and has been pioneering the joint DIA-ASA Interdisciplinary Safety Evaluation (DAISE) scientific working group, to advocate for aggregate safety assessments and cross-disciplinary scientific engagement.

Mac Gordon, *Janssen Research & Development*

Mac Gordon has a master's in statistics and graduate certificates in public health, pharmacovigilance and pharmacoepidemiology and has been with Janssen for 15 years and in industry for 20 years. He has been involved with lupus research since joining the organisation, with focus areas in late-development immunology and clinical trial safety. Mac has been heavily involved in pharmacovigilance, signal detection and safety data visualisation for most of his career, including membership in several multi-disciplinary industry/regulatory working groups. Prior to joining Janssen, Mac developed a safety surveillance and signal detection team at Cephalon. He is currently the Clinical Team Statistical Lead across 11 indications and several therapeutic areas. Outside of clinical research, Mac is involved in many internal teams focused on safety statistics and process development initiatives and continues to represent the organisation in external safety working groups.

Peg Fletcher, *MedAssessment*

Peg Fletcher received her MD and PhD (in biochemistry) from the University of Chicago and boards in oncology and clinical pharmacology. A safety executive with over 25 years' experience in development and pharmacovigilance in both large and small pharma, Peg has led teams defining and implementing AE groupings in safety reviews, submissions and signal detection. For the past 12 years she has led MedAssessment, a small pharmacovigilance CRO focused on helping small and medium pharma and biotech evaluate safety data and balance corporate obligations with patient safety, particularly in early development.

Scott Proestel, *FDA*

Scott Proestel, MD, is Acting Associate Director of the Biomedical Informatics and Regulatory Review Science Team at the US Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER). He completed his internal medicine training at Johns Hopkins Hospital and obtained his medical degree from Columbia University Vagelos College of Physicians and Surgeons. Scott has previously worked as an FDA medical officer and team leader conducting and supervising pre-market reviews of new drug applications, overseen HIV clinical trial conduct as an Office Director at the US National Institutes of Health, and worked as an FDA Division Director responsible for post-market safety surveillance at CDER as well as the FDA's Center for Biologics Evaluation and Research. Scott's most recent informatics research assessed the use of artificial intelligence to evaluate spontaneous safety reports submitted to the FDA Adverse Event Reporting System and Vaccine Adverse Event Reporting System.

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