PharmaSUG 2024 - Paper DV- 283

Exploring the Application of FDA Medical Query (FMQ) in Visualizing Adverse Event Data

Tongda Che, Merck & Co., Inc., Rahway, NJ, USA;
Danfeng Fu, MSD China

ABSTRACT

The analysis and visualization of adverse event (AE) data is critical for evaluating drug safety in clinical trials. This paper explores the application of the FDA Medical Query (FMQ) using R programming language to conduct safety analyses and create meaningful visualizations of AE data.

FMQ provides a standardized approach to identify adverse events of interest. By leveraging FMQ with R, automated safety data workflows can be created to accelerate drug safety reviews.

In this paper, adverse event data coded with the MedDRA dictionary was mapped to FMQ list.

The resulting analysis datasets are visually represented interactively using R Shiny to display various R graphs, such as Lollipop plots, pie charts, and circular bar charts. These visualizations offer insights into AE incidence, severity, timing, durations, and relationships.

INTRODUCTION

IMPORTANCE OF MONITORING ADVERSE EVENTS

Adverse Events (AE) monitoring is an important component of clinical trials. Generally investigators are required to monitor AE throughout the entire phase of the clinical trial in order to identify and mitigate potential risks or adverse effects associated with the investigational product or intervention being studied. Furthermore, monitoring AE can help identify patterns or trends in the occurrence of specific adverse events, enabling informed decision-making and appropriate interventions.

An AE is defined as ‘any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment’.

AE monitoring usually includes monitoring AE’s incidence, time, causality, duration, relationship to the drug, severity, special AE that is of clinical interest.

WHY FDA MEDICAL QUERIES (FMQS)?

One of the basic questions when designing the AE monitoring system is AE coding/grouping. Currently, the most commonly used system for AE coding is MedDRA.

The Medical Dictionary for Regulatory Activities (MedDRA) is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities in the pharmaceutical industry. The hierarchical structure of MedDRA consists of 5 levels, arranged from general to specific: System Organ Classes (SOCs), High Level Group Terms (HLGTs), High Level Terms (HLTs), Preferred Terms (PTs), and Lowest Level Terms (LLTs).

Standardized MedDRA Queries (SMQs) (https://www.meddra.org/standardised-meddra-queries) are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. It includes a large list of Preferred Terms(PTs)which may span across different SOCs which are used for assessing a safety topic of interest.

In August 2022, FDA issued a draft guidance on Standard Safety Tables and Figures (SSTF), comprising 60 standard mockup tables, with 19 specifically pertaining to FDA Medical Queries (FMQs).

The following figure explains the rationale behind FDA Medical Queries.

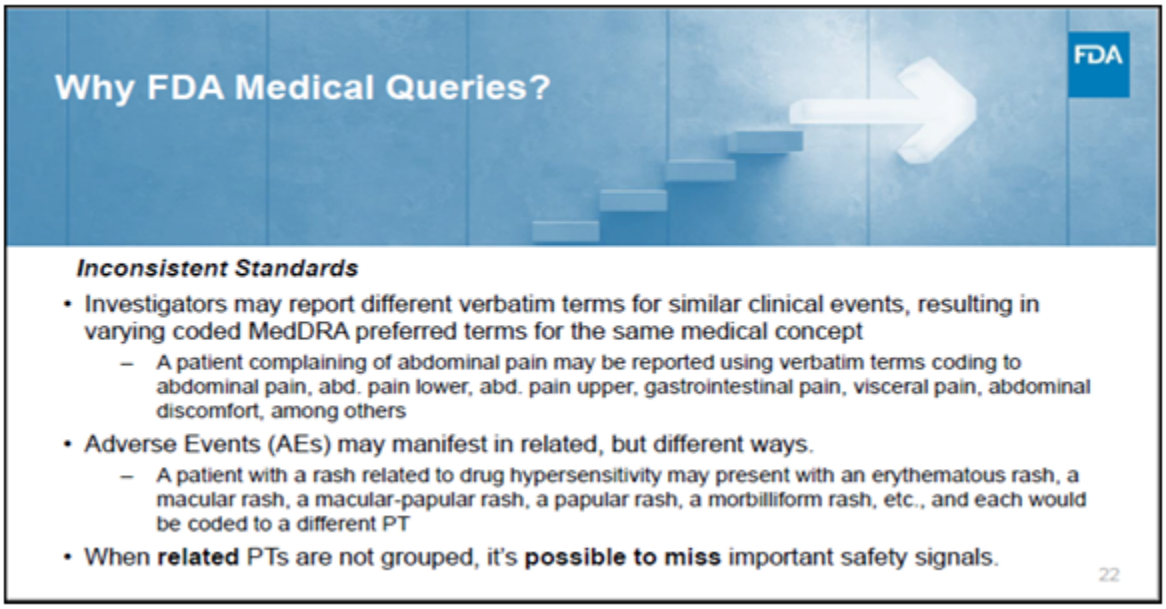

Figure 1. Why FDA Medical Queries

The FMQs are standardized groupings of related PTs, which are categorized as either narrow or broad. These groupings have been developed by FDA reviewers with the purpose of facilitate safety signal detection in the premarket safety database.

- Narrow FMQ terms: Specific for the medical concept, indicate that the FMQ occurred, more than ~90% probability.
- Broad FMQ terms: Less specific, provide reasonable assurance (more than ~30% probability) that the medical concept occurred.
- Algorithmic FMQs: Use data from AE, laboratory, concomitant medications, medical history data sets and temporal relationships to leverage the available information.

R SHINY AS INTERACTIVE VISUALIZATION TOOLS

The typical approach for monitoring adverse events (AE) involves generating tables or plots using an enriched dataset. However, the advancement of new technology has opened up possibilities for incorporating interactive visualization, which can provide additional benefits in this regard. By incorporating simple clicking and filtering options, it becomes easier to use and trace AE records by viewing relevant data.

R Shiny is a powerful and versatile visualization tool that allows users to create interactive web applications directly from R. With its user-friendly interface and extensive library of widgets, R Shiny enables users to effortlessly develop and deploy interactive visualizations, dashboards, and data-driven applications.

Based on the given information, we have created an R Shiny application that utilizes FMQ terms to analyze adverse event data and visually monitor Adverse Events.

BACKGROUND

ADVERSE EVENT DATA

This visualization tools would use 2 kinds of AE datasets.

- AE data from EDC (Electronic Data Capture) system directly

To ensure early monitoring of adverse events (AEs), we opted to utilize AE raw data obtained from the Electronic Data Capture (EDC) system. This system collects and documents electronic Case Report Form (eCRF) data. The AE terms in the data is coded with MedDRA dictionary.

- ADAE

  The Adverse Event Analysis Dataset contains additional information compared to the raw AE data. This dataset allows us to incorporate treatment details such as treatment group and time to treatment start date when generating output plots.

COMBINING WITH FMQ LIST

After combining FMQ list based on AEDECOD/PT, two variables FMQNAM (FDA Medical Query Name) and FMQCLASS (FDA Medical Query Scope) are added.

R codes for combining:

```
adae <- read_sas("./raw_ae.sas7bdat")

tfmq <- read_sas("./tfmq.sas7bdat")

tfmq2 <-tfmq %>% rename(AEDECOD=PT)

temp <- left_join(adae, tfmq2, by ="aedecod" )

temp3 <- temp %>%

pivot_longer(starts_with("fmq"), names_to="fmq_n",values_to="fmqnam") %>%

filter(fmqnam != "") %>%

select(-fmq_n)%>%

pivot_longer(starts_with("scope"),names_to="scope_n",values_to="fmqclass")%>%

filter(fmqclass!= "")%>%

select(-scope_n)
```

OUTPUT R SHINY APP

LOGIC AND DESIGN

FMQ Data Preparation

Source data

We permit users to designate their source data for each study when preparing combined AE-FMQ data: AE data and defined FMQ category data from the FDA.

AE data: as previously stated, the system not only supports derived ADAE but also directly processes SDTM AE data from the database. Both data sources will be accurately managed based on the variables detected within the data.

FMQ category data: The source data utilized by the application was constructed using the Excel file (FDA-2022-N-1961-0001_attachment_1.xlsm) provided by FDA upon releasing the FMQ guidance in 2022. Each preferred AE term is recorded with its corresponding FMQ name and class specified[3].

The Shiny application presents these two source datasets, enabling users to effortlessly locate their desired information.

Derived AE-FMQ data

An R function has been developed to generate a temporary dataset for further display. Each AE record will be aligned with the AE term in the FMQ category data, and subsequently the corresponding FMQ

name and class will be appended to the record. In cases where multiple classes are present, the record will be replicated, with each replication having a distinct class.

FMQ Table and Figure Design

Upon generating the AE-FMQ data, we derive unique values for the FMQ name and AE body system class, transforming them into selectable items within the application. These values facilitate the filtering of original data, thereby creating a subset for further examination. In our design, the data displayed in the table must consistently align with the data utilized in figure creation, both pre- and post-filtering.

Tables

All data: At present, the application will generate two tables once the AE-FMQ data is prepared. The first table encompasses all variables and records derived from the data. The second table, however, only contains four variables: FMQNAME (FMQ Name), FMQCLASS (FMQ Class), AEBODSYS (AE Body System), and AEDECOD (AE Preferred Term). Duplicate records have been eliminated from this table, preserving only unique combinations of these four variables.

Filtered data: The two tables can be refined according to the user's choice of FMQ name, FMQ class, or AEBODSYS, enabling a straightforward view of all relevant FMQ information. This filtering function is linked to the creation of individual FMQ plots, as discussed below. Thus, while reviewing the plots, users can simultaneously access the data utilized for plot generation.

Figures

Once the AE-FMQ table is prepared in the application, figures can be generated based on various analytical objectives, accommodating users' dynamic selections.

All figures are categorized into two types: 1. Overall Plots and 2. Subcategory Plots. The creation of each plot is linked to distinct buttons (Figure 2), with each button triggering the generation of either a single plot or a series of plots.

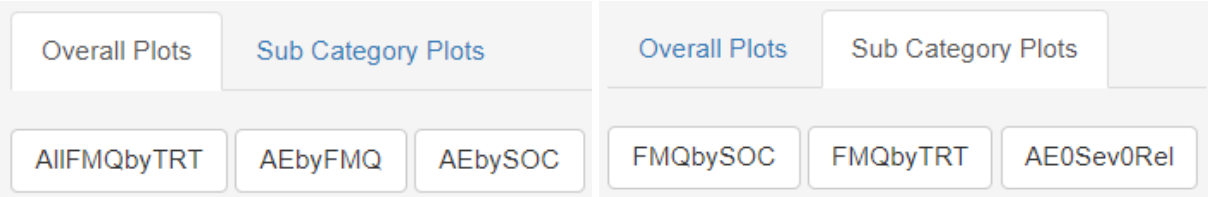

Figure 2. Buttons in Two Categories

For example, “AllFMQbyTRT” button under “Overall Plots” category generates a plot with all FMQ categories in the AE-FMQ dataset under either broad or narrow class, shown in Figure X.

Indeed, the application accommodates the use of six buttons to generate eight specified plots. However, due to Shiny's flexibility, additional plots can be seamlessly integrated, contingent upon the requirements of a new plot and the preparedness of the corresponding function.

Logics for Table and Figure Display

Shiny's reactivity is a significant advantage, facilitating dynamic data manipulation and output creation for users. However, it also presents challenges, particularly when generating plots based on user-selected FMQ names or SOC. This selection process filters the original data to produce the figure. To address this, we have ensured consistent alignment between tables and figures, enabling reliable cross-referencing for users.

Every time a user selects an FMQ name or SOC, the application will respond accordingly. Initially, we filter the data to create an AE-FMQ data subset, which is then utilized to generate plots.

As previously noted, plots can often be interconnected. In such instances, we ensure a series of figures are displayed concurrently, allowing for a comprehensive review of information from various plots on a single page. This approach enhances the ability to monitor diverse data and analysis results.

MAIN PAGE

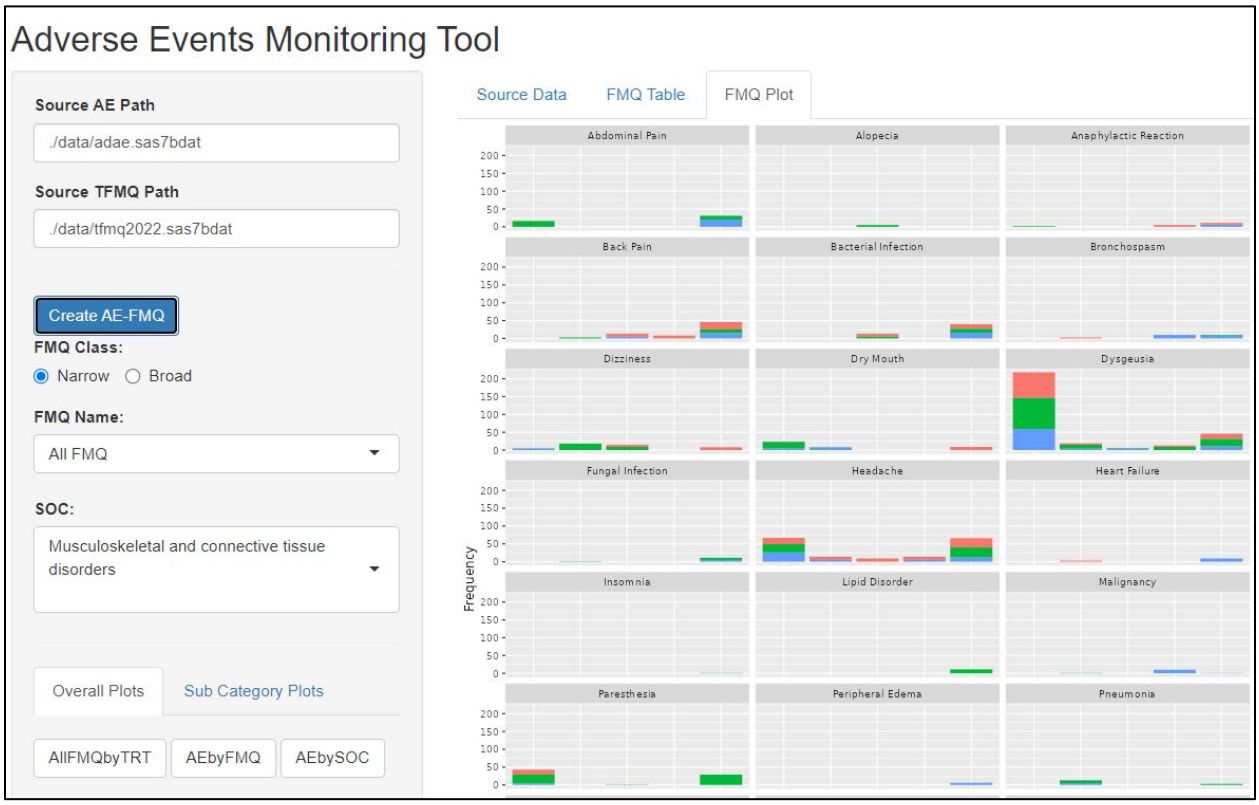

Figure 3. Overall Layout of AE Monitoring Application

OUTPUT

General Output

The app generates two main types of pages: one for overall analysis and another for subset categories such as SOC and FMQ term (narrow and broad). The overall analysis page displays plots depicting AE incidence, allowing us to observe AE trends and identify categories that require further investigation. We can then select specific subset categories that require additional attention to determine the intensity, duration, and causality of the AEs.

Output for Overall

It presents Adverse Event lists categorized by FMQ term and by SOC. In this way, the user will gain a comprehensive understanding of the entire situation.

Lollipop plot by FMQ term

The plot illustrates the incidence of Adverse Events (AE) based on FMQ terms, with the options of Broad and Narrow. The specific example plot provided pertains to the FMQ narrow term. The numerical value displayed above each point represents the corresponding number of AE incidences.

R codes for plot:

```
ov_fmq_narrow_p <- ggplot(ov_fmq_narrow, aes(x=fmqnam, y=freq) )+
geom_segment( aes(x=fmqnam, xend=fmqnam, y=0, yend=freq), color="grey", linewidth=0.7) +
geom_point( color="orange", size=2) + coord_flip() + theme(legend.position="none" ) +
geom_text(aes(label=freq),vjust=-0.5) +
xlab("FMQ (Narrow)") +
ylab("AE incidence") +
ggtitle("List of Adverse Event")
```

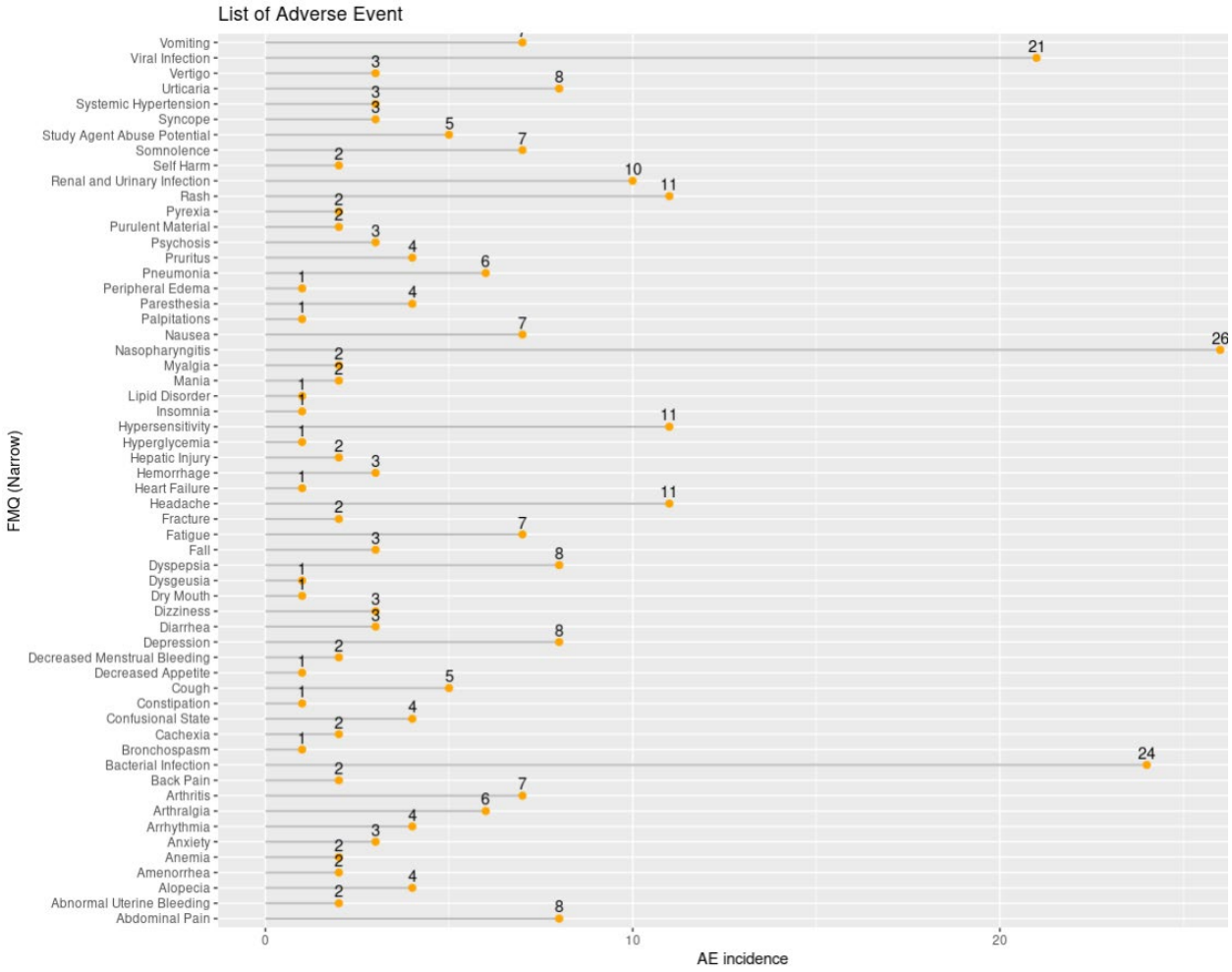

Figure 4. List of Adverse Events by FMQ (Narrow)

Horizontal bar plot by AE body system

This plot presents the incidence of adverse events (AEs) categorized by body system, with the order based on the number of incidences.

R codes for plot:

```
ov_soc_narrow_p<-ggplot(ov_soc_narrow, aes(x=aebodsys, y=freq)) +
geom_bar(stat = "identity") +
coord_flip() +
labs(x='Incidence', y='System Organ Class')+
ggtitle('Adverse Event list by System Organ Class')
```

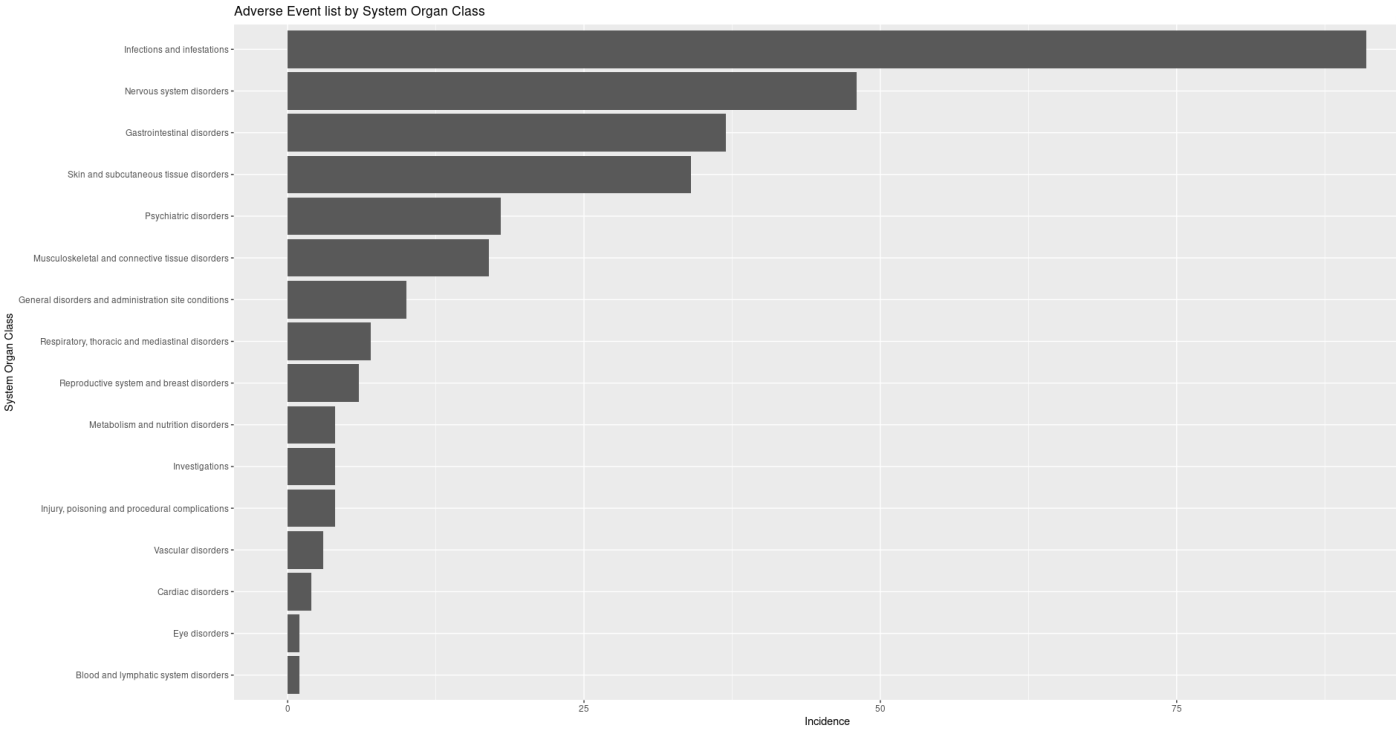

Figure 5. List of Adverse Events by SOC

Page for individual AE body system

If the user would like to examine a specific body system, they can select it from the option menu. The display will then provide the incidence of FMQ terms related to that particular body system.

R codes for plot:

```
soc_ind_p <-ggplot(soc_iai) +
geom_hline( aes(yintercept = y), data.frame(y = c(0:4) * 5), color = "lightgrey") +
geom_col( aes( x = reorder(str_wrap(fmqnam, 5), fmqnam), y = freq, fill = freq ), position = "dodge2", show.legend = TRUE,
alpha = .9 ) + coord_polar()+
labs(x = "Incidence") +
ggtitle('Incidence by FMQ (Narrow) within the SOC')
```

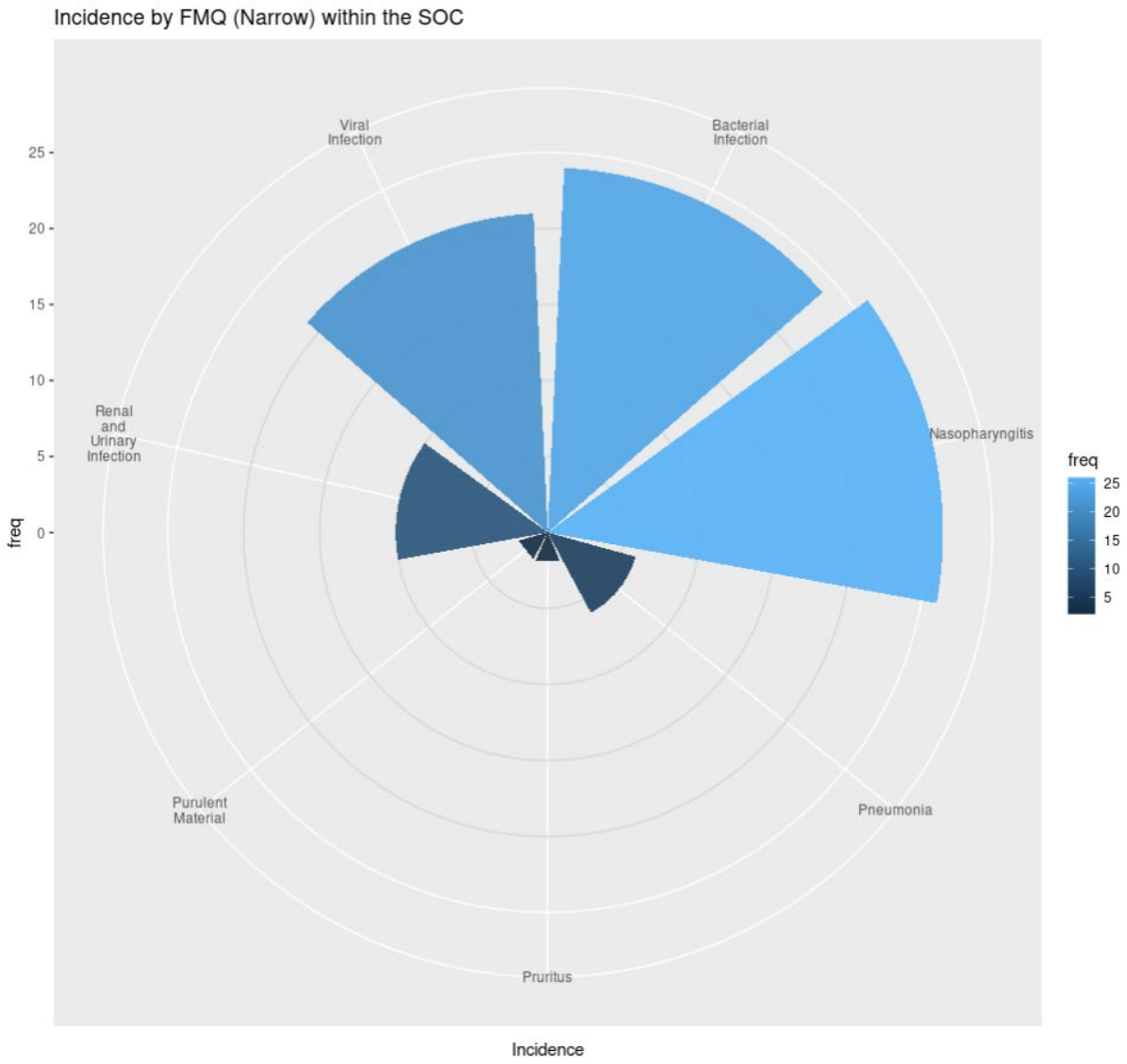

Figure 6. Incidence by FMQ (Narrow) within the SOC

Page for individual FMQ term

When choosing each FMQ term, plots depicting intensity, start time, and causality will be shown. And related data could also be accessed.

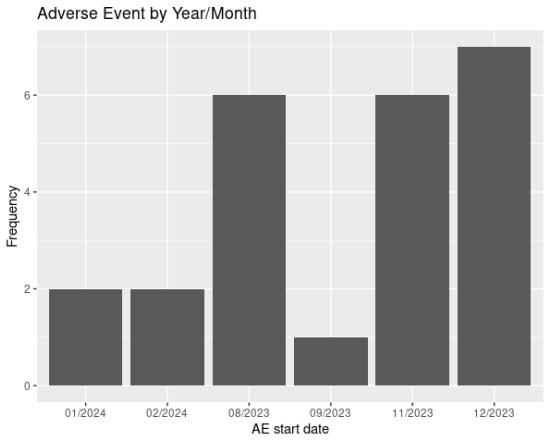

Figure 7. Adverse Events by AE start time for selected FMQ term

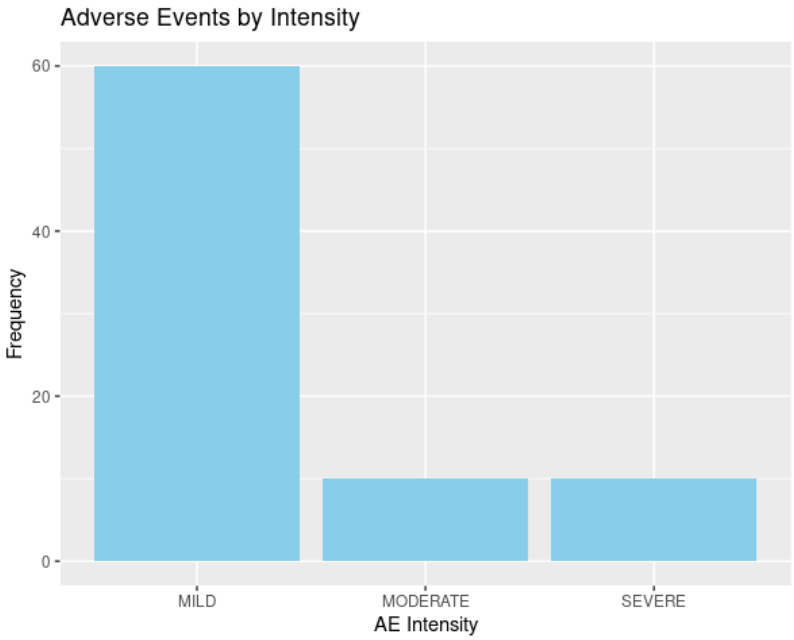

Figure 8. Adverse Events by intensity for selected FMQ term

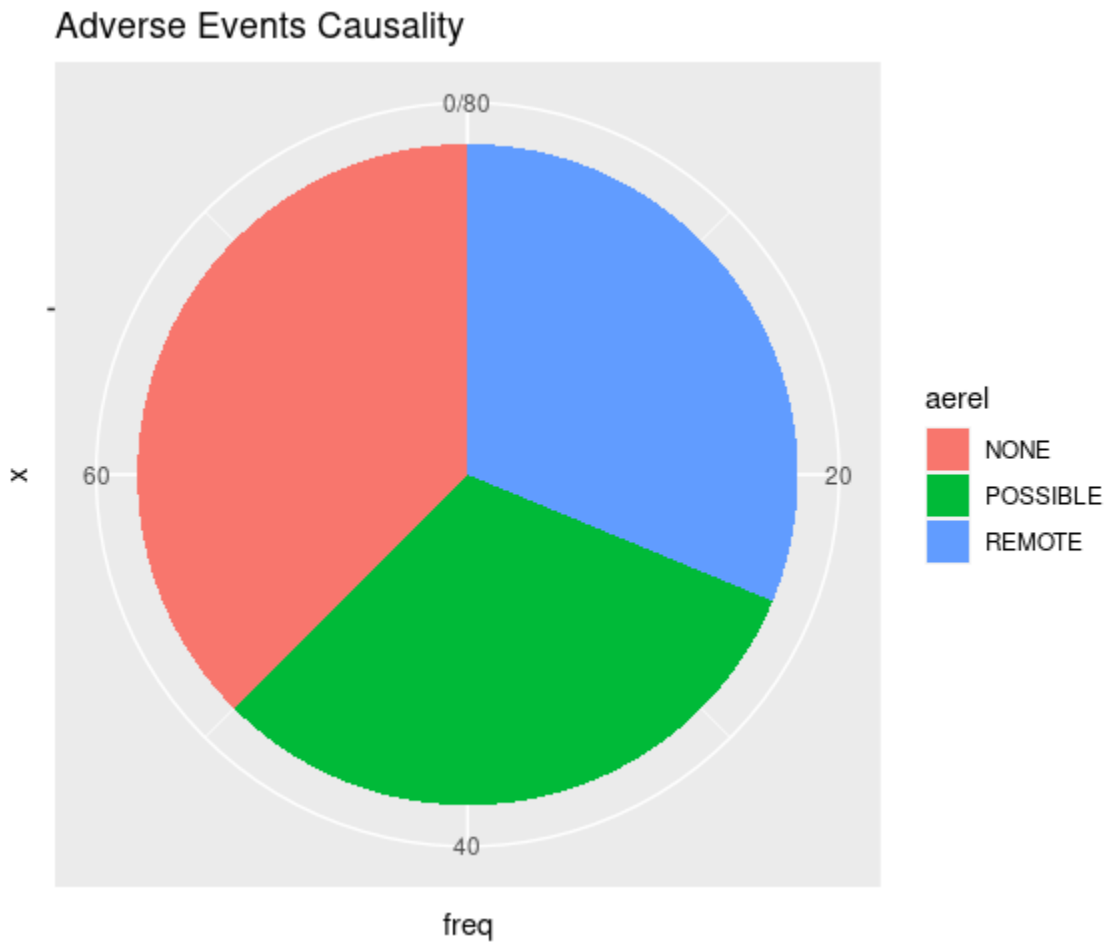

Figure 9. Adverse Events Causality for selected FMQ term

Output with treatment Information

This page presents plots illustrating the incidence with respect to time to first dose category for various treatment groups. The output includes both an overall collection and individual plots for each specific FMQ term.

R codes for plot: nest_bar_plot_narrow <- ggplot(bar_freq_narrow, aes(x=aedurcat,y=freq,fill=trta)) +

geom_bar(stat='identity') +

facet_wrap(~ fmqnam, nrow = floor(sqrt(length(unique(bar_freq_narrow$fmqnam)))), ncol = ceiling(sqrt(length(unique(bar_freq_narrow$fmqnam)))))+

labs(x='Time to First Occurence', y='Frequency') (insert picture)

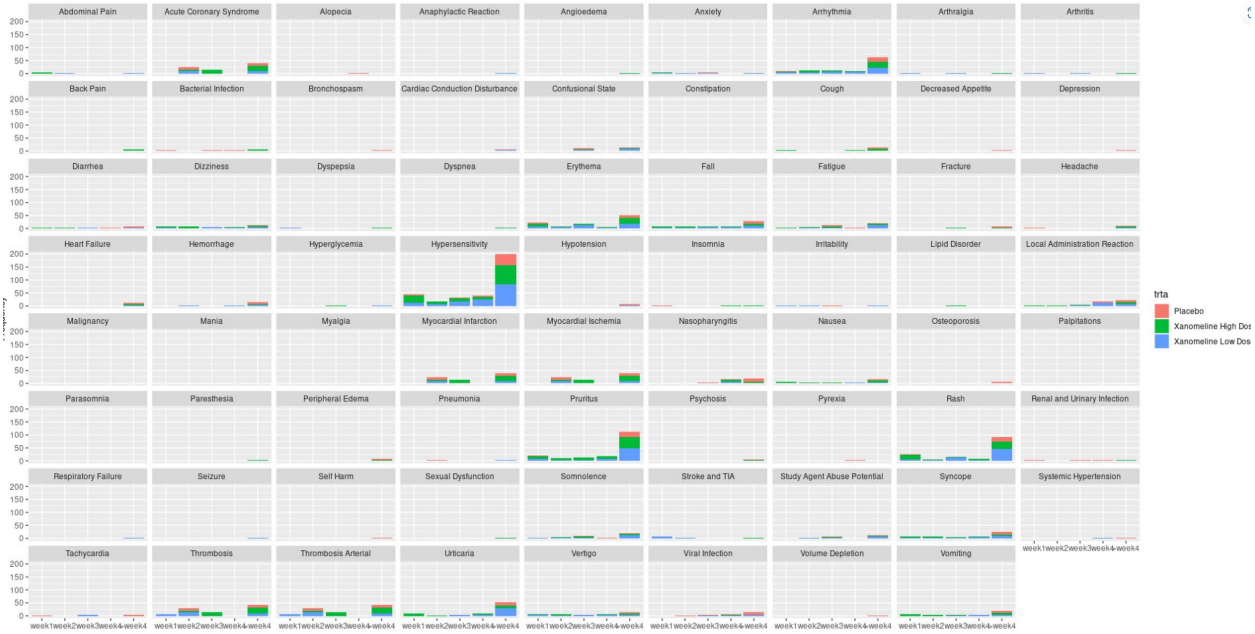

Figure 10. Adverse Events Duration for all FMQ terms

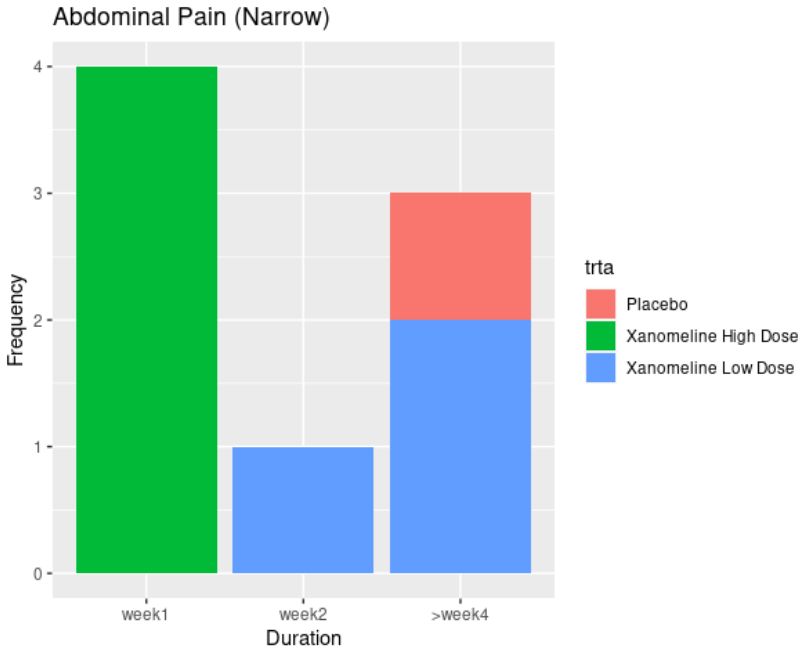

Figure 11. Adverse Events Duration for selected FMQ term

FURTHER IMPROVEMENT CONSIDERATION

This app is a starting point for using interactive visualization to monitor adverse events. It has many areas for improvement.

- Provide more filtering options, such as demographic information like gender and age categories.
- Integrate other safety assessments, such as lab results. This will allow for the display of algorithmic FMQ, which may have criteria based on LAB data.
- Embed a warning system for clinically interesting cases. For example, the app can flag cases that meet certain criteria, helping the team prioritize and streamline their efforts to address them.

By incorporating these improvements, the app can offer a more comprehensive and user-friendly platform for monitoring adverse events.

CONCLUSION

The utilization of interactive visualization tools to monitor adverse events (AE) proves to be an effective and valuable measure. The FDA has taken a significant step in ensuring safety by introducing the FDA Medical Query (FMQ), which is integrated into the standard safety table package. By combining the monitoring of adverse events with the FMQ list, it can ensure consistency with the final submission package. This comprehensive approach not only enhances safety monitoring but also streamlines the regulatory process. Employing interactive visualization tools and integrating them with the FMQ system is a commendable strategy for maintaining the highest standards of safety and compliance in adverse event monitoring.

REFERENCES

Food and Drug Administration (FDA) released docket ID FDA-2022-N-1961. 05 September 2022. https://www.regulations.gov/docket/FDA-2022-N-1961/document.

Food and Drug Administration (FDA) & Duke-Margolis workshop final slide deck and video recording. 14 September 2022. https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics.

Guowei Wu2023. Prepare FMQ Analysis Datasets to Accommodate Standard Safety Table Creation

The R Graph Gallery – Help and inspiration for R charts (r-graph-gallery.com)

Clio Wu 2023. “Why FDA Medical Queries (FMQs) for Adverse Events of Special Interest? Implementation and Case Study” PharmaSUG 2023

ACKNOWLEDGMENTS

The authors want to thank Merck BARDS programming team leader team for their comments and suggestions.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Tonda Che
Merck & Co., Inc., Rahway, NJ, USA
E-mail: tong.da.che@merck.com

Danfeng Fu,
MSD China,
E-mail: dan.feng.fu@merck.com