**Paper ET06**

# Enhancing the (ASAP) Aggregate Safety Assessment Planning Framework with an Interactive R Markdown Application: Seeing is believing!

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## ABSTRACT

When developing a compound for multiple diseases indications across various therapeutic areas, planning for ongoing integrated safety review and aggregate analyses can be challenging. Maintaining uniformity across studies for definitions and analyses is imperative. Unblinded safety review for ongoing studies are performed by compound level Data Monitoring Committee, and post study completion, the aggregate safety analyses are carried out using a comprehensive Integrated Safety Assessment Plan. Enhancing the ongoing aggregate safety review during clinical development still pose significant challenges. Since the introduction of ASAP[1], organizations have been attempting to implement the process into their standard safety review and thereby develop tools to support the ongoing safety data review. Here, we present an interactive R-Markdown application, developed to facilitate aggregate review in near 'real-time', supporting the new draft regulatory guidance on aggregate safety review during clinical development. We will discuss the importance of coordination across disease indications to support these processes, need for multi-disciplinary teamwork, consistency and standards to ensure accurate and usable compound level safety database.

## INTRODUCTION

In line with the advice from the Safety Planning and Evaluation Reporting Team (SPERT), which was formed by the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2009, the Program Safety Analysis Plan (PSAP) was introduced to proactively organize integrated analyses of product safety data. The PSAP was a crucial initial step towards methodical planning for comprehensive safety evaluations. Building upon the PSAP and considering the changing regulatory environment, the Drug Information Association–American Statistical Association (DIA–ASA) Interdisciplinary Safety Evaluation scientific working group proposed the Aggregate Safety Assessment Plan (ASAP) process. The ASAP is designed to adapt throughout the entire life cycle of a product, encouraging collaborative and systematic planning for safety, along with continuous monitoring and evaluation of the developing safety profile. The key goals of ASAP are to achieve consensus on relevant safety topics, identify gaps in safety knowledge, organize aggregate safety evaluations, and prepare for effective communication of safety information. It aims to customize the analyses for specific drug development programs while maintaining standardized approaches across various studies in those programs.

Throughout the different stages of a compound's development, especially when it is aimed at multiple disease indications across various therapeutic areas or within larger programs with fewer indications, planning for continuous integrated safety reviews and aggregate analyses can be challenging. It is crucial to ensure consistency across studies in terms of definitions and analytical approaches. Consistency in unblinded safety reviews can be ensured by establishment of a compound-level Data Monitoring Committee, while post-study consistency can be maintained through the use of Integrated Safety Analysis Plan. However, it is highly imperative to shift focus on the ongoing safety review during clinical development to fully characterize the evolving benefit-risk profile of the compound. Since the introduction of ASAP, organizations have been attempting to implement the process in their standard safety review process and develop tools to support the safety data review. This paper discusses the key objectives of the ASAP and presents an R Markdown application designed to facilitate aggregate safety review in 'real time' as outlines in the ASAP in an interactive process. It aligns with the new draft regulatory guidance on aggregate safety reviews during clinical development. The paper also emphasizes the necessity for interdisciplinary collaboration, consistency, and standards to create an accurate and functional compound-level safety database and analysis methods, integral to the ASAP implementation process.

## AGGREGATE SAFETY ANALYSIS PLAN (ASAP)

The ASAP is an End-to-End (E2E) process that enables teams to establish and access a product's safety profile with greater efficiency and enhance the identification of unanticipated or rare safety issues by leveraging the aggregate safety data accumulated during the course of clinical development. The ASAP process enables reimagining the safety assessment process in a continuous manner. It also involves a shift from statistical testing and confirming to learning and medical decision making within a quantitative framework (see figure below).

1 Aggregate Safety Analysis Plan

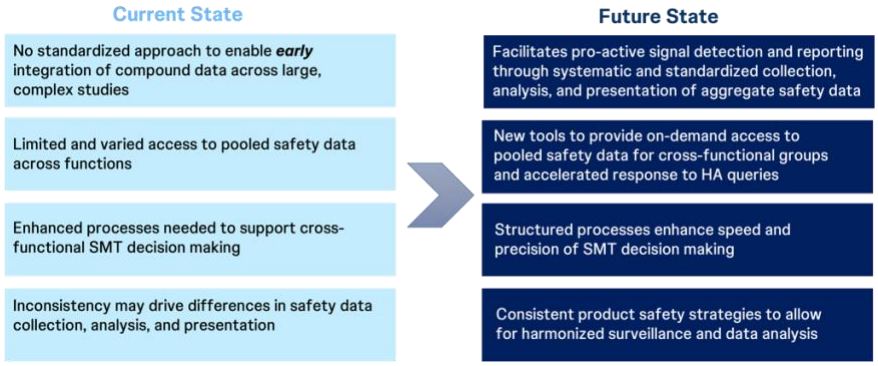



*Figure 1 ASAP Framework*

The ASAP process is designed on a modular framework and includes the following components:

a) ASAP process overview and governance model
b) Safety topic of interest
c) Consistent approach to data collection (pooling strategies) across the program
d) Data analysis approaches
e) Analysis of key gaps and future data collection
f) Ongoing aggregate safety evaluation
g) Communication of safety information

The implementation of the ASAP process involves the following stages:

a) Establishing a working group of key players (clinical, safety, programming, statistics, data management, and project management).
b) Perform comprehensive evaluation of the available safety information such as – target product profile, risk management plan, benefit risk assessment, or any other relevant safety related regulatory guidance or product specific feedback.
c) Develop ASAP governance model
d) Alignment on safety topics of interest and pooling strategies for studies included in the aggregate analyses. The pooling algorithms may change over time.
e) Analysis of key safety topics of interest. Identify/develop an interactive tool to facilitate the review of the aggregate safety analyses/outputs.
f) Analysis of key gaps and future data collection
g) Ongoing aggregate safety evaluation using quantitative frameworks and medical judgment
h) Communication of safety findings using safety story board

**CHALLENGES AND OPPORTUNITIES**

Aggregate safety reporting involves enormous amounts of data and keeps growing every day. Large volume of static safety analysis outputs become onerous. Typical safety output related to the treatment-emergent adverse events (TEAE) is difficult to 'weed' through given the multiple versions of these outputs for various subsets (e.g. Serious TEAEs, Related TEAEs, TEAEs of Special Interest etc.). Resourcing needs increase over the lifecycle due to the amount of data and outputs that need to be reviewed by the Sponsor's Safety Management Team. This triggers us to rethink how we can gain efficiency, standardize and improve the current process.

An interactive data analysis and visualization tool can help with the aggregate safety review and capture safety signals embedded in large volume of data presented via traditional static outputs. It can help drive the safety findings communication in an orderly manner by adopting a story telling approach through the use of explanatory visuals and interactive data displays. The ASAP puts more emphasis on interdisciplinary safety planning and collaboration than a traditional statistical analysis plan. Having a tool to assist with and drive the data review can greatly improve the efficiency of the process. The alignment between the key stakeholders based on data help form a "safety storyboard", which is periodically updated to reflect expanding knowledge of the product's safety profile. The safety storyboard facilitates consistency in the safety messaging across internal and external documents.

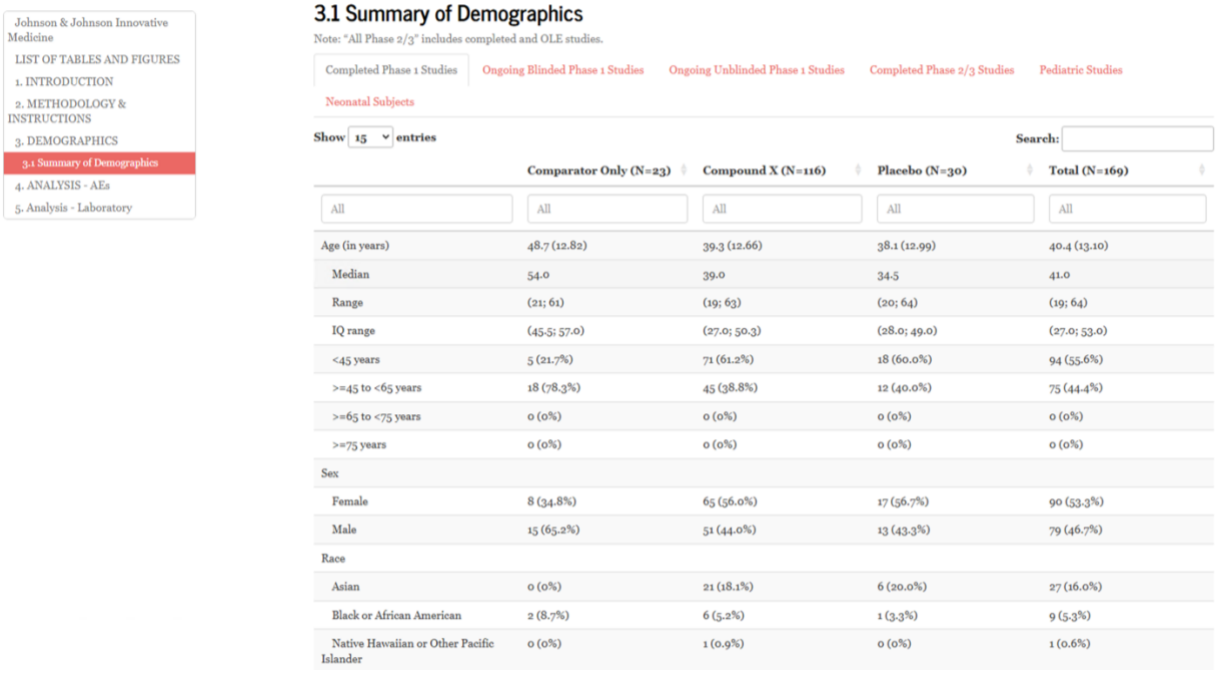
In the following section we will discuss the Aggregate Safety Reporting (ASR) tool, developed using R-Markdown and based on a modular design framework. Each module focuses on particular type of analyses including data wrangling and creation of analysis datasets. It is built using the open-source platform, therefore can be easily adopted and could

be build upon by the cross-pharma working groups and other research communities focusing on the aggregate safety analysis in clinical trials.

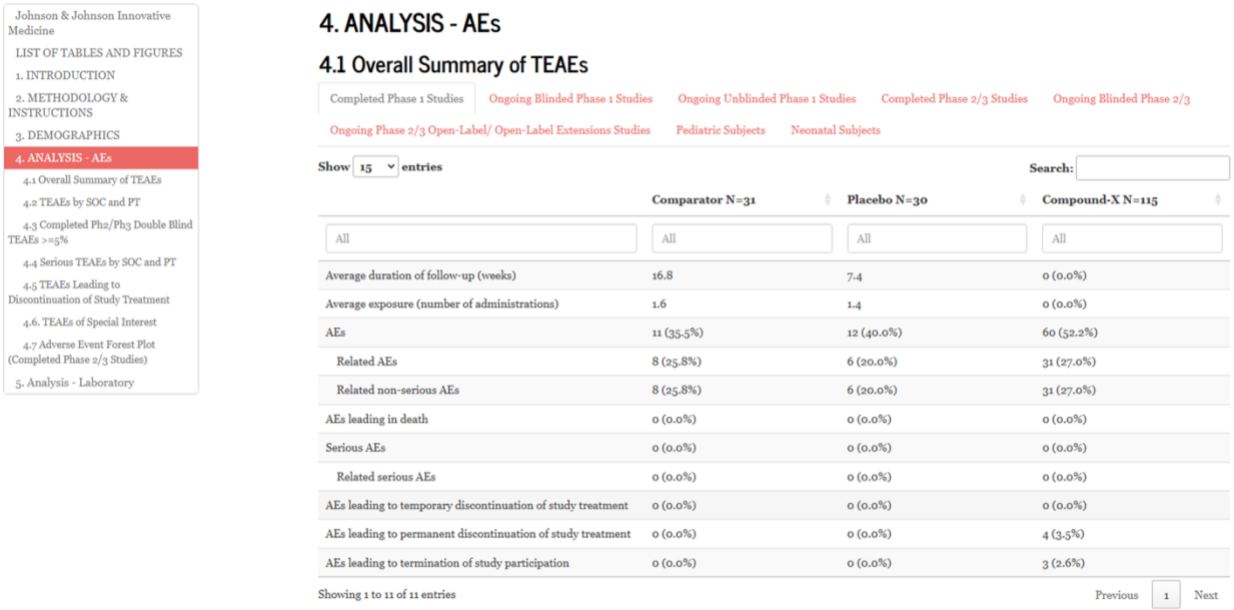
## AGGREGATE SAFETY REPORTING (ASR) TOOL

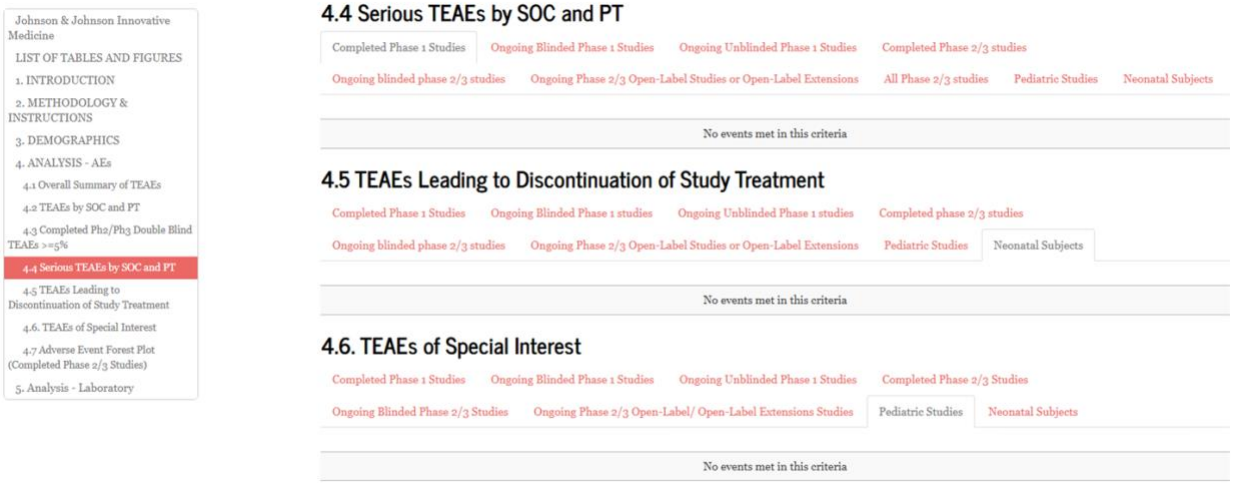
The ASR tool was developed using R and the user interface was developed using R-Markdown. The R-Markdown was knitted to generate an html output which served as the user interface that supports interactivity. The choice of R-Markdown versus R-Shiny app was carefully evaluated and was decided based on the requirements of the fit-for-purpose analyses modules. The analyses were performed using the pooled ADaM datasets generated as per the pooling algorithm specified in the ASAP document.

First module focuses on the overview of the compound development program, outlining the studies included in the ASAP, followed by summary of demographics for individual studies as well as indications. Module one also includes summary of exposure for the open-label and completed studies. Blinded ongoing studies are not included in the analyses.



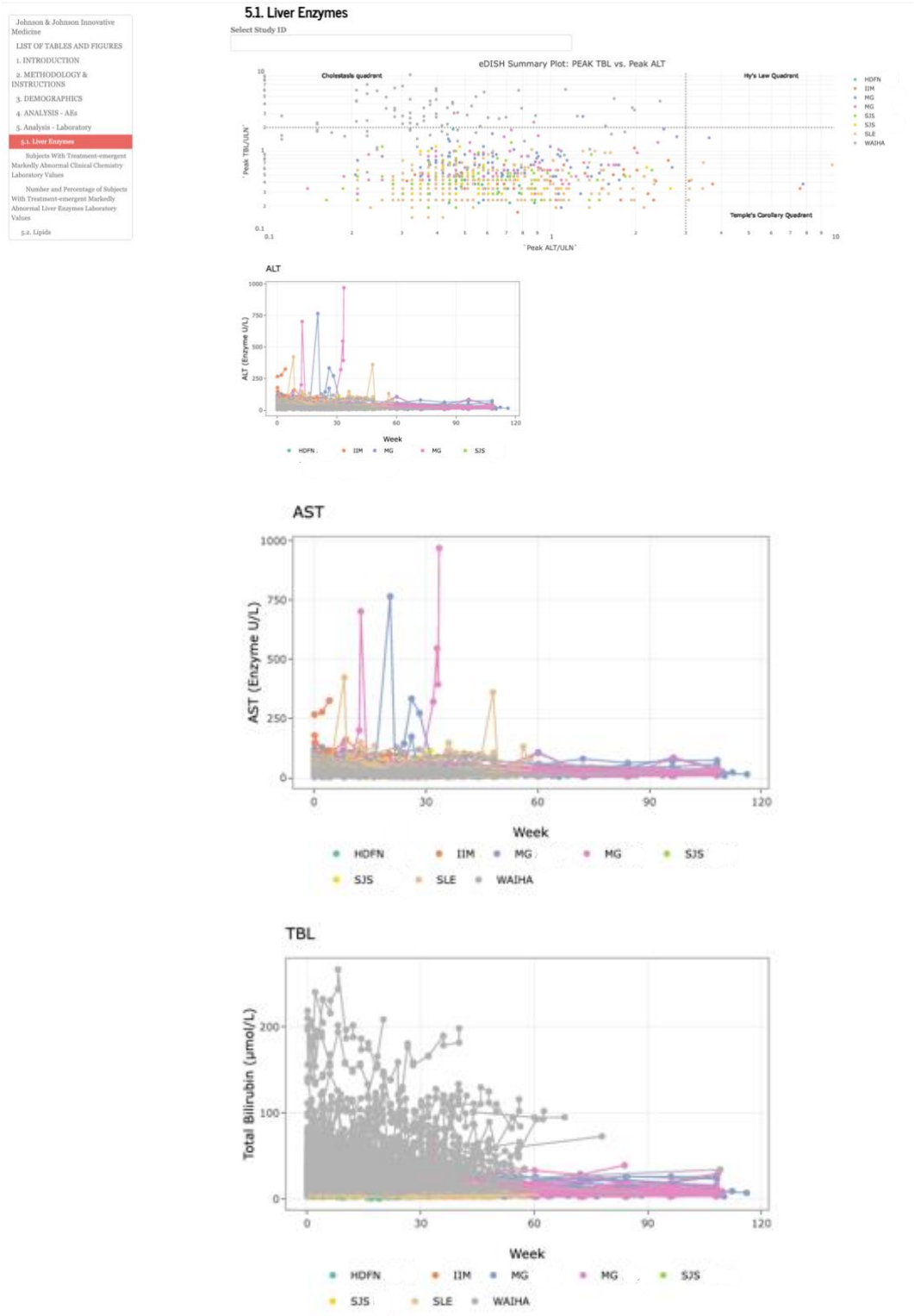

Second module focuses on the analyses of treatment-emergent adverse events (TEAEs), including the summary of all TEAEs, serious TEAEs, drug related TEAEs, and adverse events that led to treatment discontinuation or had fatal outcome.



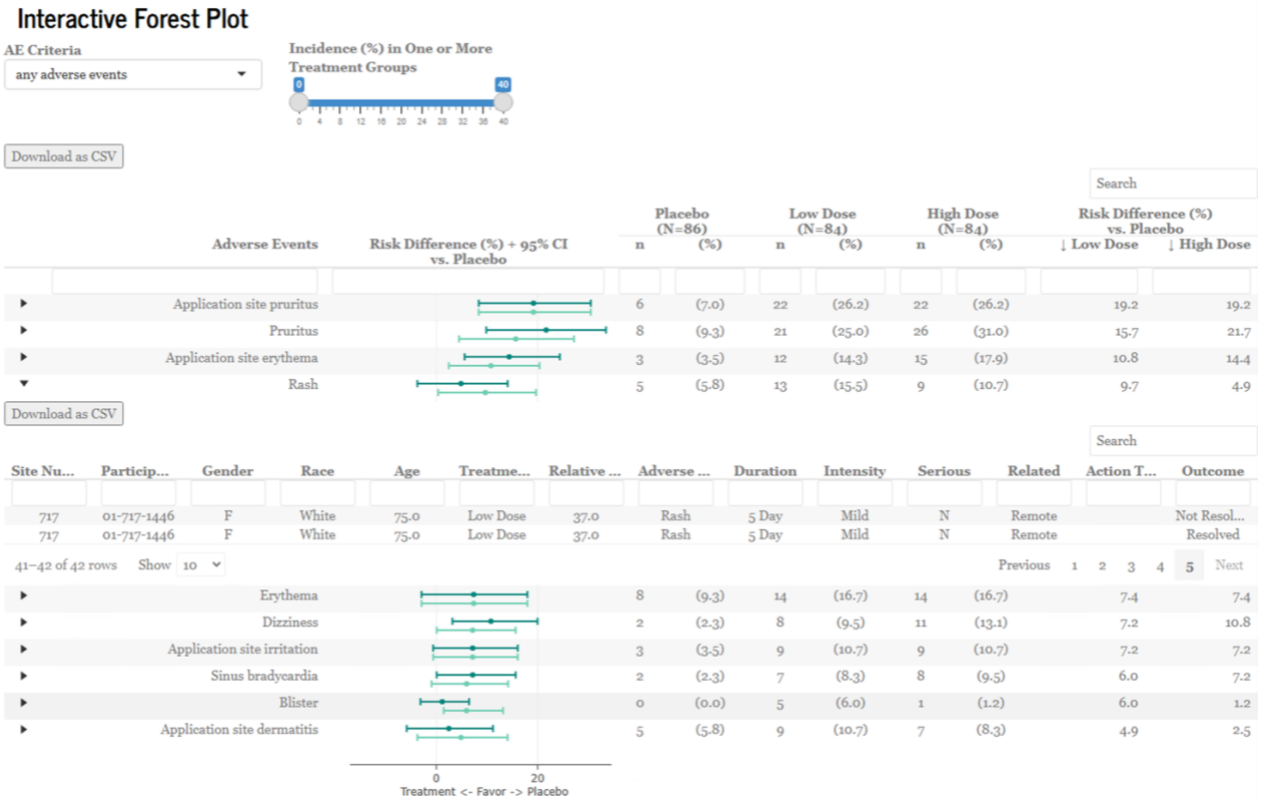

These interactive tables were developed using the DT package in R that allow for search, sort, and filter actions. These features greatly help while reviewing the aggregate safety data as opposed to viewing static outputs spanning across multiple pages. Moreover, the visual cue for incidence rate (blue bar in % column) helps to easily identify the magnitude of incidence rates and the difference of incidence rates across various groups. The tabbed layout helps to organize the outputs based on the phase of studies and indications. This organization and seamless flow of outputs across the same html page helps to tell the story more effectively in a sequential manner. With traditional static outputs, it was challenging to identify signals while flipping through pages after pages. It was difficult to connect the dots.

Third module focuses on laboratory abnormalities and toxicities. In this module we included an interactive eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plot for identification of potential Hy's law cases.




This interactive eDISH plot allows to select a group of subjects and observe the trend of their individual liver enzymes over time. These plots are linked using the R crosstalk package.

Lastly, we have also built upon the interactive forest plot module developed by a PHUSE working group a year ago. The interactive forest plot is very helpful for visualizing the risk difference and the associated 95% confidence interval across two or more treatment groups. The fact that it allows to drill down to subject level data for each adverse event is very helpful for global medical safety reviewers. In addition, it also allows to filter by incidence rate and type of adverse events using the slider and drop-down list respectively.




This is not the exhaustive list of outputs and analysis modules included in the ASR tool rather was presented to depict the user interface and the interactive features which aid in data review process and serves as a story board for effectively communicating the safety messages.

## CONCLUSION

The ASR tool affords the clinical and medical safety reviewers' access to the ongoing data across a program (both aggregate and individual study level) during the development process instead of waiting for the completion of a study. A close to 'real time' ability to monitor safety across a compound affords more effective and wholistic safety review, development of a product safety profile and enhances ability to efficiently respond to both internal and external queries.

However, there are potential barriers to implementation and adoption of the ASR Tool including but not limited to, integration with existing pharmacovigilance systems. The computational scalability for large datasets needs to be thoroughly evaluated. Lastly, training requirements for clinical safety teams unfamiliar with R-based tools needs to be considered. With advent of Gen AI, advanced machine learning and data structures, and increased computational processing power help rethink the potential barriers and plan for an end-to-end integrated process. Effective change management is warranted.

## GLOSSARY

ASAP: Aggregate Safety Analysis Plan

ASR: Aggregate Safety Reporting

## REFERENCES

Hendrickson, B.A., Wang, W., Ball, G. et al. Aggregate Safety Assessment Planning for the Drug Development Lifecycle. Ther Innov Regul Sci 55, 717–732 (2021). https://doi.org/10.1007/s43441-021-00271-2

Hendrickson, B.A., Agarwal, A., Bennett, D. et al. Value and Implementation of the Aggregate Safety Assessment Plan. Pharm Med 37, 171–181 (2023). https://doi.org/10.1007/s40290-023-00470-2

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