

Standardised MedDRA Queries (SMQs): Programmers Approach from Statistical Analysis Plan (SAP) to Analysis Dataset and Reporting

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ABSTRACT

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term level that relate to a defined medical condition. SMQ information is provided by MedDRA in the form of SMQ files (SMQ_LIST, SMQ_CONTENT) and Production SMQ Spreadsheet. One of them should be used to create look-up table/SAS dataset which will be merged with adverse event dataset to derive SMQ information in analysis dataset which will be further used to do reporting. Now the question is how this SMQ information has to be implemented at study level - how many SMQs will be involved? Is Customized Query also involved? Which reports should be generated based on SMQ? Answer to these questions can be found in SAP.

In this paper all the topics have been covered step by step with examples that will help even novice programmer to understand and implement SMQ at study level. First basics of SMQ (Narrow and Broad Scope, SMQ Category, Algorithm Search, Hierarchical Structure) has been explained. Then detailed guideline has been mentioned how a programmer can create look-up table from SMQ Spreadsheet or SMQ files. Then variables capturing details of SMQ as per Occurrence Data Structure (OCCDS) version 1.0 has been explained. Then scenarios have been explained which will help a user to decide if he needs to use Standardized MedDRA Query or Customized Query or both? At last, example of SAP is shown which will explain how to decode SAP along with SMQ implementation at analysis dataset (ADAE) and reporting level.

INTRODUCTION

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, 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. In this paper, Several SMQ examples have been shown in the form of figures and tables, all of them are based on version 22.0 of MedDRA.

DESIGN CHARACTERISTIC OF SMQ

Understanding basic structure of SMQs includes below topics.

- Narrow and Broad Scope
- SMQ Category
- Algorithm Search
- Hierarchical Structure

NARROW AND BROAD SCOPE

SMQs may have a mixture of very specific terms and less specific terms that are consistent with a description of the overall clinical syndrome associated with a particular adverse event and drug exposure. This approach accommodates those instances in which a user may need to identify cases that are highly likely to represent the condition of interest (a “narrow” scope) and those instances in which a user seeks to identify all possible cases, including some that may prove to be of little or no interest on closer inspection (a “broad” scope). A “broad” search includes both the “narrow” scope terms and the additional “broad” scope terms. See Figure 1.

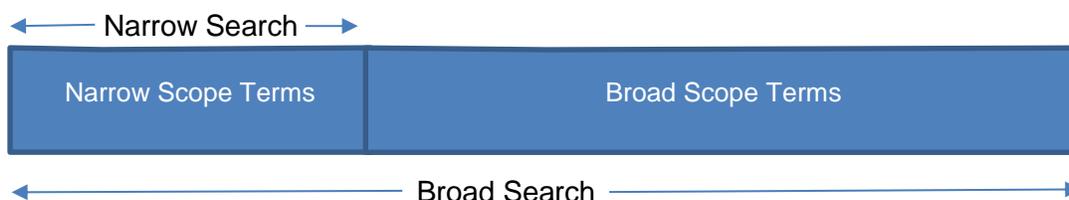


Figure 1. Narrow Search vs. Broad Search

Within an SMQ, all PTs are categorized either as Narrow or Broad scope. Figure 2 shows all the PTs available under Hypotonic-hyporesponsive episode (SMQ), one term is categorized as narrow scope and 20 terms are categorized as Broad scope. If SAP says to use narrow search, then only one PT has to be selected having narrow scope. Similarly, If SAP says to use Broad search, then all 21 PTs have to be selected having narrow scope or broad scope.

1	2	3	4	5	6	A	B	C	D	E
-	7415	Hypotonic-hyporesponsive episode (SMQ)								
.	7416		Narrow	A	Hypotonic-hyporesponsive episode	10021121				
.	7417		Broad	B	Hypotonia	10021118				
.	7418		Broad	B	Hypotonia neonatal	10021119				
.	7419		Broad	C	Altered state of consciousness	10001854				
.	7420		Broad	C	Depressed level of consciousness	10012373				
.	7421		Broad	C	Hypokinesia	10021021				
.	7422		Broad	C	Hypokinesia neonatal	10021022				
.	7423		Broad	C	Hyporesponsive to stimuli	10071552				
.	7424		Broad	C	Loss of consciousness	10024855				
.	7425		Broad	C	Neurogenic shock	10058119				
.	7426		Broad	C	Presyncope	10036653				
.	7427		Broad	C	Procedural shock	10080894				
.	7428		Broad	C	Shock	10040560				
.	7429		Broad	C	Shock symptom	10040581				
.	7430		Broad	C	Syncope	10042772				
.	7431		Broad	C	Unresponsive to stimuli	10045555				
.	7432		Broad	D	Cyanosis	10011703				
.	7433		Broad	D	Cyanosis central	10011704				
.	7434		Broad	D	Cyanosis neonatal	10011705				
.	7435		Broad	D	Pallor	10033546				
.	7436		Broad	D	Skin discolouration	10040829				

Figure 2. Hypotonic-hyporesponsive episode (SMQ)

SMQ CATEGORY

In SMQs broad search terms are divided into various Categories like B, C, D, etc. but narrow search terms are always Category A. For example, in Acute pancreatitis (SMQ), the broad search terms are grouped into two categories: Category B (a list of laboratory values) and Category C (a list of signs and symptoms). If analysis is needed for Acute pancreatitis (SMQ) based on signs and symptoms, then only records having Category C should be selected. See Figure 3 (Note that only sample PTs have been shown)

1	2	3	4	5	6	A	B	C	D	E	
-	552	Acute pancreatitis (SMQ)									
.	553		Narrow	A	Cullen's sign	10059029					
.	567		Narrow	A	Pancreatitis	10033645					
.	579		Broad	B	Hyperamylasaemia	10062770					
.	580		Broad	B	Hyperbilirubinaemia	10020578					
.	581		Broad	B	Hyperlipasaemia	10067725					
.	582		Broad	B	Lipase abnormal	10054821					
.	591		Broad	C	Abdominal distension	10000060					
.	592		Broad	C	Abdominal pain	10000081					
.	597		Broad	C	Acute abdomen	10000647					
.	598		Broad	C	Ascites	10003445					

Figure 3. Acute pancreatitis (SMQ)

ALGORITHM SEARCH

In addition to narrow and broad searches, for some SMQs an algorithmic search approach is available. This is a combination of search terms from various sub-categories of the broad search terms to further refine the identification of cases of interest compared to the broad search category. A typical example is Acute pancreatitis (SMQ) where the broad search terms are grouped into two categories: Category B (a list of laboratory values) and Category C (a list of signs and symptoms). The algorithm for Acute pancreatitis (SMQ) defines a case of interest as a record coded with either at least one term of Category A (narrow scope), or coded with a combination of at least one term of Category B AND one term of Category C. See Figure 3 (Note that only sample PTs have been shown). Algorithmic search is not available for all SMQs. Details of Algorithm can be found in Production SMQ Spreadsheet.

HIERARCHICAL STRUCTURE

Some SMQs are stand-alone query which contains no further sub-SMQs like Hypotonic-hyporesponsive episode (SMQ) shown in Figure 2, while other SMQs are a series of sub-queries related to one another in a hierarchical relationship. These consist of one or more subordinate SMQs that could be combined to create a superordinate. In some hierarchical SMQs, there are no separate "narrow" and "broad" categories within the subordinate SMQs (sub-SMQs).

User can utilize the facility of Hierarchical Structure for various scenarios. For example, a user may wish to apply the entire scope of the SMQ topic (e.g., the entire Hepatic disorders (SMQ) including all sub-SMQs) to retrieve all cases related to hepatic disorders in a database (See Figure 4 and Figure 5).

Any SMQ can have maximum 5 levels of hierarchy. Hepatic disorders (SMQ) is perfect example of the same.

1st level is Hepatic disorders (SMQ) which has 5 sub-SMQs at 2nd level shown in yellow color (Figure 4).

3rd Level has 4 sub-SMQs shown in green color (Figure 5).

4th Level has 4 sub-SMQs shown in pink color (Figure 5).

5th Level has 2 sub-SMQs shown in violet color (Figure 5).

1	2	3	4	5	6	A	D
-		6117	Hepatic disorders (SMQ)				
+		6118				Congenital, familial, neonatal and genetic disorders of the liver (SMQ)	
+		6149				Drug related hepatic disorders - comprehensive search (SMQ)	
+		6470				Hepatic disorders specifically reported as alcohol-related (SMQ)	
+		6477				Liver infections (SMQ)	
+		6555				Pregnancy-related hepatic disorders (SMQ)	

Figure 4. All sub-SMQs of Hepatic disorders (SMQ)

1	2	3	4	5	6	A	D	E	F	G	H	I	J	K
-		6117	Hepatic disorders (SMQ)											
+		6118				Congenital, familial, neonatal and genetic disorders of the liver (SMQ)								
-		6149				Drug related hepatic disorders - comprehensive search (SMQ)								
+		6150				Cholestasis and jaundice of hepatic origin (SMQ)								
-		6168				Drug related hepatic disorders - severe events only (SMQ)								
+		6169				Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)								
+		6270				Hepatitis, non-infectious (SMQ)								
+		6294				Liver neoplasms, benign (incl cysts and polyps) (SMQ)								
-		6306				Liver neoplasms, malignant and unspecified (SMQ)								
+		6307				Liver malignant tumours (SMQ)								
+		6325				Liver tumours of unspecified malignancy (SMQ)								
+		6328				Liver related investigations, signs and symptoms (SMQ)								
+		6429				Liver-related coagulation and bleeding disturbances (SMQ)								
+		6470				Hepatic disorders specifically reported as alcohol-related (SMQ)								
+		6477				Liver infections (SMQ)								
+		6555				Pregnancy-related hepatic disorders (SMQ)								

Figure 5. Full Hierarchical Structure of Hepatic disorders (SMQ)

A user may also elect to apply a single sub-SMQ of Hepatic disorders (SMQ) (e.g., Pregnancy-related hepatic disorders (SMQ), See Figure 6)

1	2	3	4	5	6	A	C	D	E	F
-		6117	Hepatic disorders (SMQ)							
+		6118				Congenital, familial, neonatal and genetic disorders of the liver (SMQ)				
+		6149				Drug related hepatic disorders - comprehensive search (SMQ)				
+		6470				Hepatic disorders specifically reported as alcohol-related (SMQ)				
+		6477				Liver infections (SMQ)				
-		6555				Pregnancy-related hepatic disorders (SMQ)				
.		6556	Narrow	A		Acute fatty liver of pregnancy				10000746
.		6557	Narrow	A		Cholestasis of pregnancy				10049055

Figure 6. Pregnancy-related hepatic disorders (SMQ) - sub-SMQ of Hepatic disorders (SMQ)

LOOK-UP TABLE / SAS DATASET CREATION

If SMQ has to be implemented at ADaM level, then we need to create Look-up table/SAS Dataset based on SMQ. There are two approaches:

1. Based on Production SMQ Spreadsheet which is provided with each new release of MedDRA
2. Based on SMQ files (SMQ_CONTENT. ASC, SMQ_LIST. ASC) which is provided with each new release of MedDRA

BASED ON PRODUCTION SMQ SPREADSHEET

With each new release of MedDRA, an updated EXCEL file is provided having details of SMQ. SMQ spreadsheet only lists active PTs in each SMQ. Apart from PT name, other details like PT code, SMQ category (A, B, C, etc.) and scope (Broad or Narrow) is mentioned for each PT. SMQ hierarchical information is provided in separate tab.

Below Table 1 shows sample observations for Torsade de pointes/QT prolongation (SMQ). Name of the SMQ is mentioned in first row. Rest of rows shows PTs included under specific SMQ. 1st column tells scope (Narrow or Broad), 2nd column tells SMQ category, 3rd and 4th columns shows PT details (PT name and PT code).

Torsade de pointes/QT prolongation (SMQ)				
	Narrow	A	Electrocardiogram QT interval abnormal	10063748
	Narrow	A	Electrocardiogram QT prolonged	10014387
	Broad	A	Ventricular fibrillation	10047290
	Broad	A	Ventricular flutter	10047294
	Broad	A	Ventricular tachyarrhythmia	10065341

Table 1. Torsade de pointes/QT prolongation (SMQ)

If user decides to use SMQ Spreadsheet, then user needs to copy the required rows of SMQ to a separate excel sheet which will act as look-up table. Example - If analysis has to be performed for Torsade de pointes/QT prolongation (SMQ) using narrow scope, then user needs to copy all Narrow Scope PTs belonging to Torsade de pointes/QT prolongation (SMQ) to a separate excel sheet which will act as look-up table.

BASED ON SMQ FILES

SMQ related information is stored in 2 files. Details are mentioned below. Please note that SAS code for this approach has been added at the end of paper.

SMQ_LIST

This file contains one record per SMQ which has details like unique code and name assigned to each SMQ. There are total 9 fields which are separated by '\$'. Details are mentioned below in Table 2:

Field Name	Type	Description
smq_code	Num	Eight-digit numeric code assigned to the SMQ, which starts with '2'
smq_name	Char	Name for the SMQ, each SMQ carries "(SMQ)" at the end of the name
smq_level	Num	Value between 1 and 5 identifying the level of the SMQ within the hierarchy of SMQs; 1 is the most general, 5 is the most narrow
smq_description	Char	Description of the SMQ
smq_source	Char	Source for the development of the SMQ (e.g., medical references)
smq_note	Char	Note for users to better understand the scope and development process for the SMQ. The description of the algorithm used is included (if applicable), as well as the definition of categories
MedDRA_version	Char	MedDRA version to use in conjunction with this SMQ
Status	Char	Status of the SMQ. "A" = An active SMQ; "I" = An inactive SMQ
smq_algorithm	Char	If the SMQ was developed for use with an algorithm, the Boolean expression of the algorithm is included. "N" if the SMQ does not utilize an algorithm

Table 2. SMQ_LIST Details (Important fields are highlighted in yellow)

SMQ_CONTENT

This file contains multiple records per SMQ. Each SMQ can have multiple PTs (Preferred Terms), LLTs (Lower Level Terms) and sub-SMQs (Due to hierarchical structure) which result in more than one observation per SMQ. There are total 9 fields which are separated by '\$'. Details are mentioned below in Table 3.

Field Name	Type	Description
smq_code	Num	Eight-digit code assigned to the SMQ
term_code	Num	Subordinate term code; it could be a code for MedDRA PT, LLT, or child SMQ
term_level	Num	MedDRA hierarchy level of the term (4=PT, 5=LLT) or 0 (zero) for a child SMQ
term_scope	Num	Defines the MedDRA term as a member of the broad scope (1), narrow scope (2) of the SMQ search, or a child SMQ (0) (zero)
term_category	Char	The category is assigned a single alphabetical letter depending upon the algorithm applied. If the SMQ does not use algorithms, then all Term_category values are assigned "A." For a child SMQ, this field is assigned "S."
term_weight	Num	Term weight is used for some SMQ algorithms. "0" is used as default
term_status	Char	Identifies a term as active within this SMQ or inactive within this SMQ. When a term is added to an SMQ, the value is set to "A" for Active. The term can be flagged as "I" for inactive if the term is no longer used in the SMQ.
term_addition_version	Char	Identifies the version of MedDRA in which this term was added to the SMQ
term_last_modified_version	Char	Identifies the version of MedDRA in which this term was last modified in this SMQ

Table 3. SMQ_CONTENT Details (Important fields are highlighted in yellow)

Following Steps should be followed to prepare look-up table/SAS dataset:

1. Read SMQ_LIST.ASC file with SAS Program using INFILE statement (DSD option) and INPUT statement. Only select active SMQs (STATUS="A")
2. Read SMQ_CONTENT.ASC file with SAS Program using INFILE statement (DSD option) and INPUT statement. Only select active terms associated with SMQs (TERM_STATUS="A")
3. Merge datasets created in Step 1 and Step 2 using SMQ_CODE as merge key. This will provide the list of active SMQs with active PTs/LLTs/sub-SMQs

Screenshot of merged dataset has been pasted in below Table 4. First 8 observations shows PTs and LLTs for Torsade de pointes/QT prolongation (SMQ). Rest of the records shows hierarchical structure for Hepatic disorders (SMQ) which is same as Figure 5. Only difference is that below screenshot is from dataset created using SMQ files whereas Figure 5 has shown screenshot of Production SMQ Spreadsheet.

SMQ_CODE	SMQ_NAME	SMQ_LEVEL	TERM_CODE	TERM_LEVEL	TERM_CATEGORY
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10077361	4	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10047302	4	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10024855	4	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10049993	4	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10045481	5	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10041914	5	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10016569	5	A
20000001	Torsade de pointes/QT prolongation (SMQ)	1	10042436	5	A
20000005	Hepatic disorders (SMQ)	1	20000014	0	S

20000005	Hepatic disorders (SMQ)	1	20000018	0	S
20000005	Hepatic disorders (SMQ)	1	20000016	0	S
20000005	Hepatic disorders (SMQ)	1	20000017	0	S
20000005	Hepatic disorders (SMQ)	1	20000006	0	S
20000006	Drug related hepatic disorders - comprehensive search (SMQ)	2	20000009	0	S
20000006	Drug related hepatic disorders - comprehensive search (SMQ)		20000007	0	S
20000006	Drug related hepatic disorders - comprehensive search (SMQ)	2	20000008	0	S
20000006	Drug related hepatic disorders - comprehensive search (SMQ)	2	20000015	0	S
20000007	Drug related hepatic disorders - severe events only (SMQ)	3	20000011	0	S
20000007	Drug related hepatic disorders - severe events only (SMQ)	3	20000010	0	S
20000007	Drug related hepatic disorders - severe events only (SMQ)	3	20000013	0	S
20000007	Drug related hepatic disorders - severe events only (SMQ)	3	20000012	0	S
20000011	Liver neoplasms, malignant and unspecified (SMQ)	4	20000209	0	S
20000011	Liver neoplasms, malignant and unspecified (SMQ)	4	20000208	0	S

Table 4. Screenshot of merged dataset using SMQ Files (SMQ_LIST, SMQ_CONTENT)

Hepatic disorders (SMQ) has 5 children - 20000014, 20000018, 20000016, 20000017, 20000006 (See Table 5). PTs and LLTs of Hepatic disorders (SMQ) include the list of all PTs and LLTs of its children.

SMQ_CODE	SMQ_LEVEL					
20000005	1	20000006	20000014	20000016	20000017	20000018
20000006	2	20000007	20000008	20000009	20000015	
20000007	3	20000010	20000011	20000012	20000013	
20000011	4	20000208	20000209			

Table 5. sub-SMQs of Hepatic disorders (SMQ) and its children

4. SAS programming has been applied on dataset created in step 3 to create full details of parent child relationship of SMQs. Output has been shown below in Table 6.

SMQ_CODE	SMQ_NAME	SMQ_LEVEL	RELATION
20000001	Torsade de pointes/QT prolongation (SMQ)	1	20000001
20000004	Cardiac failure (SMQ)	1	20000004
20000005	Hepatic disorders (SMQ)	1	20000010@20000208@20000209@20000012@20000013@20000008@20000009@20000015@20000014@20000016@20000017@20000018
20000006	Drug related hepatic disorders - comprehensive search (SMQ)	2	20000010@20000208@20000209@20000012@20000013@20000008@20000009@20000015

20000007	Drug related hepatic disorders - severe events only (SMQ)	3	20000010@20000208@20000209@20000012@20000013
20000011	Liver neoplasms, malignant and unspecified (SMQ)	4	20000208@20000209
20000208	Liver malignant tumours (SMQ)	5	20000208
20000209	Liver tumours of unspecified malignancy (SMQ)	5	20000209

Table 6. List of all children a SMQs

RELATION column is derived programmatically. It lists all children of a SMQ. SMQ 20000001 has no child so it has only one value 20000001(itself) in RELATION column. SMQ 20000011 has 2 children so RELATION column has 2 values 20000208 and 20000209 separated by '@' sign. To access SMQ 20000011, all PTs from SMQ 20000208 and 20000209 will be listed in a SAS dataset. This can be done programmatically using SAS. Similarly, to access Hepatic disorders (SMQ), all PTs from its 12 children will be listed.

5. Since SMQ file has only term code for PTs and LLTs. PTs and LLTs names can be derived in SAS dataset using PT.ASC and LLT.ASC file provided in MedDRA package.
 - PT.ASC has 2 fields - PT_NAME (Preferred Term Name) and PT_CODE (Preferred Term Code). PT_CODE should be used as primary key to derive PT_NAME for each record in SMQ_CONTENT where TERM_LEVEL is 4. TERM_CODE will be used as merge key from SMQ_CONTENT.
 - LLT.ASC has 2 fields - LLT_NAME (Lowest Level Term Name) and LLT_CODE (Lowest Level Term Code).LLT_CODE should be used as primary key to derive LLT_NAME for each record in SMQ_CONTENT where TERM_LEVEL is 5. TERM_CODE will be used as merge key from SMQ_CONTENT.

This step is optional and can be avoided.

IMPLEMENTATION IN CDISC STANDARD

Based on Occurrence Data Structure (OCCDS) version 1.0, adverse event ADaM dataset can have different variables for Standardized MedDRA Query and Customized Query. For Standardized MedDRA Query, 4 variables SMQzzNAM, SMQzzCD, SMQzzSC and SMQzzSCN are defined whereas for Customized Query, only one variable CQzzNAM is defined. See below Table 7 having details of the variables.

Variable Name	Variable Label	Type	Core	Description
SMQzzNAM	SMQ zz Name	Char	Cond	Name of standardized MedDRA query. Would be blank for terms that are not in the SMQ. Therefore this variable could be blank for all records if no terms within the study were included in the SMQ. This is conditional variable.
SMQzzCD	SMQ zz Code	Num	Perm	Code of standardized MedDRA query. This is permissible variable.
SMQzzSC	SMQ zz Scope	Char	Cond	It can have value BROAD or NARROW based on search strategy. This is conditional variable.

SMQzzSCN	SMQ zz Scope (N)	Num	Perm	Numeric version of SMQzzSC 1 = BROAD, 2 = NARROW This is permissible variable.
CQzzNAM	Customized Query zz Name	Char	Cond	Name of customized query (CQ). This is conditional variable.

Table 7. Occurrence Data Structure (OCCDS)

'zz' indicates a number starting with 01 for each SMQ or CQ of interest. This ordering can be based on importance or some other producer-defined criteria. This provides flexibility to assign same variable name to any SMQ across all studies at compound level. For example - "Torsade de pointes/QT prolongation (SMQ)" can be assigned in variable SMQ10NAM in all studies at compound level. Note that no restriction is given on value of 'zz' so for first SMQ can be assigned name like SMQ15NAM. There is no need for next SMQ to have sequential name like SMQ16NAM, It can have any value of 'zz' like SMQ27NAM.

STANDARDIZED MEDDRA QUERY (SMQ) AND CUSTOMIZED QUERY (CQ)

Every PT available in adverse event dataset (e.g. ADAE) can be categorized into SMQ or CQ if it has been found in the look-up table prepared for analysis.

A query can be considered as SMQ in following different ways:

- If all the PTs from the SMQ has been selected for look-up table without any modification
- If Some PTs have been removed from the SMQ based on built-in filtering criteria like:
 - If some PTs have been excluded based on Narrow or Broad search
 - If some PTs have been excluded based on SMQ category (A, B, C, etc.)

If any modifications are made to term content or structure of SMQ, it can't be called as SMQ but it should be referred as CQ. A query can be considered as CQ in following different ways:

- A Specific list of PTs has been provided by sponsor. Example - 'drug-related pyrexia (PT=pyrexia, hyperpyrexia, chills)' has been provided by sponsor so CQ will have name as 'drug-related pyrexia' and will include 3 PTs (pyrexia, hyperpyrexia and chills)
- A list of PTs has been created from a SMQs but Some PTs have been removed without built-in filtering criteria (e.g. Narrow search or Broad search or SMQ category). Example - hypersensitivity (SMQ): (exclude Stevens-Johnson syndrome, Toxic epidermal necrolysis). Here 2 PTs are supposed to be excluded from the list of all PTs, so it can't be called as SMQ and will be considered as CQ.
- A list of PTs has been created by combining one or more SMQs

STATISTICAL ANALYSIS PLAN (SAP)

Below is the SAP text which tells that SMQs has to be used while doing ADaM/TLFs.

TEAEs of special interest (AESI) will be identified with SMQ narrow search as below:

- hepatic disorders (SMQ: "Drug Related Hepatic Disorders-comprehensive search")
- drug-related pyrexia (PT=pyrexia, hyperpyrexia, chills)
- hypersensitivity (SMQ: hypersensitivity)
- QTc prolongation (SMQ: Torsade de pointes / QT prolongation)

Following approach should be used:

- It has been clearly mentioned that only Narrow search has to be used, so only PTs having Narrow scope will be selected for mentioned SMQs in SAP.
- In General, MedDRA version of SMQ and the coded data being searched should be same. SMQ terms are always getting updated in each new release of MedDRA i.e. a PT can be added or

deactivated from the SMQ. So using different version for MedDRA for SMQ and coded data being searched could produce unexpected result. Always confirm the MedDRA version of SMQ from sponsor if not mentioned in SAP.

- All the PTs having narrow scope from below SMQs should be selected:
 - Drug related hepatic disorders - comprehensive search (SMQ) - sub-SMQ of Hepatic disorders (SMQ)
 - Hypersensitivity (SMQ)
 - Torsade de pointes/QT prolongation (SMQ)
- *drug-related pyrexia (PT=pyrexia, hyperpyrexia, chills)* comes under the category of Customized Query(CQ) because no standard SMQ is having such name. Three PTs *pyrexia, hyperpyrexia and chills* will come under this category.
- Excel sheet/SAS dataset having below structure (e.g. Table 8) will be needed. This will be merged with PTs present in ADAE dataset to derived variables for SMQs and CQs. Table contains only sample observations to show the example. Last 3 rows represents the customized query where SMQ code, Scope and PT code is missing because it has been entered manually in the table rather than copying from SMQ spreadsheet.

SMQ Term	SMQ Code	Scope	AEDECOD (PT)	AEPTCD (PT Code)
Drug related hepatic disorders - comprehensive search (SMQ)	20000006	Narrow	Cholaemia	10048611
Hypersensitivity (SMQ)	20000214	Narrow	Administration site rash	10071156
Torsade de pointes/QT prolongation (SMQ)	20000001	Narrow	Long QT syndrome	10024803
drug-related pyrexia (CQ)			Pyrexia	
drug-related pyrexia (CQ)			Hyperpyrexia	
drug-related pyrexia (CQ)			Chills	

Table 8. Look-up table for analysis

DERIVE SMQ INFORMATION AT ADAM LEVEL

Using Production SMQ Spreadsheet or SMQ files, an EXCEL can be created having list of all PTs for SMQs needed for analysis. EXCEL has been shown below (Table 9). It is good to create EXCEL so that Statistician and Sponsor can verify if this list is correct. Note that last 3 PTs for CQ has been provided by sponsor and same has been copied manually.

Row	SMQ Term	SMQ Code	Scope	AEDECOD	AEPTCD
1	Hepatic disorders (SMQ)	20000005	Narrow	Cholaemia	10048611
2	Hepatic disorders (SMQ)	20000005	Narrow	Cholestasis	10008635
3	Hepatic disorders (SMQ)	20000005	Narrow	Jaundice	10023126
4	Hepatic disorders (SMQ)	20000005	Narrow	Allergic hepatitis	10071198
5	Hypersensitivity (SMQ)	20000214	Narrow	Allergic hepatitis	10071198
6	Hypersensitivity (SMQ)	20000214	Narrow	Eye allergy	10015907
7	Hypersensitivity (SMQ)	20000214	Narrow	Eye swelling	10015967
8	Hypersensitivity (SMQ)	20000214	Narrow	Rash	10037844
9	Hypersensitivity (SMQ)	20000214	Narrow	Shock	10040560
10	drug-related pyrexia (CQ)			pyrexia	
11	drug-related pyrexia (CQ)			hyperpyrexia	
12	drug-related pyrexia (CQ)			chills	

Table 9. Look-up table for analysis

Since in the above look-up table, 2 SMQs are present, So 2 pairs of SMQ variables will be created - SMQ01NAM, SMQ01CD, SMQ01SC, SMQ01SCN and SMQ15NAM, SMQ15CD, SMQ15SC,

SMQ15SCN. Since in the above look-up table only 1 CQ is present, so only one variable CQ01NAM will be created.

ADaM dataset ADAE has Preferred Term information (5 records shown in Table 10). ADAE dataset will be merged with above look-up table (Table 9) using AEDECOD (Preferred Term Name) or AEPTCD (Preferred Term Code) as merge key.

ADAE will be merged with above look-up table 3 times - once for each SMQ/CQ. Below is brief details of merge steps.

First time for Hepatic disorders (SMQ) - SMQ01NAM and related variables will be created (Table 10)

Second time for Hypersensitivity (SMQ) - SMQ15NAM and related variables will be created (Table 11)

Third time for drug-related pyrexia (CQ) - CQ01NAM variable will be created (Table 12)

Above steps can be performed using macros if more SMQs are involved in the study.

Output ADAE dataset will have structure like below table:

Row	AEDECOD	AEPTCD	SMQ01NAM	SMQ01CD	SMQ01SC	SMQ01SCN
1	Cholestasis	10008635	Hepatic disorders (SMQ)	20000005	Narrow	2
2	Allergic hepatitis	10071198	Hepatic disorders (SMQ)	20000005	Narrow	2
3	Eye swelling	10015967				
4	Pyrexia	10037660				
5	hyperpyrexia	10020741				

Table 10. Variables for Hepatic disorders (SMQ)

Row	AEDECOD	AEPTCD	SMQ15NAM	SMQ15CD	SMQ15SC	SMQ15SCN
1 (cont)	Cholestasis	10008635				
2 (cont)	Allergic hepatitis	10071198	Hypersensitivity (SMQ)	20000214	Narrow	2
3 (cont)	Eye swelling	10015967	Hypersensitivity (SMQ)	20000214	Narrow	2
4 (cont)	pyrexia	10037660				
5 (cont)	hyperpyrexia	10020741				

Table 11. Variables for Hypersensitivity (SMQ)

Row	AEDECOD	AEPTCD	CQ01NAM
1 (cont)	Cholestasis	10008635	
2 (cont)	Allergic hepatitis	10071198	
3 (cont)	Eye swelling	10015967	
4 (cont)	pyrexia	10037660	drug-related pyrexia (CQ)
5 (cont)	hyperpyrexia	10020741	drug-related pyrexia (CQ)

Table 12. Variables for drug-related pyrexia (CQ)

For PT='Cholestasis' (row 1), SMQ01NAM is populated and SMQ02NAM and CQ01NAM are missing because ADAE.AEDECOD matches with 2nd row of the look-up table (Table 9).

For PT='Allergic hepatitis' (row2), SMQ01NAM and SMQ02NAM are populated but CQ01NAM is missing because ADAE.AEDECOD matches with 4th and 5th row of the look-up table. PT='Allergic hepatitis' is common PT in both Hepatic disorders (SMQ) and Hypersensitivity (SMQ).

For PTs = 'pyrexia' (row 4), 'hyperpyrexia' (row 5), CQ01NAM is populated and SMQ01NAM and SMQ02NAM are missing because ADAE.AEDECOD matches with 10th and 11th row of the look-up table.

Information for LLTs is available in SMQ files which is missing in Production SMQ spreadsheet. Production SMQ spreadsheet has only active PTs available. So if ADaM dataset don't have PTs information and merge has to be done at LLT level, SMQ look-up table/dataset for analysis should be created using SMQ files only. In MedDRA dictionary, One LLT is identical to its PT for data entry purposes which is not being followed in SMQ files, so PTs (TERM_LEVEL=4) are not duplicated at LLT

level (TERM_LEVEL=5) in SMQ files. So all terms having TERM_CODE = 4 or 5 should be considered as LLT if merge has to be performed at LLT level.

REPORTING

Summary tables are the most common way for analyzing adverse events through SMQ terms. Consider Summary of Treatment-Emergent Adverse Events of Special Interest by AESI category, Preferred Term. Mock for this is shown below in Table 13. Here AESI means Adverse Event of Special interest i.e. SMQ. Frequency count of each SMQ/CQ and corresponding PTs have been listed. Percentage is calculated based on N i.e. no of subjects in each treatment group.

Summary of Treatment-Emergent Adverse Events of Special Interest by AESI category, Preferred Term				
AESI category/ Preferred Term	Group X1 (N=xx) n (%)	Group X2 (N=xx) n (%)	Group X3 (N=xx) n (%)	Overall (N=xx) n (%)
Subjects with at Least One TEAE	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
SMQ Name 1	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 1	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 2	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
.				
SMQ Name 2	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 1	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 2	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
.				
.				
CQ Name 1	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 1	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Preferred Term 2	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
.				
.				

Table 13. Mock Table

CONCLUSION

Adverse event reports are critical point of consideration in safety analysis. If SMQ is involved, much care shall be taken by programmer. Programmers must read the SAP carefully before starting any activity (e.g. specification writing, ADaM programming, TLFs programming) because major information on how SMQ has to be implemented at study level is clearly mentioned in SAP. If few number of SMQs (e.g. two or three) have to be analyzed in the study, manual creation of the look-up table using Production SMQ spreadsheet is suggested, as it will not take much time. On the other hand, if large number of SMQs have to be analyzed in the study, look-up table should be created using programming from SMQ files, as it will save both time and manual effort.

REFERENCES

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3. Production SMQ spreadsheet provided in each release of MedDRA (Version 22.0)
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5. ADaM Structure for Occurrence Data (OCCDS) Version 1.0
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```

*****
*Below Code will Generated look-up table/SAS Dataset
*SAS and PROC SQL has been used
*SMQ_LI_CO_FINAL SAS dataset has PT/LLT details for each SMQ.
*SMQ_RELATION has list of all child for each SMQ
*EXTRACT_SMQ Macro will fetch Records of SMQ
*****;

/** Reading SMQ_LIST from SMQ_LIST.ASC file (Active SMQs only) **/
data smq_list;
  attrib
    smq_code length = 8 smq_name length = $100
    smq_level length = 8 smq_description length = $10000
    smq_source length = $10000 smq_note length = $1000
    MedDRA_version length = $5 status length = $1
    smq_algorithm length = $100;
  infile 'H:\SMQ_22\MedAscii\smq_list.asc' delimiter='$' dsd;
  input smq_code smq_name smq_level smq_description smq_source smq_note
    MedDRA_version status smq_algorithm;
  if status eq 'A';
  keep smq_code smq_name smq_level smq_algorithm;
run;

/** Reading SMQ_CONTENT from SMQ_CONTENT.ASC file (Active Terms only) **/
data smq_content;
  attrib
    smq_code length = 8 term_code length = 8 term_level length=8
    term_scope length = 8 term_category length = $1
    term_weight length = 8 term_status length = $1
    term_addition_version length = $5
    term_last_modified_version length = $5;
  infile 'H:\SMQ_22\MedAscii\smq_content.asc' delimiter='$' dsd;
  input smq_code term_code term_level term_scope term_category term_weight
    term_status term_addition_version term_last_modified_version;
  if term_status eq 'A';
  drop term_status term_addition_version term_last_modified_version;
run;

/** Reading LLT from LLT.ASC file **/
data llt;
  attrib
    llt_code length = 8 llt_name length = $100 pt_code length = 8
    llt_whoart_code length = $100 llt_harts_code length = 8
    llt_costart_sym length = $100 llt_icd9_code length = $100
    llt_icd9cm_code length = $100 llt_icd10_code length = $100
    llt_currency length = $100 llt_jart_code length = $100;
  infile 'H:\SMQ_22\MedAscii\llt.asc' delimiter='$' dsd;
  input llt_code llt_name pt_code llt_whoart_code llt_harts_code
    llt_costart_sym llt_icd9_code llt_icd9cm_code llt_icd10_code
    llt_currency llt_jart_code;
  keep llt_code llt_name pt_code;
run;

```

```

/** Reading PT from PT.ASC file */
data pt;
attrib
    pt_code length = 8 pt_name length = $100 null_field length = $100
    pt_soc_code length = 8 pt_whoart_code length = $100
    pt_harts_code length = 8 pt_costart_sym length = $100
    pt_icd9_code length = $100 pt_icd9cm_code length = $100
    pt_icd10_code length = $100 pt_jart_code length = $100;
infile 'H:\SMQ_22\MedAscii\pt.asc' delimiter='$' dsd;
input pt_code pt_name null_field pt_soc_code pt_whoart_code pt_harts_code
    pt_costart_sym pt_icd9_code pt_icd9cm_code pt_icd10_code pt_jart_code;
keep pt_code pt_name;
run;

/** Getting SMQ, PT, LLT NAME for their code */
proc sql;
create table pt_llt(drop=pt_code_) as select *
    from pt a full join llt(rename=(pt_code=pt_code_)) b
    on a.pt_code eq b.pt_code_;

create table smq_li_co(drop=smq_code_) as select *
    from smq_list a full join smq_content(rename=(smq_code=smq_code_)) b
    on a.smq_code eq b.smq_code_;

create table smq_name as select distinct smq_code, smq_name
    from smq_li_co;

create table pt_name as select distinct pt_code, pt_name
    from pt_llt;

create table llt_name as select distinct llt_code, llt_name
    from pt_llt;
quit;

/** Dataset having SMQ, PT, LLT details */
proc sql;
/** Geting name for Term_code(PT LLT SMQ) */
create table smq_li_co_1 as select a.*,b.smq_name as term_name_1
    from smq_li_co a left join smq_name b
    on a.term_code eq b.smq_code;
create table smq_li_co_2 as select a.*,b.pt_name as term_name_2
    from smq_li_co_1 a left join pt_name b
    on a.term_code eq b.pt_code;
create table smq_li_co_3 as select a.*,b.llt_name as term_name_3
    from smq_li_co_2 a left join llt_name b
    on a.term_code eq b.llt_code;
/** Final data having SMQ details */
create table smq_li_co_final(drop=term_name_:) as select
    *, coalescec(term_name_1, term_name_2, term_name_3) as term_name,
    case term_level
        when 0 then strip(put(term_code,best.))||' @
        '||coalescec(term_name_1, term_name_2, term_name_3)
        else ''
    end as smq_tran
    from smq_li_co_3;
quit;

```

```

/***** Child Parent Relation Derivation *****/
proc sort data = smq_li_co_final out = _xxx_1 nodupkey;
  by smq_code smq_level term_code;
  where term_level eq 0;
run;

proc transpose data = _xxx_1 out=_xxx_2(drop=_:);
  by smq_code smq_level;
  var smq_tran;
run;

data _xxx_3;
  set _xxx_2;
  array ar coll - col7;
  do over ar;
    ar=strip(scan(ar,1,'@'));
  end;
  _col=catx('@', of coll-col7);
  call symput('_',strip(put(smq_code,best.)),_col);
run;

proc sql;
  select smq_code into :list_smq separated by ' '
  from _xxx_2 where smq_level ne 1;
quit;

/** REPLACING PARENT WITH ITS CHILD **/
%macro relation(inds=, outds=, level=);

  data &outds;
    set &inds;
    if smq_level eq &level then do;
      array ar coll - col7;
      do over ar;
        if ar in (&list_smq) then ar=symget('_',ar);
      end;
    end;
run;

  data _xxx_;
    set &outds;
    _col=catx('@', of coll-col7);
    call symput('_',strip(put(smq_code,best.)),_col);
run;

  proc sql noprint;
    select smq_code into :list_smq separated by ' '
    from _xxx_ where smq_level not in (1);
  quit;
  %put &list_smq;

%mend;

%relation(inds=_xxx_3, outds=_xxx_4, level=4);
%relation(inds=_xxx_4, outds=_xxx_5, level=3);
%relation(inds=_xxx_5, outds=_xxx_6, level=2);
%relation(inds=_xxx_6, outds=_xxx_7, level=1);

```

```

proc sort data = smq_li_co_final;
    by smq_code smq_level;
run;

proc sort data = _xxx_7;
    by smq_code smq_level;
run;

/** Details of SMQ and its CHILD (if available). This will be used to fetch
SMQ records **/
/** Table 6. List of all children a SMQs is screenshot of below dataset **/
data smq_relation(keep=smq_code smq_name smq_level _relation);
    merge smq_li_co_final _xxx_7;
    by smq_code smq_level;
    _relation=coalescec(catx('@', of coll-col7),
strip(put(smq_code,best.)));
    if first.smq_code;
run;

*****
*Macro to fetch records of SMQs as per need
*Macro Parameters:
*   SMQ_NAME:
*       Name of SMQ to be searched
*   OUTDS:
*       Name of Output dataset
*   TERM_SCOPE:
*       1=BROAD, 2=NARROW, 1 2=Both BROAD and NARROW(Default)
*   TERM_LEVEL:
*       4=PT(Default), 5=LLT
*****;

%MACRO EXTRACT_SMQ(SMQ_NAME=, OUTDS=, TERM_LEVEL=4, TERM_SCOPE= 1 2);

    data _null_;
        set smq_relation;
        where smq_name eq "&smq_name";
        call symput('smq_code', tranwrd(_relation, '@', ' '));
        call symput('smq_code_parent', strip(put(smq_code,best.)));
    run;

    data &outds;
        set smq_li_co_final;
        where smq_code in (&smq_code) and term_level in ( &term_level)
        and term_scope in (&term_scope);
        drop smq_tran term_weight term_category ;
        smq_name_="&smq_name";
        smq_code_="&smq_code_parent";
    run;
%mend;

```

```
*****
*Sample Macro Call
*This macro will generate SAS dataset _OUTPUT_SMQ_1 having list of PTs
*for TORSADE DE POINTES/QT PROLONGATION (SMQ) having NARROW SCOPE
*search
*****;

%extract_smq(    smq_name      = Torsade de pointes/QT prolongation (SMQ),
                 Outds        = _output_smq_1,
                 term_scope   = 2
                 );
```