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Utilization of Adverse Event Groupings in Clinical Trial Safety Assessment

Revision History

Version	Date	Summary

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1: Overview: Purpose of this document:

Groupings of clinical trial adverse events (AEs) are used to identify and describe medical conditions by encompassing the full range of relevant adverse events. Published groupings of AE terms include Standardised MedDRA Queries (SMQs) and the FDA Medical Queries (FMQs); however, unpublished custom AE queries have been frequently used by individual sponsors. Any of these queries may be used when assessing the safety of a molecule and in communicating the type and magnitude of safety risks.

This document outlines why using standard AE groupings for queries is key to understanding a drug's safety profile, discusses some assumptions underlying use of standard queries for estimation, and outlines the benefits of standard queries when available. When standard queries are not available but detailed analysis of a specific medical condition is needed, this document recommends a process to develop and maintain a custom query that can be replicated by regulatory authorities. In addition, we touch on planning, documentation, possible table and figure structures, and interpretation for analyses using either standard or custom AE queries.

The primary audience for this document includes:

- Authors of the safety section of statistical analysis plans, program safety analysis plans, integrated safety analysis plans and/or aggregate safety assessment plans
- Subject matter experts identified for safety topics of interest
- Multidisciplinary safety management teams involved in pre-marketing product development
- Clinical development team members involved in developing and assessing safety endpoints (e.g., major adverse cardiovascular events, or MACE)

The goal is to improve signal detection, safety assessments, and risk communication during clinical development by ensuring that evaluation of each important medical condition includes all relevant AEs in these processes.

2: Scope:

This white paper is intended to provide awareness, knowledge, and recommendations to sponsors who are considering using standard or custom AE queries in their safety tool kit during clinical trial safety assessments. Published AE queries (e.g., SMQs and FMQs), custom AE queries, and their utility, advantages, and disadvantages will be discussed. Development of actual AE groupings is not a goal of this white paper, and the detailed structure of the MedDRA hierarchy will not be discussed. While the focus of this paper is on the use of AE groupings in Phase 2-3 clinical trials and integrated analyses for

regulatory submission, there are brief discussions of their use in earlier development.

The following are out of scope of this white paper:

- Comparison of specific content across published AE queries
- Development of specific AE queries for a label or to communicate risk to the public
- Use of AE queries (e.g. SMQs, FMQs, custom) in post-marketing pharmacovigilance activities

3: Abbreviations:

Term	Definition
ADaM	analysis dataset model
AE	adverse event
AEGiS	AE Groupings in Safety
AESI	adverse event of special interest
ASAP	Aggregate Safety Assessment Planning
BA/BE	bioavailability / bioequivalence
CDER	Center for Drug Evaluation and Research
CIOMS	Council for International Organizations of Medical Sciences
CSR	clinical study report
DMC	Data Monitoring Committee
ECG	electrocardiogram
EWG	Expert Working Group
FDA	Food and Drug Administration
FMQ	FDA Medical Query

Term	Definition
ADaM	analysis dataset model
HLGT	High Level Grouped Term
HLT	High Level Term
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
iSAP	integrated Safety Analysis Plan
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA Labeling Grouping
MSSO	Maintenance and Support Services Organization (for MedDRA)
PSAP	Program Safety Analysis Plan
PT	Preferred Term
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
SMT	Safety Management Team
SOC	System Organ Class
STOI	Safety Topic of Interest

4: Definitions:

Adverse event (AE): Any untoward medical occurrence experienced during the specified time period, whether or not it is considered related to study procedures or study drug. For purposes of clinical trial research, the time period in which AEs are collected is specified in the study protocol or AE collection

instructions. This definition is a slight modification of those provided from other sources (2005 FDA CDER Clinical Safety Review Guidance [1], Code of Federal Regulations [2]) so that it is more broadly applicable across various study designs (e.g., designs with study periods in which participants aren't receiving any study drug or procedures).

Adverse reaction / adverse drug reaction : An adverse event reasonably likely to be caused by a study drug, which may occur as part of the pharmacological action of the study drug or may be unpredictable in its occurrence. See the 2005 FDA CDER Clinical Safety Review Guidance [1] and the FDA Guidance on Safety Reporting Requirements for INDs and BA/BE Studies [3].

AE grouping (or AE query): a defined grouping of coded AE terms related to a specific medical condition, which may be used for multiple purposes, including identification and retrieval of data, analysis, creation of a product label, and communication of risk.

- **Standard AE queries** have been prepared and reviewed by multi-disciplinary committees, are published and are maintained by the publishing organization and are widely accessible to all users. See FDA Medical Queries and Standardized MedDRA Queries.
- **Custom AE queries** refer to any unpublished grouping.

Aggregate Analysis: quantitative and medical review of safety data for a compound that goes beyond individual case review. Aggregate data are not necessarily pooled.

Aggregate Safety Assessment Plan (ASAP): The ASAP (planning document for the ASAP process) is a clinical trial sponsor's internal document which is used to characterize the emerging safety profile of a product. The ASAP promotes interdisciplinary, systematic safety planning as well as ongoing data review and thus evolves over a product's life-cycle [4].

FDA Medical Queries (FMQs): FDA Medical Queries (FMQs) are groupings of AE terms developed by FDA staff that are used to improve safety signal detection during the analyses of clinical trial datasets. https://www.fda.gov/media/164639/download

Integrated Safety Analysis Plan (iSAP): While this term has no established definition, it is often used to describe a submission-level planning document describing the analyses and definitions required to conduct the planned analyses for the Summary of Clinical Safety and Integrated Summary of Safety for a specific submission.

Program Safety Analysis Plan (PSAP): A compound-level planning document describing the analyses and definitions required to conduct the planned analyses for Phase 2-3 studies and the Summary of Clinical

Safety for a compound [4,5].

Pooling: combining data across 2 or more studies and/or cohorts to increase power and precision.

Safety topics of interest (STOI): STOI include: 1) important identified and potential risks of the product; 2) AEs of special interest (AESIs, a concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate); 3) Other STOI such as potential drug toxicities that all products should consider (e.g., hepatic-related events), and events of concern for the study population which are anticipated to be of high interest to the regulatory agencies. STOI typically require specialized data collection, monitoring or analyses (i.e., actions beyond "routine") and have the potential to impact the product's beneft:risk profile. STOI could be related to clinical AEs or changes in laboratory, vital signs, electrocardiogram (ECG) measurements, or other safety parameters being evaluated.

Standardised MedDRA Queries (SMQs): are groupings of MedDRA terms developed by MSSO and Council for International Organizations of Medical Sciences (CIOMS) subject matter experts, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded. https://www.meddra.org/standardised-meddra-queries)

Statistical Analysis Plan (SAP): A study-level planning document describing the analyses and definitions required to conduct the planned analyses for the study.

5: Problem Statement:

AE queries are lists of terms created to identify and retrieve AE reports representing a specific medical condition (i.e., diagnosis) for analysis. AE reports are provided as "verbatim" terms by clinicians and coded to standardized language using the Medical Dictionary for Regulatory Activities (MedDRA), which provides very precise Preferred Terms for each possible symptom, sign, location of abnormality, or diagnosis. Clinicians may use any verbiage as they describe key aspects of a specific AE; for clarity the words provided are characterized as a 'verbatim term'. Further variability in the data is introduced by regional and specialized differences in medical nomenclature. "Verbatim" terms for different aspects of a single medical condition thus may code to different MedDRA PTs. For instance, a hypersensitivity skin

reaction might be described by the physician as red, macular, or maculo-papular rash, or blisters, all of which would be coded to different PTs. These granular terms preserve data as created but make it difficult to write a query to retrieve "all" reports of a given medical condition. Furthermore, the same underlying physiology can present in different organs, thus coding to PTs in completely different SOCs.

For example, "an allergic-type adverse event that has respiratory (wheezing) and dermatologic (rash, urticaria) manifestations should be classified as a single adverse reaction (e.g., hypersensitivity)." [6]

This problem of grouping AE terms to include "all reports" of a specific medical condition is a significant obstacle to identifying emerging safety signals and quantifying the risk for adverse reactions. When events representing a medical condition are not retrieved by a query, the risk of that condition may be obscured, which can lead to missing an important safety signal. Regulatory authorities worldwide have recognized the need for grouping AE terms to estimate the risk of some medical conditions. [6,7]

As early as 2002, groups including the MedDRA Maintenance and Support Service Organization (MSSO) and CIOMS began work on creating and standardizing AE groupings to address the granularity issue and potential for missing safety issues. In the past 20 years, they have developed over 100 SMQs covering the most severe and widely recognized drug reactions. Recently FDA released FMQs (https://www.fda.gov/media/164639/download), which only partially overlap with SMQs. The identification of events which are relevant to an observed medical condition is a critical step in assessing drug-related toxicity.

When an appropriate published query doesn't exist for a STOI, sponsors often consider creating a custom query of MedDRA PTs. One downside to custom AE queries is that individual sponsors include different sets of terms for the same medical condition, making review of data across molecules more challenging. In addition, maintaining these custom AE queries across an organization as well as ensuring consistency for submissions and aggregate analyses requires a significant investment in time and resources.

This white paper discusses selection and use of SMQs, FMQs, or, if necessary, creation of a custom query, and will provide recommendations on implementation, documentation, design, and presentation of analyses of AE queries, as well as processes for maintaining custom queries.

6: Background:

The PHUSE Computational Science Collaboration is an initiative involving PHUSE, the FDA, academics, and industry that identifies computational science priorities that could be addressed by collaboration,

crowd sourcing, and innovation. Several working groups have been created to address many of these challenges. The AE Groupings in Safety (AEGiS) cross-functional project team within the Safety Analytics Working Group has led the development of this white paper.

Members of the AEGiS team shared their learning when drafting this white paper, and MSSO was consulted on SMQ matters as needed. Contributors to this white paper included industry statisticians, clinicians, programmers, and data experts, as well as FDA clinical reviewers. The white paper was then posted in the PHUSE environment for public comment before being finalized.

7: AE Groupings in Queries:

This section discusses the structure, definitions, and use of standard AE queries developed by the MSSO, FDA, and CIOMS, and suggests best practices and considerations for building a custom AE query if a medical condition is not described by one of the standard queries.

AE queries may be either standard queries, examples of which include MedDRA SMQs and FDA's FMQs, or custom AE queries developed by an individual clinical trial sponsor or other group. Typically, all types of AE queries are specified at the MedDRA PT level. Details regarding the creation, use and maintenance of each type of AE query are found in sections 6.2 – 6.5. Medical conditions covered by either an SMQ, an FMQ, or both as of the time of this publication are listed in Appendix 1.

The SMQs and FMQs have been developed after years of work and testing by groups of medical experts. SMQs typically cover serious medical conditions that can be caused by drugs, whereas the FMQs in addition include non-serious AEs that impact the overall safety profile. In some cases, there is both an SMQ and FMQ for a given medical condition, often with a different perspective. When no standard query exists for a topic of interest, creating a custom query is appropriate. When possible, such AE grouping(s) should be defined a priori to minimize bias and ensure the integrity of analyses. Note that developing/programming additional analyses using custom AE queries requires dedicated and knowledgeable resources to implement effectively.

Also note that if an issue is identified in an SMQ, it is recommended to directly contact the MedDRA MSSO, or if in an FMQ, the Biomedical Informatics Team at FDA: ONDBiomedicalinformatics@fda.hhs.gov.

7.1: MedDRA Hierarchy as a Grouping:

The structure, use, and maintenance of MedDRA is detailed in the instructional materials at http://www.meddra.org. The basic MedDRA hierarchy clusters related AE terms under higher levels

(e.g., HLTs) but at the top, the System Organ Class (SOC) level organizes terms by organ (e.g. *Cardiac disorders*), causative agent (e.g. Infections and infestations), or type of observation (e.g. Investigations, Social circumstances) rather than by medical condition. As a result, terms for a symptom of toxicity (e.g. yellow skin as a sign of liver failure) may be located in the SOC for the organ where the abnormality was seen (skin) rather than the disease SOC (hepatobiliary). Abnormal laboratory results are found in a separate Investigations SOC even when diagnostic of a medical condition. These difficulties are compounded by data entry conventions that prioritize matching an AE code to the verbatim term provided, over identifying the medical condition. These conventions exist to prevent incorrect assumptions about the presence of a diagnosis based on a report that is only suggestive of a disease (e.g., not all yellow skin is jaundice). In addition, in the Investigations SOC, both increases and decreases are found in the same HLTs. Thus, from a medical perspective, using the MedDRA hierarchy alone may result in both false positive and false negative safety signals.

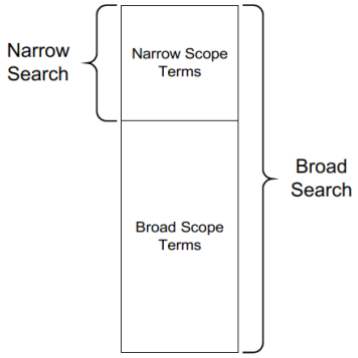
7.2: Standardized MedDRA Queries:

7.2.1: MedDRA SMQ Structure and AE Terms:

The Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddra.org) is comprised of terms that are hierarchical, multiaxial, multilingual, regularly updated, and strictly maintained. MedDRA SMQs are pre-determined sets of MedDRA PTs associated with a particular area of interest or medical condition and consist of related signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data as well as procedures. Each SMQ, comprised of individual PT level terms and their directly linked LLT terms, is conceptually organized to address a specific medical condition or area of interest. While the MedDRA Dictionary has multi-axial components in some SOCs (e.g., a PT could be coded to one of several different SOCs), in cumulative output each PT appears under the primary SOC. SMQs are not subject to these restrictions and can contain terms from any relevant SOC. For example, the SMQ *Cardiac failure* includes terms from the SOCs *Cardiac Disorders, Investigations,* and *Surgical and Medical Procedures SOCs* among others.

SMQ term lists may be narrow (providing specificity) and/or broad (increasing sensitivity); both spanning across different SOCs. Narrow terms are those that are highly likely to represent the condition of interest. For example, the PTs *Pancreatitis acute* and *Pancreatitis haemorrhagic* are narrow terms in the SMQ *Acute pancreatitis*. Broad terms may or may not be indicative of the condition of interest since they are less specific. In this SMQ example, PTs Amylase increased, Lipase increased, and Blood bilirubin increased are broad terms because not all instances of these terms are indicative of acute pancreatitis. Thus, users have the option to perform a narrow search consisting of only narrow terms or a broad

search with both narrow and broad terms. Note that by default, the broad search list includes the narrow list (figure 1).



Source: Introductory Guide for Standardised Medical Queries (SMQs) Version 26.0, March 2023, International Council Harmonization, p3

7.2.2: Development Process and Ground Rules:

SMQs represent medical conditions of interest to both industry and regulatory users that have the potential to have an impact on benefit:risk evaluations of a product. Extensive validation is required of an SMQ's terms to assure that true cases of interest will be identified. To support this, MSSO and CIOMS developed the SMQs together. Joint review, testing, analysis, and expert discussion ensure SMQs do not have the appearance of bias, are scientifically rigorous, and will be recognized by regulatory agencies. The rules for creation of each SMQ are found in the Introductory Guide for Standardised Medical Queries [8].

The description of each SMQ provides a definition of the condition of interest and specific inclusion and exclusion criteria that underlie the choice of the terms. The inclusion and exclusion criteria for each search strategy should be considered before employing an SMQ to ensure that the SMQ meets one's intended needs. As the individual SMQ groups of terms were developed by different sets of regulatory and industry experts, there is some variance in the type and level of depth for the terms included across the different SMQs.

Insight into the differences between partially overlapping SMQs with similar names is provided by comparing three SMQs for kidney disorders: *Acute renal failure*; *chronic kidney disease (Broad)*; and *Renovascular disorders*. Both of the first two SMQs include terms capturing laboratory abnormalities

such as the PT *Blood creatinine increased*, while the *Renovascular disorders* SMQ does not. However, *Renovascular disorders* captures imaging abnormalities such as the PT *Arteriogram renal abnormal* and the PT *Renal scan abnormal* not found in the first two SMQs.

These differences are explained in the inclusion/exclusion criteria for each SMQ. The *Acute renal failure* SMQ "is focused on the sudden, reversible failure of kidney function. Terms for prolonged reactions are excluded" (e.g., *focal glomerulosclerosis*, which occurs when scar tissue forms in some glomeruli in the kidney; and conditions in which loss of kidney function occurs over weeks to months (*proliferative glomerulonephritis, rapidly progressive glomerulonephritis*). The aptly named *Chronic renal disease* SMQ includes events outside of the 'acute' time window as well as therapeutic procedures associated with chronic kidney disease. In contrast, the *Renovascular diseases* SMQ focuses on disorders that "can result in renal dysfunction, usually evidenced by high plasma renin levels,"[8] and thus includes events such as renovascular hypertension and renal artery stenosis, which are not included in the other two SMQs. The Broad category of this SMQ includes imaging terms such as *Arteriogram renal abnormal* and *Renal scan abnormal.*

7.2.3: Hierarchical SMQs:

Much like MedDRA itself, a number of SMQs have a hierarchical structure. Each sub-SMQ can be searched individually. An example of nested SMQs would be that for *Hepatic disorders,* which includes the subordinate SMQs of *Congenital, familial, neonatal and genetic disorders of the liver, Drug related hepatic disorders - comprehensive search, liver-related investigations, signs and symptoms,* and *Liver-related coagulation and bleeding disturbances*. In addition, the sub-SMQ of *Drug related hepatic disorders - severe events only*, includes four SMQs, *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, Hepatitis, non-infectious, Liver neoplasms, benign (in cysts and polyps),* and *Liver neoplasms, malignant and unspecified.* The last of these are further sub-divided into SMQs of *Liver malignant tumors* and *Liver tumors of unspecified malignancy.* This allows for searches in any of the overarching SMQs as well as more specific searches by using the subordinate SMQs as appropriate.

7.2.4: Algorithmic SMQs:

Another SMQ search approach uses defined algorithms to refine queries for certain medical concepts. With algorithmic SMQs, broad terms are divided into categories and may be weighed to indicate relevancy. Algorithmic categories can be grouped by terms for laboratory values or signs and symptoms as is done for the *Acute pancreatitis* SMQ algorithm. Category A terms encompass those included in the narrow SMQ. Broad terms for *Acute pancreatitis* are grouped into Category B, consisting of PTs related to laboratory values, and Category C, with terms consisting of signs, symptoms, and diagnoses. The algorithmic SMQs were developed to provide more sensitivity than a narrow hierarchical search and

more specificity than a broad hierarchical search. Currently, the data included in algorithmic SMQs are limited to PTs for symptoms and diagnoses, including those of abnormal laboratory or other testing. To date, MSSO hasn't directly incorporated laboratory values or other data as is done with algorithmic FMQs discussed below.

7.2.5: Accessing SMQs:

In summary, SMQs are a useful tool to group MedDRA PTs. As of MedDRA v27.1, 110 SMQs are in production. Following their initial release, SMQs are maintained by the MSSO to reflect changes in MedDRA at each version release. Additional SMQs may be requested from MSSO, and if approved will be developed as the need arises and implemented with the next version release. The official MedDRA SMQ website (https://www.meddra.org/standardised-meddra-queries) provides the SMQ Matrix files along with links to training. The *Introductory Guide for Standardized MedDRA Queries (SMQs)*, found under "Support Documentation," provides in-depth information about design concepts, definitions, implementation, and specific SMQs. MedDRA subscribers can access MedDRA through either the MedDRA Web-based Browser or a downloadable desktop browser. Both browsers allow for SMQ search capability and use of the SMQ Analysis Tool. The MedDRA official website provides additional overview and guidance documents.

A change request process is available for SMQs. However, the time and effort required for new SMQs to be developed, validated, and approved is extensive. Despite this, we encourage full engagement from all users of SMQs to suggest updates to existing SMQs and to suggest new SMQs as needed. Use of an alternative grouping or custom grouping may be required while the change request is in the process of review.

7.3: FDA Medical Queries:

To improve safety signal detection, the FDA has developed over 100 groupings of PTs known as "FDA Medical Queries" (FMQs), which are focused on commonly labeled drug reactions, including those that are non-serious, as well as medically important but less common reactions that historically have been known to be related to drug exposure [9]. The FDA is uniquely positioned to create these groupings, since they have the ability to analyze data submitted from numerous clinical trial sponsors over time. These FMQs were developed pragmatically, drawing from experience analyzing real data from global clinical trials across numerous sponsors. FMQs are intended to capture medical conditions that may be reflected by dozens or even hundreds of PTs, to streamline the analyses that are needed to explore and understand the safety data, and to reduce the development burden on sponsors. For instance, to understand the overall frequency of insomnia in a clinical trial, the FMQ Insomnia was developed, which includes PTs such as "*Initial insomnia*," "*Middle insomnia*," and "*Early morning awakening*." These PTs,

along with others, need to be combined during safety analyses if one wants to understand the occurrence of insomnia during a trial.

7.3.1: FMQ Structure and AE Terms:

The vast majority of AE terms within the FMQs are current or former PTs. During the development of FMQs, MedDRA versions 7.0 through the current version were searched and all terms meeting the FMQ Ground Rules (see Section 7.3.2) were added. Therefore, the current FMQ version can be applied to trial data that uses any version of MedDRA since version 7.0. In addition, AEs that have been submitted to the FDA as coded terms from sources other than MedDRA have also been included in the FMQs, including misspellings. This was done to enable the use of FMQs on the widest possible range of clinical trial datasets. The FMQs are to be updated yearly with each major release of MedDRA and may also be updated at other times as needed. Feedback concerning FMQs can be directed to the FDA (ONDBiomedicalinformatics@fda.hhs.gov).

7.3.2: FMQ Ground Rules:

Ground Rules were created to help maintain consistency in the application of medical judgment to the creation of AE groupings (see Table 2).

Table 2: Ground Rules for FDA Medical Queries

Narrow	Broad
1. PTs that are near synonyms of the FMQ concept. Example: PT *Abdominal discomfort* in FMQ Abdominal Pain 2. PTs are subgroups of the FMQ concept. Example: PT *Anemia neonatal* in FMQ Anemia 3. PTs that specify an etiology for the FMQ concept. Example: PT *Uraemic pruritus* in FMQ Pruritus 4. PTs that ensure the occurrence of the FMQ concept. Example: PT *Aortic rupture* in FMQ Hemorrhage	1. PTs that may result in the FMQ concept. Example: PT *Osteopenia* in FMQ Osteoporosis 2. PTs that provide laboratory, radiologic, or other diagnostic test results reasonably suggestive of an FMQ, including PTs with ambiguous results such as "abnormal." Example: PT *Troponin I increased* in FMQ Myocardial Infarction 3. PTs reasonably suggestive of the FMQ concept, but not required by the FMQ concept. Example: PT *Bronchospasm* in FMQ Hypersensitivity 4. PTs that indicate a "carrier" status for FMQ concepts that specify an infectious disease. Example: PT *Bacterial disease carrier* in FMQ Bacterial Infection

Source: https://www.fda.gov/media/164639/download

The Ground Rules distinguish between two types of AEs within an FMQ, i.e., "Narrow" and "Broad." The Narrow terms are intended to be highly specific for the medical condition, such that if the AE occurred then the medical condition indicated by the FMQ occurred with a high degree of certainty (i.e., at least 90% probability). The Broad category "casts a wider net" as it includes all Narrow terms plus additional terms that are not as specific as the Narrow terms but provide reasonable assurance that the FMQ concept occurred (i.e., with at least 30% probability). During the process of assigning AEs to FMQs, it was typically difficult to quantify specific likelihoods for which an AE might indicate that an FMQ concept occurred. However, the critical element of the standard for a Broad FMQ is that there needs to be substantially more than a theoretical possibility that if the AE occurred then the medical condition addressed by the FMQ occurred. The Broad category is not anticipated to lead to regulatory determinations about a medical product's safety or changes in labeling but may be the basis for initial signal detection activities or requests for additional information.

In addition to the Ground Rules used to identify Narrow and Broad AEs, rules were also used to exclude AEs that were unlikely to be helpful in safety signal detection:

1. PTs that are neither a required component nor reasonably specific for the FMQ concept. Example: PT *Nausea* would not be included in FMQ Migraine.
2. PTs that provide the names of laboratory, radiologic, or other diagnostic tests without a result (example: PT *Clostridium test*). PTs that provide test names without a result, but that would only be performed in the presence of disease, should be included if they otherwise qualify (example: PT *Antipsychotic drug level* in FMQ Psychosis).

7.3.3: Algorithmic FMQs:

Algorithmic FMQs have been developed for four medical conditions: rhabdomyolysis, hyperglycemia, hypoglycemia, and hypersensitivity. These FMQs contain Narrow and Broad AEs similar to other FMQs, but also use combinations of AEs, laboratory data, concomitant medications and temporal association to make better use of the clinical trial data in identifying safety signals [9]. The algorithms use the co-occurrence of otherwise less specific AEs to enable the identification of the medical condition of interest that were not identified during the trial. Likewise, combining laboratory data and AE data is expected to provide a more comprehensive view of the AEs that are occurring during a trial. For example, a case of 'Rhabdomyolysis' is identified algorithmically as one with any of the following:

- Any Rhabdomyolysis FMQ Narrow term
- Urine myoglobin >ULN

- CPK >5 x ULN AND NO (CPK-MB/CPK >0.05 with start date within 3 days OR CPK >ULN at baseline)
- [PT Myalgia + PT Muscular Weakness + (PT Myoglobin Urine Present OR PT Chromaturia)] with start date within 7 days

7.4: Custom AE Queries:

At times, a STOI is not included in the current SMQs or FMQs, or the existing definition needs to be modified to fit current observations. After reviewing the relevant SMQs and FMQs, if none is suitable, developing a custom AE query may be appropriate. In general, custom queries should be created only when no current standard query (e.g., SMQ, FMQ) captures the medical condition. Comparisons across clinical trials can be highly problematic due to differences in the populations studied, and variations in safety data capture, analysis, and display. Data interpretation is even more challenging if the queries from different studies comprise different lists of terms. One benefit of creating a pre-defined custom AE query where no standard query exists, is to produce alignment across a program or organization in the approach to identify that medical condition, particularly when the medical concept represents a shared STOI

If any modifications are made to an SMQ or FMQ, the search should be considered a custom query and must be given a new name [8,9] and may no longer be called an SMQ or FMQ.

- Custom AE queries should not be created solely to remove “irrelevant” population-specific terms (such as “neonatal”). Events not found in a study population will not appear in tables as PTs with no events are not listed.
- Modification of standard queries by exclusion of PTs considered unrelated to the topic is typically inadvisable and interferes with full transparency. If necessary, summaries for any subgroup of the query can be created post-hoc to facilitate risk assessment or risk communication but should continue to indicate which PTs were excluded and the rationale for exclusion.

Disadvantages of custom AE queries include lack of recognition by regulatory authorities, a possible appearance of bias in creation, the need for full and ongoing documentation, and the need to update the custom query with each new MedDRA version.

Like SMQs and FMQs, custom AE queries typically comprise a list of PTs indicative of or predictive of the medical condition. Best practices gleaned from the experiences of the authors include:

- Involve clinicians with subject matter expertise from relevant therapeutic area(s) in creating a custom AE query and for subsequent updates.
- Document the reason for creating a custom AE query and provide an evidence-based definition of the medical condition, with references. If a newly defined concept, provide details.
- When developing a custom query for a STOI that will be applied across multiple datasets, review the appropriate MedDRA categories to create a comprehensive list of PTs that includes all terms relevant to the medical concept.
- To start designing a custom AE query for a medical concept that isn't covered by standard queries, if the safety concern arises from an ongoing clinical trial, review the data to start a draft list of terms. This type of list should only be used for the dataset on which it was created.
- Develop and document rules for inclusion and exclusion of PTs.
- Create AE queries at the PT level as these queries are used for the purpose of analysis, which is conducted at the PT level.
- When AE terms are removed from an existing standard query, clear documentation is particularly important.
- It is neither necessary nor appropriate to modify a current standard grouping to remove "irrelevant" terms (e.g. fetal PTs in an adult study), as such events will simply not appear in search results.
- Document a robust audit trail of changes over time and with each new MedDRA version.
- For full transparency, the complete list of included terms should be reported in regulatory submissions, with links to the list placed in the SAP, text, and tables.

Once the medical concept has been defined, the core process should be designed to ensure that the custom AE query identifies all relevant PTs. If the medical concept is similar to or contains an existing MedDRA grouping (e.g. one or more HLTs, or an overlapping SMQ or FMQ), it is usually most efficient to start with the existing list and add or delete as needed. A MedDRA Web-based browser search of the selected categories (https://tools.meddra.org/wbb/) provides the complete list of PTs, which can be exported into an Excel format for medical review. Review of existing data from a clinical program is limited to terms already reported and risks missing relevant new events as data accumulates.

Developing a custom AE query requires substantial care to be sure that all of the appropriate terms reflecting the medical condition are included. During a health authority review and/or inspection, custom AE queries are likely to come under more stringent inspection; detailed documentation is helpful. The necessary documentation fits well within the ASAP or similar process [4], which should be maintained throughout development.

Documentation of a custom AE query is separate from the statistical analysis plans for individual clinical study reports (CSRs) and integrated safety analyses. The ASAP or ASAP-like document should capture the name and version of each AE grouping used in the program, the rationale and definition for the medical concept that each is intending to capture, and the subcategories used (i.e., Narrow, Broad or SMQ subcategories). Occasionally, as the understanding of a new medical condition being observed in a development program changes, the list of PTs used to define that medical condition may need to be updated. If this happens, detailed documentation of the evolving understanding of the medical concept and the rationale for changes to a custom AE query are key.

Like standard queries, custom AE queries will need to be reviewed and maintained with each MedDRA dictionary update. Documentation of each version should include the list of terms, a description of the development process, and the processes to evaluate MedDRA upgrades and ensure that results are reproducible throughout the development lifecycle. The Sponsor will be solely responsible for maintenance and documentation of such queries. A typical update process would include:

- Oversight by a Subject Matter Expert (typically, Global Safety personnel or a Safety Advisory Committee comprised of individuals with clinical expertise)
- Identification of impacted MedDRA PTs
- Medical review of any PT changes that impact the custom list, with additional clinical assessment as necessary
- Documentation of the updates and the rationale for the updates (or lack of update)
- Statistics assistance (providing review tools and updating the ASAP or ASAP-like document)
- Entry of the updated custom AE query and the grouping flag in the Analysis Dataset Model (ADaM) dataset by Data Management/ Programming.

For medical concepts that could occur with more than one product, Sponsors are requested to consider recommending the custom AE query to the MSSO/FDA for inclusion in their groupings.

7.5: MedDRA Labeling Groupings:

Many would like to have AE groupings that could be used in product labeling, to simplify risk communication to clinicians and participants. However, at this time no organization has developed and validated groupings for this purpose. The Council for International Organizations of Medical Sciences (CIOMS) is an international non-governmental organization with a mission to "...advance public health through guidance on health research and policy including ethics, medical product development and safety." (https://cioms.ch) Among other activities, CIOMS has supported the work of the MedDRA Labeling Group (MLG) Expert Work Group (EWG), which has pursued the development of MLGs. This

Work Group has defined MLGs as groupings of near-synonymous MedDRA PTs which are intended to provide accurate and consistent presentation of adverse reactions and enhance safety communication to healthcare providers via the product label.

The EWG recommends the following principles for the development and use of MLGs to improve the clarity of safety information in product labels:

1. MedDRA PTs that convey substantially similar clinical concepts should be combined into MLGs when presented in product labeling.
2. The process of grouping PTs into MLGs should not result in the loss of clinically meaningful safety information.
3. The use of MLGs, while recommended, should be voluntary.
4. The content of MLGs, when used publicly, should be specified in order to ensure transparency.
5. The use of MLGs is intended to foster international harmonization in a manner consistent with existing regulatory frameworks.
6. MLGs should be made easily accessible and widely available to ensure transparency and consistency.

Of note, MLGs would not be intended to be used for safety signal detection or to alter the approach to safety data analyses. The EWG believes that the above principles will most likely be achieved if a single organization with broad representation from multiple relevant stakeholders takes on the role of MLG development and maintenance (ref to new article to be released shortly).

7.6: Summary and Comparison of AE Queries:

SMQs and FMQs, which are available to all members of the pharma research community, were both developed by expert committees and tested on global datasets, but with somewhat differing approaches to defining the specified medical conditions. Comparison suggests some common best practices and cautions for creation of any other AE groupings. Both SMQs and FMQs comprise lists of MedDRA PTs grouped into narrow and broad subcategories which provide two levels of specificity and sensitivity for the medical condition in question. One practical advantage to using an SMQ or FMQ is that little new documentation is required beyond recording the name and version number in the planning document and resulting tables. Rules for inclusion and exclusion of terms in both SMQs and FMQs are published. Both will be maintained and updated following updates to the MedDRA dictionary. The authors of both SMQs and FMQs provide files to facilitate programming of SMQ or FMQ tables. Medical conditions covered by either an SMQ, an FMQ, or both are listed in Appendix 1 (under revision, will be circulated separately).

When choosing a specific query to represent 'all cases' of a medical condition, the PTs included must be reviewed. A given SMQ and FMQ with the same or similar names may differ in the actual medical condition represented. For instance, The SMQ 'Taste and Smell Disorders' contains almost all of the terms in the FMQ 'Dysguesia' but also contains terms related to loss of smell; there is no FMQ related to abnormal smell. Often, the approach to categorization between the two is simply different: FMQs categorize many infections according to type of agent (e.g. bacterial, fungal, viral, etc.) but also provides 'Nasopharyngitis', while SMQs generally categorize infections by affected organ (ocular, urinary tract, etc.). Both queries include 'Opportunistic infections', but the FMQ focuses on "infections associated with immunocompromise" and excludes "infections known to commonly occur in immunocompetent individuals" such as genital herpes simplex virus infection. In contrast, the SMQ includes a comprehensive list of unusual pathogens, infections at unusual sites and pathogens listed in prevention guidelines for immunocompromised participants.

Narrow groupings typically contain the terms that are most closely associated with the medical condition and are best suited for evaluating a signal and informing labeling. Use of the Broad groupings, which include the Broad and Narrow categories together, is more exploratory and sometimes contentious. Queries using the Broad PT list will retrieve cases where only symptoms were reported, or where a diagnosis may have been uncertain; consequently, Broad searches will also retrieve cases with the same symptom caused by a different medical condition (e.g., cough from asthma vs. from pneumonia). Given their lower specificity, the combined Broad categories are most useful as hypothesis-generating queries for evaluating a potential signal but are not likely to be the basis for regulatory decision-making. Use of the Broad categories requires medical review of the serious cases retrieved to adjudicate whether they represent the medical condition of interest and should be included. Adjudication decisions should be documented. Alternatively, learnings from review of a Broad PT search can inform additional assessments of other relevant product safety data.

Thus, when selecting the most appropriate AE grouping for a safety topic related to a particular product and population of participants, careful review of the relevant standard groupings is needed. In addition, clear documentation of the grouping selected must be present in every regulatory submission. As standard groupings are updated, the version used must also be provided in any analysis or summary. If one or more custom AE queries are created, consistent and transparent naming conventions are important to communicate which MedDRA version was used. Additionally, when possible, defining the grouping(s) used a priori is an important aspect to minimize bias and ensure integrity of analyses. It is important to recognize that the SMQs and FMQs were developed after years of extensive work by medical experts and utilization of these pre-defined groupings is recommended as compared to a custom grouping. However, developing custom groupings for a topic of interest when an SMQ or FMQ

does not exist is an appropriate approach.

8: Analysis, Presentation, and Interpretation of AE Queries:

Well-documented AE groupings provide consistent and aligned definitions across studies for combined analysis. In early development, the focus of analysis is typically signal detection and characterization. When an AE Query appears to show an imbalance across treatment arms, assessing the individual AE terms within the query to determine what is driving the imbalance is key. As the treated population grows during development, the focus of analysis often shifts to quantifying and monitoring risk, exploring defined populations, and communicating these results. Signal detection and risk monitoring continue after approval.

8.1: Analysis, Presentation, and Review of AE Queries:

Much like standard AE tables, data sources for AE queries can include a single study with one or more treatment arms, or multiple studies with a variety of designs. Analysis of AE query results requires the same care and considerations in designing table and figures and can use similar presentations. Although data from separate studies are usually reviewed in parallel in early development, analyses of STOI and submission data often pool data from similar studies. While details of pooling strategies are beyond the scope of this paper, in general, data to be integrated across studies should be in the same MedDRA version. Therefore, prior to analysis, both the AE datasets and each AE query analyzed should be upcoded to the most recent version of MedDRA. When pooling data from multiple studies, meta-analytic methods are needed [10, 11].

The choice of query type (Narrow or Broad) is based on the purpose of the analysis. The Narrow component of an AE query is most specific, while the Broad queries are designed to retrieve cases with the same symptom caused by a different medical condition. Analyzing the individual AE terms within either type of query is key to determine what is driving any imbalance. Even the Narrow component of an AE Query may contain distinctly different diagnoses, given the granularity of MedDRA and the uncertainty associated with many medical diagnoses.

Furthermore, individual PTs that might be considered unlikely to be caused by medications can be informative to include in a query (e.g. including Alcoholic pancreatitis in a Pancreatitis query). For instance, participants with high alcohol use may be more susceptible to pancreatitis when exposed to certain medications, even though pancreatitis is also commonly caused by alcohol use disorder. Excluding these events risks missing signals of an interaction.

Therefore, tables presenting the results of an AE query should show both the overall summary and the

individual PTs sorted by decreasing risk difference (or risk ratio), as demonstrated in Table 37 from the September 2022 FDA standard tables and figures document [12] and Table 12.8 from the PHUSE AE white paper [13]. This approach highlights PTs with the largest imbalance in frequency, allowing rapid elimination of categories and terms where there is no meaningful increased risk. Throughout a development program, in addition to reviewing analyses of AE queries, it is key that each individual PT be reviewed for imbalances indicating a safety signal. In general, a rolled-up summary of totals for each FMQ, without review of the contributing PTs, will not provide adequate detail about the safety profile.

When the output of an analysis using an AE grouping shows an imbalance among groups or a medically concerning frequency of a specific medical condition, a case listing should be created to aid in review. Depending on the topic, specific laboratory results or other findings will be particularly useful to the reviewing clinicians, who should collaborate in the design of listings. Listings of individual subject data are particularly important for nonserious PTs, where information is limited to that collected at routine study visits.

When an AE Query appears to show an imbalance across treatment arms, reviewers need to assess the individual AE terms within the query to determine what is driving the imbalance. For instance, the imbalance may be entirely due to one or two AEs. In that case, it may be most appropriate to consider those specific AEs to be adverse reactions, rather than concluding that the FMQ concept they reside in is the adverse reaction. At the opposite extreme, when many terms all show a slight imbalance, the FMQ concept best represents the identified safety concern, as the individual terms only become concerning when they are combined. As with other safety analyses, assessing imbalances is only one of the important considerations when assessing causality. For each event, one should also assess other factors, such as temporal relationship, evidence of a dose-response, biologic plausibility, concomitant medications, known effects with other drugs in class, and consistency with nonclinical findings.

8.2: AE Queries for Safety Monitoring in Early Development:

During the conduct of clinical trials, ongoing safety monitoring is mandated to identify, quantify and characterize unexpected effects of the investigational drug on patients [2]. Early in development, when there is limited safety data available, aggregate analysis of standard AE tables allows a comprehensive review for imbalances in AE frequency and identifies topics where an appropriate AE query could be useful. At this stage of development, treatment arms may vary in unexpected and non-random ways. Early aggregate analysis can confirm both signals and risks to data collection or quality. This analysis may provide the chance to improve ongoing data capture processes or identify poor tolerability that can be addressed with changes in drug dosing. For example, when an AE Query appears to show an imbalance across treatment arms, assessment of individual AE terms within the query may identify a safety signal –

or it may identify correctable differences among sites and regions in AE reporting processes resulting from study conduct logistics (e.g. early, low-dose cohorts were enrolled at sites with specialist investigators, while higher-dose cohorts enrolled at sites managed by general practitioners who used different verbatim terms for the same medical condition). This analysis helps to further define STOI.

At this stage in development, data presentations that allow the safety team to easily review accumulated AE and laboratory data in parallel, across the whole study population and according to dose level, significantly strengthen signal detection, compared with the review of data from individual participants. Review of all individual PTs combined with review of the summary of totals for each Narrow FMQ or SMQ could perhaps serve as an initial screening for a signal; this approach has not yet been widely tested and would require resources for programming. The value of a rolled-up summary of FMQs or SMQs that includes the broad terms for each grouping is questionable, given the low specificity.

8.3: AE Queries for Safety Topics of Interest:

Safety Topics of Interest (STOIs), which are identified during development and commonly overseen by a safety management team (SMT), have the potential to drive the benefit risk profile of the product and typically warrant additional data collection or analyses beyond that which is routine for all AEs. Aligning within the SMT on the list of STOI and how they will be identified during the course of clinical development (and in the post-marketing setting) is a vital aspect of safety planning. Without such planning, misalignment in approach across various studies and/or indications may impair the ability to integrate the safety data at submission for approval and lead to inconsistent safety messaging.

While STOI may be identified based on preclinical or clinical data, the product's mechanism of action, or data from other members of the product class, operationally STOIs can be defined by a standard or custom AE query. Certain STOI represent common concerns in drug development (e.g. liver injury) or for the population (e.g. suicidal ideation in participants with psoriasis). Additional STOIs may be identified during development when an event appears more frequently than anticipated, when a Data Monitoring Committee recommends closer surveillance, or when Sponsor wishes to collect specified information regarding tolerability or participant management. Whenever possible, the AEs applicable to an STOI can be identified for analysis using an appropriate FMQ or SMQ; if there is no standard grouping for the topic, development of custom AE queries is detailed in section 7.4.

All AE queries used to define STOIs should be documented in the ASAP for use at the product level (the level used for a Development Safety Update Report), whether using an FMQ, SMQ, or custom AE query. When a signal is first identified, the inclusion of less-specific terms, typically seen in 'Broad' groupings,

enhances the ability to formulate hypotheses on what is leading to an apparent association of the medical condition with product administration and to identify the information needed to further evaluate those hypotheses. In this approach, the Broad query may be used to cast a wide net of potential cases of interest, followed by medical review in which cases are adjudicated against pre-specified criteria. When sufficient evidence has concluded a casual association with the product and the STOI has become an identified risk, the Narrow search criteria typically provide a more appropriate characterization of the product safety profile.

> *In a hypothetical example, assume preclinical findings led pancreatitis to be listed as an STOI. Initially, the "Pancreatitis" Broad FMQ is chosen for signal detection and evaluation purposes for the ongoing clinical trials and is listed in the ASAP. Including the additional terms identifies valid cases where only a laboratory abnormality PT was provided. Including 'Alcoholic pancreatitis' permits review of the impact of study drug administration on this baseline risk. Careful evaluation throughout development supports a causal association specifically with autoimmune pancreatitis, without altering the risk of alcoholic pancreatitis. Eventually, selected PTs representing autoimmune pancreatitis are agreed upon to calculate the adverse reaction rate. This example emphasizes that the ASAP is a "living" document, the content of which evolves over time as the knowledge of the product safety profile grows.*

If the custom AE query for an STOI is narrowed due to evidence-based research, the rationale and resulting PT list should be well-documented. All changes should be documented in the ASAP, which becomes an archive for safety planning, data collection, evaluation, and reporting. The STOI process should include details of safety data collection, analysis and communication as well as identifying safety knowledge gaps that remain to be addressed. Communicating with regulatory authorities in advance regarding custom AE queries for an STOI is recommended to avoid unnecessary ad hoc analyses.

Signal evaluation activities for an STOI typically include: 1) detailed individual case review for event details, risk factors, completeness, and accuracy of information; 2) case series analyses to evaluate any notable patterns in the events reported; 3) estimation of the event rate and comparison with the anticipated rate for the population. Aggregate safety assessment using AE queries is particularly important for events known to occur in the participant population regardless of drug exposure, as investigators may use a variety of terms to describe such events.

8.4: AE Queries in Clinical Trial Reports and Regulatory Submissions:

Authors of the PHUSE AEs white paper [12] advocated for the use of additional AE groupings beyond the MedDRA hierarchy for general safety in integrated submission documents. With the addition of FMQs to

SMQs, currently approximately 300 medical conditions are described by standard AE queries (Appendix 1). FDA has indicated that during review of a submission, reviewers are provided with tables listing the data for all FMQs. Sponsors wishing to understand how the FDA will evaluate data prior to finalizing their submission may wish to follow a similar approach.

During the later stages of clinical development, aggregate analyses should cover known safety risks, while allowing flexibility to add analyses when unexpected new potential risks are identified. Defined AE queries such as SMQs and FMQs provide consistency in retrieving cases for the subsequent medical review and/or adjudication. In this setting, narrow AE queries typically capture the aspects of signs, symptoms, and laboratory findings as well as diagnoses associated with a specific medical condition. As FMQs and SMQs may not cover every medical condition, sponsors may still need to decide whether to define a custom query. A robust ASAP or structured safety review process provides a framework for generating hypotheses about such observations, estimating risk differences, and developing efficient management plans.

Debate remains on whether and how analyses of AE queries can/should be created for individual study CSRs. Providing tables for important identified and potential risks in both CSRs and integrated submissions documents is likely warranted. All MedDRA PTs are available in general safety tables, so additional AE query tables are most useful to support the writers in communicating the details of an STOI. Otherwise, summary tables can be reserved for integrated submission documents.

9: Recommendation:

1. Whenever possible, use a standard AE query (e.g. SMQ or FMQ) instead of creating a custom AE query. It is not necessary to remove terms that do not apply to the population under study (e.g. pediatric or neonatal PTs in an adult study).
2. The definition and contents of a standard AE query should be reviewed to determine whether it meets the needs of the program, as queries with similar titles may have been created with quite different rules.
3. Any modification of a standard AE query constitutes a custom query and must be given a new name, even if only a small number of terms are changed.
4. For most applications, the Narrow FMQ or SMQ is most specific and adding the Broad terms adds little, as long as the Narrow query is aligned with the medical condition.
5. The Broad FMQ or SMQ, which includes the Narrow terms, could be useful during clinical development to detect a subtle signal, but can introduce noise, as it is less specific.
6. The Broad FMQ and SMQ are defined as including both Narrow and Broad terms; therefore,

terms in the Broad categories should not be used without those in the Narrow category.

7. If a custom AE query is necessary, it is strongly recommended that it be fully documented (preferably in the ASAP), including definition of the medical concept, list of included terms, MedDRA version, rationale, and audit trail for modifications during development, and an audit trail of changes due to MedDRA updates.
8. We recommend that a new custom AE query should be evaluated by reviewing all relevant terms in MedDRA. Changes to a custom query must be fully documented.
9. Adding standard or custom AE queries to an interactive safety review tool can be very helpful to inform ongoing safety reviews.

10: Conclusion:

AE groupings such as SMQs and FMQs, which are based on pre-defined medical conditions with known biologic mechanism(s), enable consistent analysis and review to characterize the safety profile of products in clinical trials with increasing accuracy during the course of development. When possible, we recommend using a published grouping such as an FMQ or SMQ. Where both an FMQ and SMQ are available, we recommend detailed review, as the rules for inclusion of terms may differ.

FDA has indicated that in many divisions FDA medical reviewers will receive all FMQs routinely, from internal programming resources, during evaluation of new drug applications (https://www.fda.gov/media/164639/download). The FDA does not mandate that sponsors provide either FMQs or SMQs as routine practice with such applications. Custom queries, which may be necessary if no FMQ or SMQ describes the medical condition, must be documented in full and maintained following MedDRA upgrades. All edits to a published grouping are considered a custom AE query.

For general safety/signal detection purposes (as opposed to use for specific safety topics of interest), the routine use of broad FMQs and/or SMQs is controversial, given the burden of a priori creating and reviewing the large volume of resulting data. While we recommend the routine use of narrow FMQs for general safety/signal detection purposes in integrated submissions, we do not believe the review of all broadly defined groupings is required to ensure a thorough assessment of safety. However, their inclusion in interactive safety review tools to enable such a review (in full or in part) seems warranted.

For sponsors that currently don't define AE queries a-priori, adding FMQ-based tables would be additional work; these sponsors may have difficulty understanding the value. However, an inherent advantage is that FMQs are already defined, maintained by the FDA, and much easier to implement than

the development of a custom AE query. For sponsors with an efficient creation and maintenance process for AE queries beyond the MedDRA hierarchy, transitioning to FMQs instead of their sponsor-defined queries might be a difficult decision. For sponsors that include a priori defined AEs queries, but without an efficient creation and maintenance process, FMQs will likely be considered a gift.

11: Disclaimer:

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members; respective companies/organizations or Regulator's views or policies. The content in this document should not be interpreted as a data standard and/or information required by Regulatory Authorities.

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15: Appendix 1:

The specific Preferred Terms included in standard queries with similar titles should always be reviewed and/or compared prior to selecting that query (Section 6.4 and Recommendation #2). The rules for inclusion in similar-sounding standard queries can differ significantly. Examples of categories with similar-sounding titles that include different PTs are shown below, along with examples of categories found in only FMQs, or only SMQs.

SMQs are structured hierarchically as shown.

Depression and Suicidality
- SMQs: Depression and suicide/self-injury
  - Depression (excl suicide and self-injury)
  - Suicide/self-injury
- FMQs: Depression, Self-Harm

Psychosis
- SMQs: Psychosis and psychotic disorders (*note: mania PTs classed in Broad, not Narrow*), Hostility/aggression (*note: PTs associated with psychosis classed as Broad*)
- FMQs: Psychosis, Mania

Confusion
- SMQs: <>
- FMQs: Confusional State (*confusional state, delirium, disorientation, etc. but not dementia diagnoses*)

Dementia
- SMQs: Dementia (*narrow terms include types of dementia, do not include confusional state, delirium, disorientation, etc.*)
- FMQs: <>

Drug Abuse
- SMQs: Drug abuse, dependence and withdrawal
  - Drug abuse and dependence
  - Drug withdrawal
- FMQs: <>

Stroke and TIA

- SMQs: Central nervous system vascular disorders
  - Central nervous system haemorrhages and cerebrovascular conditions:
    - {Ischaemic central nervous system vascular conditions,
    - Haemorrhagic central nervous system vascular conditions}
  - Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic
- FMQs: Stroke and TIA

CNS Vascular Pathology, Inflammation and Symptoms

- SMQs: Central nervous system vascular disorders
  - Central nervous system haemorrhages and cerebrovascular conditions:
    - {Conditions associated with central nervous system haemorrhages and cerebrovascular accidents}
- FMQs: <>

Cardiac Ischemia

- SMQs: Ischaemic heart disease
  - Myocardial infarction
  - Ischaemic heart disease
- FMQs: Acute Coronary Syndrome, Myocardial Ischemia, Myocardial Infarction

Cardiac Arrhythmias

- SMQs: Cardiac arrhythmias
  - Arrhythmia related investigations, signs and symptoms
  - Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias):
    - Bradyarrhythmias (incl conduction defects and disorders of sinus node function): {Bradyarrhythmias; Conduction defects; Disorders of sinus node function; Bradyarrhythmia terms, nonspecific}
    - Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias): {Supraventricular tachyarrhythmias; Ventricular tachyarrhythmias; Tachyarrhythmia terms, nonspecific}
    - Cardiac arrhythmia terms, nonspecific
  - Congenital and neonatal arrhythmias
- FMQs: Cardiac Conduction Disturbance, Arrhythmia, Tachycardia

Abnormal uterine or menstrual bleeding

- SMQs: <>
- FMQs: Abnormal Uterine Bleeding, Decreased Menstrual Bleeding

Hearing disorders

- SMQs: Hearing and vestibular disorders
  - Hearing impairment
  - Vestibular disorders
- FMQs: Vertigo (*note also a partial overlap with Dizziness*); no FMQ for hearing loss

Paresthesia

- SMQs: <>

- FMQs: Paresthesia

Thrombosis

- SMQs: Thrombophlebitis (*note: deep venous thrombosis is in Broad*)
- FMQs: Thrombosis, Thrombosis Arterial, Thrombosis Venous