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PP29: PHUSE Safety Analytics Working Group: AE Groupings in Safety (AEGiS) Project Team Update

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ABSTRACT: In 3Q2022 the PHUSE Safety Analytics Working Group initiated the **AEGiS (Adverse Event Groupings in Safety)** project to explore the existing widely used groupings of adverse events and provide recommendations on the different types of groupings and the utilities of each. This poster will highlight the background, activities to date and future deliverables.

Background and Membership

The AEGiS project team engages over 30 clinical and analytical experts from the FDA, industry (spanning small, medium, large pharma), academia and consulting firms with the following goals:

- (1) discuss the importance of improving safety assessment utilizing AE groupings (MedDRA SMQs and MLGs, FDA FMQs, custom)
- (2) provide recommendations concerning grouping types and ways to implement to support various objectives (e.g., signal detection, safety topics of interest, planning documentation, submissions)

Coincidentally the FDA Medical Queries (FMQs) were released in parallel, and the AEGiS project team is fortunate to have FDA representation to ensure that MedDRA SMQs, sponsor custom groupings and FMQs are discussed in the final white paper. Resourced with numerous PHUSE deliverables on the topic of safety analysis and displays, the AEGiS project team is estimating finalization of the draft white paper 4Q23.

Typical Approach:

- Sponsors likely utilize SMQs, custom queries, or will be utilizing FMQs for specific safety concerns (AESI, MACE etc.)
- Sponsors generally run AE TLFs utilizing MedDRA PTs within SOC and may create ad-hoc groupings dependent on findings – general safety review may not incorporate AE groupings

Note: The PHUSE 2017 AE White Paper noted AE groupings for general safety (signal detection and looking for ‘surprises’)

AEGiS Objectives

Objectives of the AEGiS Project Team Include:

- Define best practices for utilization of AE groupings
- Develop points to consider/recommendations on implementation of AE groupings
- Recommend efficient standardized processes and introduce ways to leverage new technologies

Groupings Included in AEGiS Project

FDA Medical Queries:

- 104 FMQs, 4 of which also have an algorithmic component
- Each grouping represents a medical concept
- Goal to improve safety signal detection in clinical trial data
- FMQs include AE terms without regard to causality including those with presumably non-drug-related causes
- Includes non-PTs, former PTs, and other terminologies

Standardized MedDRA Queries:

- ~110 SMQs with standardized medical terminology used broadly across industry
- Validated and maintained groupings for safety topics of interest
- Hierarchy includes focused ‘Sub-SMQs’ for ~25% of topics

Sponsor Developed or Custom Groupings

<https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics>
www.meddra.org

Activities to Date

Since inception in late 2022 the AEGiS Project Team has been very busy collaborating on the following activities:

- Coordinated monthly meetings to solicit input, expertise and share knowledge concerning AE groupings
- Developed White Paper table of contents
- Volunteers from the project team authored Sections (paired clinical and analytic expertise within section authors)
- Maintained ongoing review of the authored sections
- Currently refining the White Paper and identified ‘parking lot’ of additional topics for further investigation

Table 34. Patients With Serious Adverse Events¹ by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)²

System Organ Class ⁵	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI) ^{4,a}
FMQ (Narrow) ³					
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: Aug 2022 FDA Integrated Guide.

Utilize Existing
Query
(e.g. FMQ/SMQ)

Semi-Custom Query:
Alter Existing Query
(e.g. remove/add terms)

Custom Query:
Existing or alteration
won't capture
medical condition

Conclusion: Utilization of AE Groupings

Final Thoughts:

- AEGiS White Paper ~4Q24
- FMQs can help with both AESI and predefined general safety queries
- Recommending the use of narrow FMQs for general safety reviews is under consideration by the AEGiS project team
- Use existing groupings (all terms) when possible
- Safety monitoring during clinical trials should include labs, serious AND non-serious events
- Following the ASAP process – grouping for known or potential Safety Topics of Interest should be utilized
- Attention should be paid to the presentation of PT groupings as provided in the FDA standard Tables and Figures guide
- <https://www.regulations.gov/document/FDA-2022-N-1961-0046>

Note: Developing AE groupings is not in the AEGiS Project Team remit.

AE – Adverse Event
AEGiS – AE Groupings in Safety
AESI – Adverse Event of Special Interest
ASAP – Aggregate Safety Analysis Planning

FDA – Food and Drug Administration
FMQ – FDA Medical Query
MACE – Major Adverse Cardiovascular Event
MLG – MedDRA Labeling Groupings

PT – Preferred Term
SMQ – Standardized MedDRA Query
SOC – System Organ Class
TLF – Tables Listings and Figures

For more information or join PHUSE
Safety Analytics Working Group? Scan
the QR code!

