PhUSE US Connect 2019

Paper DH02

Adverse Events of Special Interest (AESI) Tabulation

ChuanFeng Shih, GlaxoSmithKline, Collegeville, PA

ABSTRACT

As indicated in ICH Topic E2F Development Safety Update Report[1] with regard to adverse event of special interest (AESI): "If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained. "

AESI has been an important part in presenting the safety profile for a compound in clinical trials. With the use of MedDRA system organ class (SOC), preferred term (PT), along with Standardized MedDRA Queries[2,3] (SMQs) and even Customized MedDRA Queries (CMQs), AESI reporting becomes more specific and detailed. MedDRA updates every six months has also increased the complexity of the reporting process.

This paper will discuss few approaches to manage the process and explore the expansion of ADAE domain or an independent ADAESI domain to handle AESI coding to support AESI reporting.

INTRODUCTION

Safety monitoring during clinical trials is a crucial component for drug development. Before a drug can receive regulatory approval for marketing, rigorous safety monitoring and reporting from preclinical to all phases of clinical trials are required. With the reference of guidance on safety reporting and availability of Medical Dictionary for Regulatory Activities (MedDRA), collecting and reporting adverse events are now more of standardized process. This paper will focus on the process of identifying and reporting AESI.

IDENTIFYING AESI

The source definition of 'Adverse Event of Special Interest' as described in CIOMS VII[4]:

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

In general, AESI are study-specific for an investigational product. They can be specified in Program Safety Analysis plan (PSAP) early in product development for safety planning, data collection, analysis and reporting on AESI data, and eventually form as the base of AESI analysis in Reporting and Analysis Plan (RAP).

Identifying AESI usually involve searching through PTs, pre-defined SMQs that can be extracted using MedDRA PTs, or the CMQs that are specific to a study but are not pre-defined within MedDRA. It will also involve adjudication process that spreadsheet output created through the searches are submitted for medical/clinical confirmation. These spreadsheets are usually in specific structure so adequate information like subject ID, AE sequence number, verbatim term, PT, SOC, onset date, resolved date, seriousness, severity, SMQs, CMQs, …, etc., are compiled to assist with the confirmation. The following are example of SMQ and CMQ variable naming convention for CDISC ADaM Occurrence Data Structure (OCCDS)[5].

Based on the adjudication process, additional flag variables can be checked by medical/clinical reviewers to confirm whether an AE included in the spreadsheet constitute an AESI.

Table 1:

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core
SMQzzNAM	SMQ zz Name	Char		Cond
SMQzzCD	SMQ zz Code	Num		Perm
SMQzzSC	SMQ zz Scope	Char	BROAD, NARROW	Cond
SMQzzSCN	SMQ zz Scope (N)	Num	1, 2	Perm
CQzzNAM	Customized Query zz Name	Char		Cond

AESI TABULATION

Tabulation of AESI can be similar to what have commonly done for summary of AEs by SOC and/or PT but can also go by grouping of SMQ and/or CMQ per medical condition.

The following is an example table of adverse events summarized by SOC and PT (Table 2), which can be created with some standardized or frequently used programs (e.g., SAS macro) within a sponsor. The needed data can be easily obtained from ADaM ADAE dataset created with current CDISC ADaM Occurrence Data Structure (OCCDS).

Table 2:

Adverse Events by MedDRA System Organ Class and Preferred Term

SYSTEM ORGAN CLASS Preferred Term	Treatment A (N=xxx) #AEs	n (n/N%)	Treatment B (N=xxx) #AEs	n (n/N%)
ANY EVENT	xxxx	xxx (xx.x%)	xxxx	xxx (xx.x%)
INFECTIONS AND INFESTATIONS				
At least one event	xxxx	xxx (xx.x%)	xxxx	xxx (xx.x%)
Upper respiratory tract infection	xxxx	xxx (xx.x%)	xxxx	xxx (xx.x%)
Urinary tract infection	xxxx	xxx (xx.x%)	xxxx	xxx (xx.x%)
. . .				

AESI are typically identified through the evaluation of SMQs, CMQs, verbatim term, system organ class and preferred term. They can be summarized by category defined with corresponding SMQs or CMQs, along with associated system organ class, preferred term or subcategory defined per specific criteria for better presenting AESI information.

For example, AEs can be summarized by system organ class and preferred term per specific SMQ/CMQ selection criteria (Table 3). With the SMQs and/or CMQs, SOC and PT defined in the dataset, the needed data can still be subset from ADAE dataset with specific rules.

Table 3:

Anaphylactic/Hypersensitivity Reactions per Anaphylactic Reaction SMQ algorithmic search

SYSTEM ORGAN CLASS Preferred Term	Treatment A (N=xxx) #AEs	n (n/N%)	Treatment B (N=xxx) #AEs	n (n/N%)
ANY EVENT	xxx	xxx (xx.x%)	xxx	xxx (xx.x%)
IMMUNE SYSTEM DISORDERS				
Any event	xxx	xxx (xx.x%)	xxx	xxx (xx.x%)
Drug hypersensitivity	xxx	xxx (xx.x%)	xxx	xxx (xx.x%)
Hypersensitivity	xxx	xxx (xx.x%)	xxx	xxx (xx.x%)
. . .				

The current ADAE structure probably can support basic AESI analysis only up to certain level but may not necessarily analysis-ready for some reporting requirements. The following is an example of general study-specific AESI profile summarized by category and sub-category defined per specific SMQ/CMQ rules and presented in a defined sequence for evaluation (Table 4).

Table 4:

Adverse Events of Special Interest

	Blinded (N=xxx) #AEs	n	(n/N%)
MALIGNANT NEOPLASM			
All Malignancies **Excluding NMSC**	xxx	xxx	(xx.x%)
All Malignancies **Including NMSC**	xxx	xxx	(xx.x%)
Solid Tumor	xxx	xxx	(xx.x%)
Hematology	xxx	xxx	(xx.x%)
Skin (All)	xxx	xxx	(xx.x%)
NMSC	xxx	xxx	(xx.x%)
Excluding NMSC	xxx	xxx	(xx.x%)
Tumours of Unspecified Malignancy Adjudicated as Malignant	xxx	xxx	(xx.x%)
INFUSION/ANAPHYLAXIS/HYPERSENSITIVITY REACTIONS			
Infusion-related Reactions/ Hypersensitivity per Anaphylactic Reaction **SMQ narrow search**	xxx	xxx	(xx.x%)
Infusion-related Reactions/ Hypersensitivity per Anaphylactic Reaction **SMQ broad search**	xxx	xxx	(xx.x%)
Infusion-related Reactions/ Hypersensitivity per Anaphylactic Reaction **SMQ algorithmic search**	xxx	xxx	(xx.x%)
Serious Anaphylaxis per **Sampson Criteria (Adjudicated AEs)**	xxx	xxx	(xx.x%)
Serious Anaphylaxis/ Hypersensitivity Reactions (Adjudicated AEs)	xxx	xxx	(xx.x%)
. . .			

With details of the summary, additional variables and/or data manipulations are most likely required in the program to generate the summary. Can another ADaM dataset be created to contain only AESI data so it is analysis-ready for broader AESI reporting purposes?

ADAESI DATASET

If we can group AESI into categories and sub-categories by medical condition, along with the existing SOCs and PTs, in an expanded structure of ADAE dataset (i.e., ADAESI), we can create more AESI tabulations simply with different combinations of AESI category (e.g., AESICACD/AESICAT), AESI sub-category (AESIDECD/AESICOD), PT and SOC.

For example, if a serious 'Herpes zoster' as an AESI will be tabulated as in Table 5, then the record in Table 6 from ADAE dataset can be structured as in Table 7 for ADAESI dataset.

Table 5:

	Blinded (N=xxx) #AEs	n	(n/N%)
All Infections			
All infections (OI, HZ, Sepsis) per Preferred Term Definition	xxx	xxx	(xx.x%)
Serious infections	xxx	xxx	(xx.x%)
Opportunistic Infections (Adjudicated AEs)	xxx	xxx	(xx.x%)
Serious Opportunistic Infections (Adjudicated AEs)	xxx	xxx	(xx.x%)
Herpes Zoster per Preferred Term Definition	xxx	xxx	(xx.x%)
Serious Herpes Zoster	xxx	xxx	(xx.x%)
Recurrent (Adjudicated AEs)	xxx	xxx	(xx.x%)
Serious Recurrent	xxx	xxx	(xx.x%)
Disseminated (Adjudicated AEs)	xxx	xxx	(xx.x%)
Serious Disseminated	xxx	xxx	(xx.x%)
Sepsis	xxx	xxx	(xx.x%)
Serious Sepsis	xxx	xxx	(xx.x%)

Table 6: Record in ADAE dataset

USUBJID	AESEQ	AEDECOD	AESOC	AESER	CQ06NAM	CQ07NAM
ABC01.001	3	Herpes zoster	Infections and infestations	Y	Opportunistic Infections	Herpes zoster

Table 7: Records in ADAESI dataset

USUBJID	AESEQ	AEDECOD	AESOC	AESER	CQ06NAM	CQ07NAM
ABC01.001	3	Herpes zoster	Infections and infestations	Y	Opportunistic Infections	Herpes zoster
ABC01.001	3	Herpes zoster	Infections and infestations	Y	Opportunistic Infections	Herpes zoster
ABC01.001	3	Herpes zoster	Infections and infestations	Y	Opportunistic Infections	Herpes zoster
ABC01.001	3	Herpes zoster	Infections and infestations	Y	Opportunistic Infections	Herpes zoster

USUBJID	AESEQ	AESICACD	AESICAT	AESICOD	AESIDECD
ABC01.001	3	003	All Infections	3001	All infections (OI, HZ, Sepsis) per Preferred Term Definition
ABC01.001	3	003	All Infections	3002	Serious infections
ABC01.001	3	003	All Infections	3005	Herpes Zoster per Preferred Term Definition
ABC01.001	3	003	All Infections	3006	Serious Herpes Zoster

Table 8 shows the example coding and decoding for AESICACD/AESICAT and AESICOD/AESIDECD based on the sequence of sub-categories within 'All Infections.'

Table 8:

```
--------------------------------------------------------------------------------
All Infections   [AESICACD=003]
  All infections (OI, HZ, Sepsis) per Preferred Term Definition  [AESICOD=3001]
    Serious infections                                           [AESICOD=3002]
    Opportunistic Infections (Adjudicated AEs)                   [AESICOD=3003]
      Serious Opportunistic Infections (Adjudicated AEs)         [AESICOD=3004]
    Herpes Zoster per Preferred Term Definition                  [AESICOD=3005]
      Serious Herpes Zoster                                      [AESICOD=3006]
    Recurrent (Adjudicated AEs)                                  [AESICOD=3007]
      Serious Recurrent                                          [AESICOD=3008]
    Disseminated (Adjudicated AEs)                               [AESICOD=3009]
      Serious Disseminated                                       [AESICOD=3010]
    Sepsis                                                       [AESICOD=3011]
      Serious Sepsis                                             [AESICOD=3012]
```

Similarly, we can also have a 'Suicide attempt' AE record in ADAE dataset (Table 10) converted into records as in Table 11 for ADAESI dataset for creating a summary like Table 9.

Table 9:

```
                                                        Blinded (N=xxx)
                                                        #AEs    n   (n/N%)
 ------------------------------------------------------------------------------
 DEPRESSION/SUICIDE/SELF-INJURY  [AESICACD=004]
   Depression                       [AESICOD=4001]      xxx   xxx (xx.x%)
     Serious Depression             [AESICOD=4002]      xxx   xxx (xx.x%)
   Suicide/self-injury              [AESICOD=4003]      xxx   xxx (xx.x%)
     Serious Suicide/self-injury    [AESICOD=4004]      xxx   xxx (xx.x%)
```

Table 10:

USUBJID	AESEQ	AEDECOD	AESOC	AESER	SMQ01NAM	CQ12NAM
ABC01.002	12	Suicide attempt	Psychiatric disorders	Y	Suicide/self-injury	Suicide/Self-injury

Table 11:

USUBJID	AESEQ	AEDECOD	AESOC	AESER	SMQ01NAM	CQ12NAM
ABC01.002	12	Suicide attempt	Psychiatric disorders	Y	Suicide/self-injury	Suicide/Self-injury
ABC01.002	12	Suicide attempt	Psychiatric disorders	Y	Suicide/self-injury	Suicide/Self-injury

USUBJID	AESEQ	AESICACD	AESICAT	AESIDECD	AESICOD
ABC01.002	12	004	Depression/suicide/self-injury	4003	Suicide/self-injury
ABC01.002	12	004	Depression/suicide/self-injury	4004	Serious Suicide/self-injury

CONCLUSION

By using the expanded structure of ADAESI dataset, not only AESI can be grouped specifically for easier identification, but also be tabulated to meet different reporting requirements. It will also need corresponding computational method and controlled terminology to support the dataset metadata. Formats correspond to the code of AESI category and sub-category can also be defined to support the tabulation.

REFERENCE

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CONTACT INFORMATION

Comments and questions are welcomed and encouraged. Author can be contacted at:

ChuanFeng Shih
GlaxoSmithKline
(215) 359-6439

chuan-feng.x.shih@gsk.com