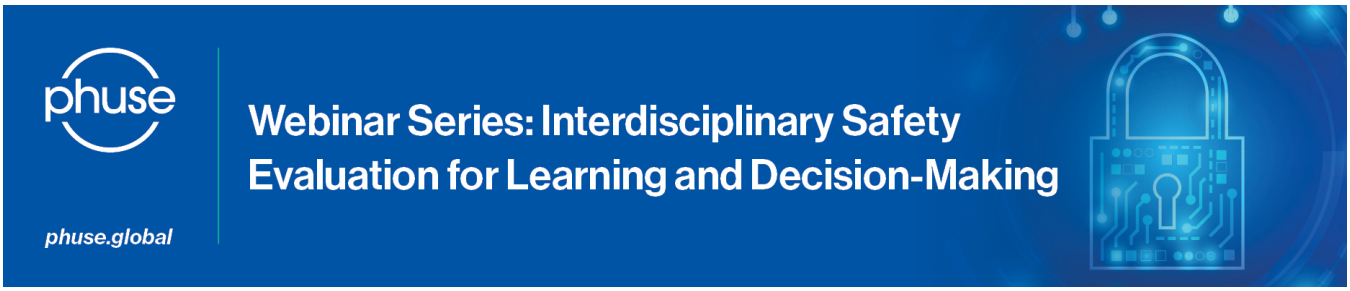
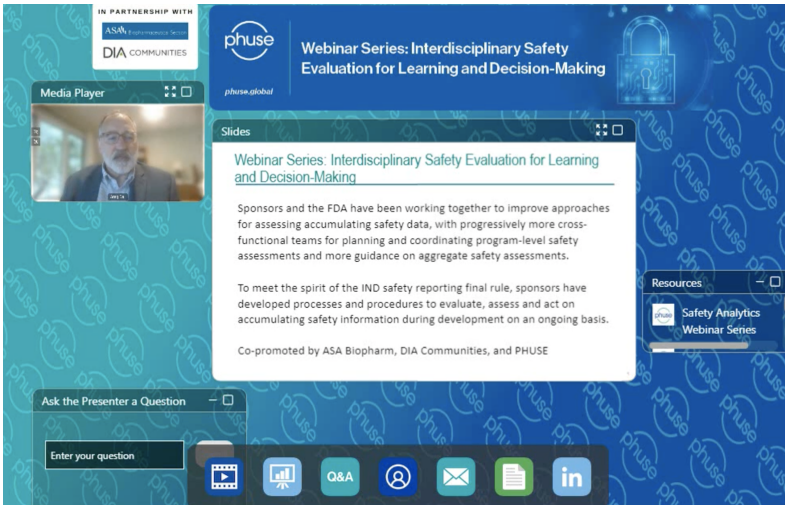
Scientific Evaluation of Safety Data and Aggregate Safety Assessment Planning for IND Safety Reporting



Catch up here!

This Webinar took place 15 June 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.

Co-promoted by ASA Biopharm, DIA Communities, and PHUSE

Webinar 1: Scientific Evaluation of Safety Data and Aggregate Safety Assessment Planning for IND Safety Reporting

Summary:

Sponsors and the FDA have been working together to improve approaches to assessing accumulating safety data,with greater emphasis on using cross-functional teams for planning and coordinating programme-level safety assessments and more guidance on aggregate safety assessments. Ja cqueline Corrigan-Curay (Principal Deputy Center Director for the FDA's Center for Drug Evaluation and Research) delivered an insightful presentation on the development and nuances of the IND Safety Reporting Final Rule, including how the FDA have addressed sponsor feedback in the most recent guidance. Sponsors have agreed with the spirit of the final rule from the outset; however, operationalising the guidance has been challenging.

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. Greg Ball (Safety Data Scientist at ASAP Process) explained how an aggregate safety assessment planning process is needed to scientifically evaluate the accumulating programme-level safety information. A proactive and systematic process supports ongoing characterisation of the product safety profile to prepare for regulatory filing activities and for responses to regulatory queries, by consistently and authoritatively communicating the safety story throughout clinical development.

Some multidisciplinary teams have been implementing procedures for review of aggregate blinded clinical trial data, thereby minimising the need to intentionally unblind data in ongoing studies. Barbara Hendrickson (former VP of Pharmacovigilance and Patient Safety at AbbVie) and Brian Waterhouse (Clinical Safety Statistician at Merck) provided a very motivating example of how an aggregate safety assessment planning (ASAP) process could leverage the scientific expertise and medical judgement of multidisciplinary safety management teams. They also demonstrated how the 'trigger method' could be used to improve the overall quality of safety reporting and to comply with requirements for IND safety reports based on data in the aggregate.

Polling questions at the end of the webinar resulted in some illuminating responses from the audience:

Question	Number of Responses
44% had applied an aggregate safety assessment planning (ASAP) process	48
55% had applied a safety surveillance plan (SSP)	42
62% had considered how to operationalise use of the trigger method	37
33% had used the trigger method	30
43% had used a DMC to help with expedited IND safety reporting	28
46% had used some other entity to help with expedited IND safety reporting	26

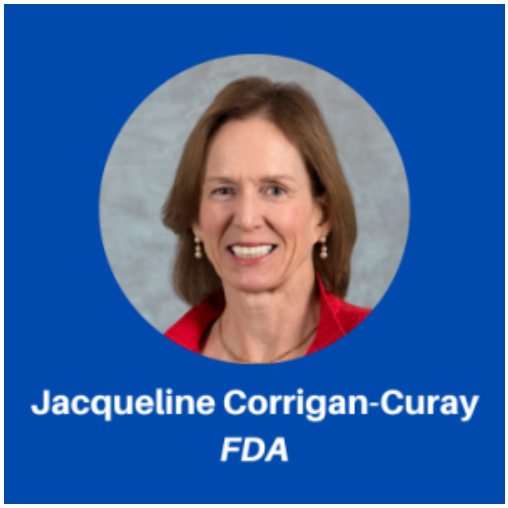
The audience also asked the following questions during the webinar:

Questions	Answers
Will we implement the safety information (shared today) differently for a combination therapy?	The safety strategy (safety topics of interest and pooling structure) and ongoing aggregate safety evaluations need to be customised for each program, including for combination therapies; however, reporting responsibilities apply equally to all programs (depending on size and number of events).
What are your thoughts (or is there guidance) on blinding open-label ph 3 studies (oncology)?	Many sponsors in this situation keep the clinical database blinded to prevent any analyses performed before the end of the study from compromising the objectivity of subsequent data collections – primarily for efficacy monitoring. The same is not necessarily true for safety monitoring, assuming the safety endpoint is not also an efficacy endpoint (such as death) and study team members are appropriately firewalled from aggregate results. However, if safety data is kept in the blind, then the same processes and procedures for ongoing blinded studies can be used (for example, applying a safety surveillance plan with the 'trigger method' and/or an entity to help with expedited IND safety reporting).
Can the head of safety, who chairs the routine safety management team, be a part of the SAC as well?	The entity (which can be called an SAC) is a firewalled internal or external individual or group of people who would oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all the trials in the development programme as well as other available important safety information. An important consideration here is the firewall between those involved in the conduct of the trials. The head of safety would not be able to be a part of the SAC if they chaired the SMT and members of the SMT were involved in the conduct of the studies.
When does the FDA anticipate finalising the 2021 FDA draft IND guidance?	The FDA are working to review the comments and finalise the guidance as quickly as possible.
If additional external clinical trial or claims data becomes available during your ongoing clinical trial, would you consider updating the threshold for background events?	Safety assessments are very different from efficacy analyses.
Does the FDA have metadata to pull PBO rates across assets in a particular indication that sponsors can leverage for expected rates and anticipated events?	Data submitted to the FDA is considered commercially confidential, even placebo arms.
Is there a working group to define the reference rates for common events (such as MI, stroke)?	Not that we are aware of; however, that would be a great idea, especially with the newly defined FDA Medical Queries.
Is unblinding requested in the EU?	We would defer such questions to the EMA. However, for aggregate safety reporting, FDA guidance says you can submit a summary of the event without all the individual unblinded events.
Anticipated vs expected – further analysis!	Anticipated events are events that may occur in the population regardless of administration of the drug, while expected events are adverse drug events that are listed in the investigator brochure.

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.



Jacqueline Corrigan-Curay, *FDA*

Jacqueline Corrigan-Curay, J.D., M.D., is the Principal Deputy Center Director in the FDA's Center for Drug Evaluation and Research (CDER), where she provides executive leadership on strategic initiatives that advance CDER's mission to deliver safe, effective and high-quality medications to the American public. Prior to taking on this role, Dr. Corrigan-Curay was the director of CDER's Office of Medical Policy leading the development, coordination and implementation of medical policy programmes and strategic initiatives, including on real-world evidence, use of technology in drug development and prescription drug promotion.

Before joining the FDA, she served as senior medical officer with the Immediate Office of the Director, National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH). She also served as Director of the Office of Biotechnology Activities (OBA), Office of Science Policy at NIH.

Dr. Corrigan-Curay earned her law degree from Harvard Law School, her medical degree from University of Maryland School of Medicine, and a bachelor's degree in history of science from Harvard/Radcliffe College in Cambridge, MA.

Dr Barbara Hendrickson, *University of Chicago*

Dr Barbara Hendrickson is on faculty at the University of Chicago and a former Vice President of Pharmacovigilance and Patient Safety at AbbVie. She is a physician with subspecialty training in paediatrics and infectious diseases and has 19 years of pharmaceutical industry experience. In addition to involvement in multiple new product and supplementary indication submissions, she has led several company safety initiatives. One initiative was a pilot project for ongoing blinded clinical trials, which implemented a process using pre-designated assessment entities to support IND safety reporting decisions based on aggregate safety data. In addition, Dr Hendrickson co-leads the DIA-ASA Aggregate Safety Assessment Planning (ASAP) Working Group, which has published suggested best practices for the ASAP process.

Brian Waterhouse, *Merck*

Brian Waterhouse is a senior principal scientist in clinical safety statistics at Merck Research Laboratories. He has more than 20 years of pharmaceutical industry experience analysing clinical trial data across many different therapeutic areas including cardiology, metabolism and endocrinology, dermatology and HIV. His research interests include safety biostatistics and using interactive graphics as investigative and communication tools. He is a co-author of the Bayesian detection of risk using inference on blinded safety (BDRIBS) methodology and the developer of the BDRIBS Shiny app (S afety Signal Exploration using BDRIBS version 2 (shinyapps.io)). Brian is the co-lead of the Benefit Risk Assessment Tool Suite (BRATS) task force within the interdisciplinary work stream of the ASA BIOP Safety Scientific Working Group.

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