



Analysis Data Model (ADaM) Data Structure for Adverse Event Analysis

Prepared by the
CDISC Analysis Data Model Team

Notes to Readers

This Analysis model uses the principles, structure and standards described in the CDISC Analysis Data Model v2.1 and Implementation Guide v1.0 documents

Revision History

| Date | Version | Description |
|--------------|---------|-------------|
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Note: Please see Appendix A for Representations and Warranties; Limitations of Liability, and Disclaimers.

Contents

| | | |
|------------|---|----|
| 1. | Introduction | 3 |
| 2. | Adverse Event Analysis | 4 |
| 2.1 | Adverse Event Attributes | 4 |
| 2.2 | Coding of Adverse Events..... | 4 |
| 2.3 | Statistical Analysis | 5 |
| 3. | Points to Consider in this Document | 6 |
| 4. | ADaM Metadata | 7 |
| 4.1 | ADAE Variables and Variable Metadata | 7 |
| 4.1.1 | ADSL Variables | 8 |
| 4.1.2 | Identifier Variables | 9 |
| 4.1.3 | Dictionary Coding Variables..... | 9 |
| 4.1.4 | Timing Variables | 12 |
| 4.1.5 | Indicator Variables..... | 15 |
| 4.1.6 | Occurrence Flag Variables..... | 16 |
| 4.1.7 | Treatment/Dose Variables..... | 17 |
| 4.1.8 | Descriptive Variables..... | 18 |
| 4.1.9 | MedDRA Query Variables..... | 20 |
| 4.1.10 | Original or Prior Coding Variables | 21 |
| 4.2 | Other Metadata..... | 22 |
| 5. | Example 1: Analysis of Treatment Emergent Adverse Events..... | 23 |
| 5.1 | Analysis Display Example Layout..... | 24 |
| 5.2 | Sample ADAE Variable Metadata | 25 |
| 5.3 | Sample ADAE Data | 28 |
| 6. | Example 2: Analysis of Hemorrhages (SMQ) among Treatment Emergent Adverse Events by Sex | 32 |
| 6.1 | Analysis Display Example Layouts | 33 |
| 6.2 | Sample ADAE Variable Metadata | 36 |
| 6.3 | Sample ADAE Data | 37 |
| 7. | Example 3: Analysis of Peripheral Sensory Neuropathy (PSN) Adverse Events by Severity and Cumulative Dose Exposure..... | 39 |
| 7.1 | Analysis Display Example Layout..... | 40 |
| 7.2 | Sample ADAE Variable Metadata | 41 |
| 7.3 | Sample ADAE Data | 42 |
| 8. | Example 4: Analysis of Treatment Emergent Adverse Events in a Cross-over Interaction Study | 43 |
| 8.1 | Analysis Display Example Layout..... | 43 |
| 8.2 | Sample ADAE Variable Metadata | 44 |
| 8.3 | Sample ADAE Data | 47 |
| 9. | References | 50 |
| Appendix A | Representations and Warranties; Limitations of Liability, and Disclaimers..... | 51 |

1. Introduction

The statistical analysis data structure presented in this document describes the general data structure and content typically found in Analysis Datasets used for common safety analysis of adverse events (AEs). Specifically, this is for analysis consisting of counting subjects with a record or term within a mapped dictionary hierarchy. The data structure is based on the ADaM Analysis Data Model V2.1 (referred to in this document as the ADaM v2.1) [1] and the ADaM Analysis Data Model Implementation Guide (ADaMIG) V1.0 [2].

As presented in the ADaMIG, most analysis methods can be performed using the ADaM Basic Data Structure (BDS) including Parameter (PARAM) and Analysis Value (AVAL). However, analysis of adverse events is one example where data analyzed as described above does not fit well into the BDS structure and are more appropriately analyzed using an SDTM structure with added analysis variables. In particular, for the analysis needs described in this document:

- There is no need for AVAL or AVALC. Occurrences are counted in analysis, and there are typically one or more records for each occurrence.
- A dictionary is used for coding the occurrence, and it includes a well-structured hierarchy of categories and terminology. Mapping this hierarchy to BDS variables PARAM and generic *CAT variables would lose the structure and meaning of the dictionary.
- Dictionary content is typically not modified for analysis purposes. In other words, there is no need for analysis versions of the dictionary hierarchy.

The AE structure presented in this document is built on the nomenclature of the Study Data Tabulation Model Implementation Guide (SDTMIG) V3.1.2, including Amendment 1 to the Study Data Tabulation Model (SDTM) v1.2 and the SDTM Implementation Guide: Human Clinical Trials V3.1.2 [3] standard for collected data, and adds attributes, variables, and data structures required for statistical analyses. The primary SDTM source domain for the AE analysis structure is AE with the corresponding SUPPAE. Many additional variables are added from Subject-Level Analysis Dataset (ADSL).

In this document, the analysis dataset for adverse events (ADAE) is described and required if SDTM AE isn't sufficient to support all AE analysis. The dataset and variable naming conventions and dataset structure described in this document should be followed. The ADAE structure for the standard adverse event safety dataset has at least one record per each AE recorded in SDTM AE domain. However, subjects not analyzed (e.g. screen failures) who have AEs recorded in SDTM AE but not in ADSL do not need to be included in ADAE. Additional rows may be added to have a one record per AE recorded in SDTM AE domain per period/phase per coding path structure if required by the analysis and clearly defined in the dataset and variable metadata. However, this doesn't exclude a Sponsor from creating additional analysis datasets for AE analysis, even using a different structure if needed for analysis (e.g. time-to-event of adverse events of special interest).

Adverse events are just one example of data that can use the structure described within this document. An ADaM sub-team is working to expand this to other data where there is no need for an analysis variable or parameter as would be seen in a BDS structure because records are simply counted for analysis. Example data for these types of analyses are concomitant medications and medical history.

2. Adverse Event Analysis

The safety evaluation of a clinical trial includes the analysis of adverse events. The definition of an adverse event, as presented in International Conference of Harmonization (ICH) E2A [4] guidelines, is

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Restated, this definition of an adverse event (AE) includes any unfavorable and unintended sign, symptom, or disease that is temporally associated with the use of a medicinal product, regardless of whether the AE is considered to be related to the product.

2.1 Adverse Event Attributes

Important attributes include the level of severity of the AE (Mild, Moderate, or Severe), whether the AE is considered to be related to the study product (Yes or No), and whether the AE is considered serious (Yes or No).

Of particular importance in the analysis of AEs is the definition of ‘treatment emergent’. The ICH E9 guidance [5] document defines treatment emergent as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. Operationally, classifying AEs as treatment emergent will utilize, in part, the start or worsening date of the AE relating to the trial or treatment start.

Other attributes of AEs include the action taken in response to the event and whether the event led to permanent discontinuation of the investigational product.

2.2 Coding of Adverse Events

Adverse events are recorded in textual or ‘verbatim’ terms. This verbatim term is a short description of the event and is generally written in free text on the case report form. Verbatim terms are then processed through a coding dictionary so that similar verbatim terms are grouped together by classifying each verbatim term into a hierarchy of medical granularity. Medical Dictionary for Regulatory Activities (MedDRA) [6] has become widely recognized as a global standard for the coding of adverse events. Examples of other coding dictionaries include WHO Adverse Reaction Terminology (WHO-ART), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), International Classification of Disease (ICD). Each coding dictionary is characterized by classifying each verbatim term into a hierarchy of medical granularity. For example, if a verbatim term was recorded as ‘stomach virus’, using MedDRA V12.0, this verbatim term would result in a System Organ Class (SOC) of ‘Infections and infestations’ and a preferred term (PT) of ‘Gastroenteritis viral’. The COSTART coding hierarchy would place this event in the ‘Body as a Whole’ body system, in the ‘General’ subcategory for this body system, and with the preferred term of ‘Flu Syndrome’.

When using coding dictionaries, it is recommended that coding rules and guidelines be developed by the sponsor prior to the classification of adverse events. The objective of these guidelines is to promote medical accuracy and consistency when using the controlled vocabulary of the dictionary. This consistency will be helpful when multiple coded adverse events are combined for two or more clinical studies.

It is also recommended that all levels of terms in the MedDRA hierarchy: System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Lowest Level Term (LLT), and Preferred Term (PT) are represented, as these are frequently useful in further analyses of AEs.

In some situations, multiple study reports are created for a single study. For example, an initial study report may be created at the time of the primary analysis for the primary efficacy endpoint. If subjects are followed for safety, a second report may be created years later so that long term safety data can be incorporated. At this time, there may

be a desire to update the coding dictionary so that all events are coded using the most recent version of a dictionary. In this situation, a recommendation is to provide the original coded terms along with the new coded terms so that the implications of the recoding can be more easily investigated.

It should be noted that a more common scenario involving the recoding of adverse events is when events are recoded for an integrated analysis and submitted to a regulatory agency for marketing approval. However, neither the current version of the ADaMIG nor this document fully cover integration of multiple studies. The ADaM and SDS teams are jointly developing a document to address integration of multiple studies. Some of the suggestions included here for handling multiple dictionaries may be revised after this Integration document is released.

2.3 Statistical Analysis

The most frequently used method for the comparison of adverse events between treatment groups is the summarization of the number of subjects who experienced a given adverse event at least once by the dictionary derived term. These counts and related percentages are presented for levels of the MedDRA hierarchy and preferred term. The denominator used for the calculation of the percentages is often determined by a population flag, such as the total number of subjects at risk or total number of subjects exposed to each treatment (e.g. SAFFL='Y'). Note that some subjects exposed to treatment may not have any adverse events, and therefore these subjects would not be represented in the SDTM AE domain and ADaM ADAE analysis dataset. Thus, the values of the denominator usually need to be obtained from ADSL (subject level analysis dataset) rather than directly from ADAE.

This ADaM model primarily discusses the creation of an analysis dataset that is needed for the presentation of frequencies and percents. However, the analysis dataset presented below could be used to conduct more in-depth analysis. For time-to-event analyses, see the ADaM Basic Data Structure for Time to Event Analyses.

3. Points to Consider in this Document

In reviewing the metadata and examples in this document, some of the points to consider are:

- **Ordering of variables:** Within this document, no specific ordering of variables within the illustrated datasets is implied. The ADaM v2.1 [1] states that ideally the ordering of the variables in the analysis dataset follows a logical ordering (not simply alphabetic). The ADaM v2.1 [1] does not provide a specific recommendation for the ordering of the variables. Within this document, the author of each example applied his or her own logical ordering.
- **Identification of source dataset:** When identifying the source dataset for a variable, the immediate predecessor is used, as described in the ADaM v2.1 [1]. For example, in ADSL the source is identified as DM.SUBJID in the analysis variable metadata. When SUBJID is used in ADAE, the source is identified as ADSL.SUBJID.
- **Analysis-ready:** ADAE should be “analysis-ready,” meaning it should contain all of the variables needed for the specific analysis, so that the analysis can be replicated by performing the actual statistical test without first having to manipulate data. Analysis-ready does not mean that a formatted display can be generated in a single statistical procedure. ADAE adheres to this principle as unique subject counts can be obtained by running a standard statistical procedure (e.g., SAS PROC, S-PLUS function, etc.) and denominators can be derived from ADSL.
- **Examples are for illustration only:** Note that the examples in this document are only intended as illustrations and should not be viewed as a statement of the standards themselves. In addition, the examples are intended to illustrate content and not appearance; it is understood that there are many different ways that data can be displayed. This document does not cover display formats.
- **Display of metadata for illustration of content only:** Though the metadata elements have been defined in the ADaM v2.1 [1], how the metadata are displayed is a function of the mechanism used to display the content. The presentation formats used in this document are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.
- **Analysis results metadata:** Analysis results metadata have not been included for any examples in this document. As stated in the ADaM v2.1 [1], analysis results metadata are not required. However, best practice is that they be provided to assist the reviewer by identifying the critical analyses, providing links between results, documentation, and datasets, and documenting the analyses performed.
- **Examples not meant to be all inclusive regarding variables:** The examples describe some of the key variables and records that would be included in the dataset. It is not intended to illustrate every possible variable that might be included in the analysis dataset; for example core variables required for subgroup analyses are not included in all the illustrations.
- **Source/Derivation Column:** The algorithms provided in the Source/Derivation column are for illustration purposes only and are not intended to imply universally accepted definitions or derivations of variables. Algorithms are producer-defined and dependent on trial and analysis design.
- **No endorsement of vendors or products:** As with other ADaM documents, references to specific vendor products are examples only and therefore should not be interpreted as an endorsement of these vendors or products.

4. ADaM Metadata

Typically, the Analysis Dataset Metadata are specified as follows:

Table 4.1 Example of ADaM ADAE Dataset Metadata¹

| Dataset Name | Dataset Description | Dataset Location | Dataset Structure | Key Variables of Dataset | Class of Dataset | Documentation |
|--------------|--------------------------------|-------------------------------------|---|--|------------------|---|
| ADAE | Adverse Event Analysis Dataset | pathname/analyses/datasets/adae.xml | one record per subject per each AE recorded in SDTM AE domain (optional: per coding path, per Analysis Period and/or Phase) | USUBJID, AEDECOD, AESEQ, (optional: AEBODSYS, APHASE, APERIODC) <i>Depending on study design and analyses, additional variables such as key flags may be needed</i> | ADAE* | ADAE.SAS <i>Example: Dictionary used is MedDRA V11.1</i> |

* Note: Class of dataset may change in a future version as the ADaM team develops a general occurrence model document

4.1 ADAE Variables and Variable Metadata

As stated earlier, the AE data structure is not BDS. There is no PARAM nor AVAL, for example. However, some of the variables described for the BDS structure in the ADaMIG version 1 [2] can be used in the AE structure, as shown below.

The more standardized variables commonly occurring in an ADaM AE analysis dataset (ADAE) are described here in tabular format. In general, include all SDTM AE and SUPPAE domain variables needed for analysis or traceability. Additional study or therapeutic specific variables may be added as needed but should follow the standard variable naming conventions described in the ADaMIG version 1 [2]. A variable should not use the prefix AE unless it is either (1) coming from the SDTM AE or SUPPAE domain or (2) the numeric version of the SDTM variable. In general, the analysis version of an SDTM variable is named by replacing the “AE” prefix with an “A” for analysis. Choose variable names with care to prevent unintended conflicts with standard names.

¹ The display presentation of the metadata should be determined between the sponsor and the recipient. The example is only intended to illustrate content and not appearance.

As described in the ADaM v2.1 [1], the two rightmost columns of metadata (“Core” and “CDISC Notes”) provide information about the variables to assist users in preparing their datasets. These columns are not meant to be metadata. The “Core” column, as defined in the ADaMIG version 1 [2], describes whether a variable is required (Req), conditionally required (Cond), or permissible (Perm). The “CDISC Notes” column provides more information about the variable. In addition, the “Type” column is being used to define whether the variable is character (Char) or numeric value (Num). More specific information will be provided in metadata.

4.1.1 ADSL Variables

Merge any ADSL variables needed for analysis or reference.

Be aware that population indicator flags may not be appropriate to include in ADAE because only subjects with an SDTM AE record would have an ADAE record. For this reason, it is recommended that population indicators and denominator counts for percentages be derived from ADSL and not from ADAE.

4.1.2 Identifier Variables

Include the identifier variables from SDTM:

Table 4.1.2.1 Identifier Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|----------------------------------|------|---------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| STUDYID | Study Identifier | Char | | Req | AE.STUDYID |
| USUBJID | Unique Subject Identifier | Char | | Req | AE.USUBJID |
| SUBJID | Subject Identifier for the Study | Char | | Perm | ADSL.SUBJID |
| SITEID | Study Site Identifier | Char | | Perm | ADSL.SITEID |
| AESEQ | Sequence Number | Num | | Req | AE.AESEQ Required for traceability back to SDTM AE. |

4.1.3 Dictionary Coding Variables

Dictionary coding variables provided in SDTM, typically MedDRA, should be included as needed for analysis, review, or traceability. It is recommended but not required that all levels of terms in the MedDRA hierarchy [System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Lowest Level Term (LLT), and Preferred Term (PT)] are represented, as these are frequently useful in further analyses of AEs. If other coding variables are included in SDTM and pertinent for analysis, these should be included in ADaM. For any public versioned dictionary, including MedDRA, the metadata for each coding variable should include both the name and version of the dictionary.

Table 4.1.3.1 Dictionary Coding Variables for MedDRA

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|--|------|---------------------------------|------|-------------|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AETERM | Reported Term for the Adverse Event | Char | | Req | AE.AETERM |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|---------------------------------|------|---------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AEDECOD | Dictionary-Derived Term | Char | MedDRA | Req | AE.AEDECOD This is typically one of the primary variables used in an AE analysis and would be brought in from the SDTM AE domain. Equivalent to the Preferred Term (PT in MedDRA). As mentioned above, all other SDTM AE and SUPPAE domain variables needed for analysis or traceability should also be included. Include the dictionary version in the variable metadata. |
| AEBODSYS | Body System or Organ Class | Char | MedDRA | Req | AE.AEBODSYS This is typically one of the primary variables used by the Sponsor in an AE analysis and would be brought in from the SDTM AE domain. As mentioned above, all other SDTM AE and SUPPAE domain variables needed for analysis or traceability should also be included. Include the dictionary version in the variable metadata. |
| AEBDSYCD | Body System or Organ Class Code | Num | MedDRA | Perm | AE.AEBDSYCD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |
| AELLT | Lowest Level Term | Char | MedDRA | Cond | AE.AELLT This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. Conditional on whether used for analysis. |
| AELLTCD | Lowest Level Term Code | Num | MedDRA | Perm | AE.AELLTCD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |
| AEPTCD | Preferred Term Code | Num | MedDRA | Perm | AE.AEPTCD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|---------------------------------|------|---------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AEHLT | High Level Term | Char | MedDRA | Cond | AE.AEHLT This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. Conditional on whether used for analysis. |
| AEHLTCD | High Level Term Code | Num | MedDRA | Perm | AE.AEHLTCD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |
| AEHLGT | High Level Group Term | Char | MedDRA | Cond | AE.AEHLGT This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. Conditional on whether used for analysis. |
| AEHLTGCD | High Level Group Term Code | Num | MedDRA | Perm | AE.AEHLTGCD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |
| AESOC | Primary System Organ Class | Char | MedDRA | Cond | AE.AESOC This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. Conditional on whether a secondary SOC was used for the primary analysis. See Amendment 1 to SDTM [3]. |
| AESOCDD | Primary System Organ Class Code | Num | MedDRA | Perm | AE.AESOCDD This would be copied from the SDTM AE domain or supplemental qualifier dataset. Include the dictionary version in the variable metadata. |

4.1.4 Timing Variables

Timing variables are copied from SDTM and derived within ADaM. Included below are the common timing variables. If other timing variables are collected in SDTM and pertinent for analysis, these should be included in ADaM. Additional timing variables, such as those for analysis period or phase, can be included. For more details on timing variables, see the BDS structure in the ADaMIG version 1 [2].

Table 4.1.4.1 Timing Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-------------------------------------|------|---------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AESTDTC | Start Date/Time of Adverse Event | Char | ISO 8601 | Perm | Copied from AE.AESTDTC |
| ASTDT | Analysis Start Date | Num | | Cond | Created from converting AE.AESTDTC from character ISO8601 format to numeric date format, applying imputation rules as specified in the SAP or metadata. Conditional on whether start date is pertinent for study and AE.AESTDTC is populated in SDTM. |
| ASTDTM | Analysis Start Date/Time | Num | | Cond | Created from converting AE.AESTDTC from character ISO8601 format to numeric date-time format, applying imputation rules as specified in the SAP or metadata. Conditional on whether start date-time is pertinent for study and AE.AESTDTC with time is populated in SDTM. |
| ASTDTF | Analysis Start Date Imputation Flag | Char | (DATEFL) | Cond | Created during conversion of AE.AESTDTC from character to numeric. Imputation flags are described in the ADaMIG V1.0 [2] General Timing Variable Convention #6. Conditional on whether any imputation is done for the start date. |
| ASTTMF | Analysis Start Time Imputation Flag | Char | (TIMEFL) | Cond | Created during conversion of AE.AESTDTC from character to numeric. Imputation flags are described in the ADaMIG V1.0 [2] General Timing Variable Convention #6. Conditional on whether any imputation is done for the start time. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-----------------------------------|------|------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AEENDTC | End Date/Time of Adverse Event | Char | ISO 8601 | Perm | Copied from AE.AEENDTC |
| AENDT | Analysis End Date | Num | | Cond | Created from converting AE.AEENDTC from character ISO8601 format to numeric date format, applying imputation rules as specified in the SAP or metadata. Conditional on whether end date is pertinent for study and AE.AEENDTC is populated in SDTM. |
| AENDTM | Analysis End Date/Time | Num | | Cond | Created from converting AE.AEENDTC from character ISO8601 format to numeric date-time format, applying imputation rules as specified in the SAP or metadata. Conditional on whether end date-time is pertinent for study and AE.AEENDTC with time is populated in SDTM. |
| AENDTF | Analysis End Date Imputation Flag | Char | (DATEFL) | Cond | Created during conversion of AE.AEENDTC from character to numeric. Imputation flags are described in the ADaMIG V1.0 [2] General Timing Variable Convention #6. Conditional on whether any imputation is done for the end date. |
| AENTMF | Analysis End Time Imputation Flag | Char | (TIMEFL) | Cond | Created during conversion of AE.AEENDTC from character to numeric. Imputation flags are described in the ADaMIG V1.0 [2] General Timing Variable Convention #6. Conditional on whether any imputation is done for the end time. |
| ASTDY | Analysis Start Relative Day | Num | | Cond | Example derivation: $ASTDY = ADSL.TRTSDT + 1$ if $ASTDT \geq TRTSDT$, else $ASTDY = ADSL.TRTSDT$ if $ASTDT < TRTSDT$ This variable may instead be copied from AESTDY. Conditional on whether analysis start relative day is pertinent to the study. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-------------------------------------|------|---------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AESTDY | Study Day of Start of Adverse Event | Num | | Perm | AE.AESTDY ASTDY may differ from AESTDY due to date imputation and the option in ADaM to use a reference date other than SDTM's RFSTDTC. Including AE.AESTDY in addition to ASTDY adds traceability. |
| AENDY | Analysis End Relative Day | Num | | Perm | Example derivation: AENDT – ADSL.TRSDT + 1 if AENDT ≥ TRSDT, else AENDT – ADSL.TRSDT if AENDT < TRSDT This variable may instead be copied from AEENDY. |
| AEENDY | Study Day of End of Adverse Event | Num | | Perm | AE.AEENDY AENDY may differ from AEENDY due to date imputation and the option in ADaM to use a reference date other than SDTM's RFSTDTC. Including AE.AEENDY in addition to AENDY adds traceability. |
| ADURN | AE Duration (N) | Num | | Perm | Derive from ASTDT (or ASTDTM) and AENDT (or AENDTM) |
| ADURU | AE Duration Units | Char | | Cond | Conditional on whether ADURN is included. |
| AEDUR | Duration of Adverse Event | Char | ISO 8601 | Perm | AE.AEDUR Because AEDUR is a collected field and ADURN is derived, the values will often differ. Including AEDUR in addition to ADURN can add traceability. |
| APERIOD | Period | Num | | Perm | The numeric value characterizing the period to which the record belongs. |
| APERIODC | Period (C) | Char | | Perm | Text characterizing to which period the record belongs. One-to-one map to APERIOD. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|----------------|------|---------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| APHASE | Phase | Char | | Perm | <p>Example derivation: If $ASTDT < ADSL.TRTSDT$, then $APHASE = 'RUN-IN'$ Else if $ASTDT > ADSL.TRTEDT + x$ days then $APHASE = 'FOLLOW-UP'$, Else $APHASE = 'TREATMENT'$. The number x is defined by the sponsor, should be consistent with the Treatment Emergent Analysis Flag (TRTEMFL) variable described below and often incorporates the known half-life of the drug.</p> |

Values in parenthesis are the names of CDISC Controlled Terminology codelists.

4.1.5 Indicator Variables

Indicator variables can be copied from SDTM or derived within ADaM. If indicator variables other than those shown here are included in SDTM and pertinent for analysis, these should be copied to ADaM. If other indicator analysis variables are needed for analysis, these can also be added.

Table 4.1.5.1 Indicator Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|----------------------------------|------|---------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| TRTEMFL | Treatment Emergent Analysis Flag | Char | Y | Cond | <p>Example derivation: If $ADSL.TRTSDT \leq ASTDT \leq ADSL.TRTEDT + x$ days then $TRTEMFL = 'Y'$ The number x is defined by the sponsor and often incorporates the known half-life of the drug. Variable TRTEMFL is to be used for any analysis of treatment-emergent AEs. This variable is conditional on whether the concept of treatment emergent is a key feature of the AE analyses.</p> |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-------------------------|------|---------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AETRTEM | Treatment Emergent Flag | Char | (NY) | Perm | SUPPAE.QVAL where QNAM='AETRTEM'. See the SDTMIG version 3.1.2 [3] for more information. TRTEMFL may differ from AETRTEM due to different definitions, date imputation, and other analysis rules. Including AETRTEM in addition to TRTEMFL will add traceability. |
| ANLzzFL | Analysis Record Flag zz | Char | Y | Cond | The ANLzzFL flag is useful in many circumstances; an example is when there is more than one coding path included for analysis, in which case separate analysis flags could be used to denote primary coding path or the records used for analysis from each coding path. See the ADaMIG version 1 [2] for more information on this flag variable. This variable is conditional on whether analysis records flags are needed for analysis. |
| PREFL | Pre-treatment Flag | Char | Y | Cond | Example derivation: If ASTDT < ADSL.TRSDT then PREFL='Y' This variable is conditional on whether the concept of pre-treatment AEs is a feature of the study and whether used for analysis. |
| FUPFL | Follow-up Flag | Char | Y | Cond | Example derivation: If ASTDT > ADSL.TRTEDT then FUPFL='Y' This variable is conditional on whether the concept of follow-up AEs is a feature of the study and whether used for analysis. |

Values in parenthesis are the names of CDISC Controlled Terminology codelists.

4.1.6 Occurrence Flag Variables

Occurrence flags can be used to prepare data for analysis. They are typically created by sorting the data in the required order and then flagging the first treatment emergent record. The more common occurrence flags for MedDRA and a structure for additional flags are show below:

Table 4.1.6.1 Occurrence Flag Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|--|---|-------------|---|-------------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AOCCFL | 1st Occurrence of Any AE Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for each subject. |
| AOCCSFL | 1st Occurrence of SOC Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for each body system for each subject. |
| AOCCPFL | 1st Occurrence of Preferred Term Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for each preferred term for each subject. |
| AOCCIFL | 1st Max Sev./Int. Occurrence Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for maximum severity for each subject. |
| AOCCSIFL | 1st Max Sev./Int. Occur Within SOC Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for maximum severity within body system for each subject. |
| AOCCPIFL | 1st Max Sev./Int. Occur Within PT Flag | Char | Y | Perm | Example derivation: Sort the data in the required order and flag the first treatment emergent record for maximum severity within preferred term for each subject. |
| AOCCzzFL | 1st Occurrence of | Char | Y | Perm | Additional flag variables as needed for analysis. Derivation rules for these flags need to be described in the metadata. |

4.1.7 Treatment/Dose Variables

The treatment variable used for analysis must be included. Typically this would be TRTP, TRTA, TRTxxP, or TRTxxA. See the ADaMIG version 1 [2] for more details on these variables. Additional dosing variables may also be included.

Table 4.1.7.1 Treatment Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-----------------------------------|------|------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| DOSEAEON | Study Drug Dose at AE Onset | Num | | Perm | Study drug dose a subject took when adverse event occurred. Example derivation: Obtained from EX.EXDOSE where AESTDTC falls between the values of EX.EXSTDTC and EX.EXENDTC |
| DOSAEONU | Study Drug Dose at AE Onset Units | Char | | Cond | Conditional on whether DOSEAEON is included. |
| DOSECUM | Cumulative Study Drug Dose | Num | | Perm | Cumulative study drug dose at the start of the AE. |
| DOSECUMU | Cumulative Study Drug Dose Units | Char | | Cond | Conditional on whether DOSECUM is included. |

4.1.8 Descriptive Variables

Variables that describe the adverse event, including severity, relationship, and toxicity grade, are often used in analysis. If the analysis version of the variable differs from the version in SDTM, additional variables must be added using the conventions below and described in Section 4.1 . Below are some common descriptive variables that are often included in ADAE. Any other SDTM variables should be included as appropriate (e.g. AEOUT, AESDTH, etc.).

Table 4.1.8.1 Descriptive Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|------------------------|------|------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| AESER | Serious Event | Char | (NY) | Req | AE.AESER |
| AESEV | Severity/Intensity | Char | (AESEV) | Perm | AE.AESEV |
| AESEVN | Severity/Intensity (N) | Num | 1, 2, 3 | Perm | Code AE.AESEV to numeric Low intensity should correspond to low value |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|---------------------------------|------|------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| ASEV | Analysis Severity/Intensity | Char | * | Perm | Apply imputation rules for missing severity of adverse events as specified in the SAP or metadata. May change case of text, such as from all uppercase in AESEV to mixed case in ASEV. |
| ASEVN | Analysis Severity/Intensity (N) | Num | 1, 2, 3 | Perm | Code ASEV to numeric Low intensity should correspond to low value |
| SEVGRy | Pooled Severity Group y | Char | * | Perm | Pooled grouping of AE Severity for analysis (e.g. mild/moderate or severe). |
| SEVGRyN | Pooled Severity Group y (N) | Num | * | Perm | Code SEVGRy to numeric Low intensity should correspond to low value |
| AEREL | Causality | Char | * | Perm | AE.AEREL |
| AERELN | Causality (N) | Num | * | Perm | Code AE.AEREL to numeric Low relation should correspond to low value |
| AREL | Analysis Causality | Char | * | Perm | Apply imputation rules for missing causality of study drug as specified in the SAP or metadata. May change case of text, such as from all uppercase in AEREL to mixed case in AREL. |
| ARELN | Analysis Causality (N) | Num | * | Perm | Code AREL to numeric |
| RELGRy | Pooled Causality Group y | Char | * | Perm | Pooled grouping of causality of study drug for analysis (e.g. related, Not related). |
| RELGRyN | Pooled Causality Group y (N) | Num | * | Perm | Code of RELGRy to numeric Low intensity should correspond to low value |
| AETOXGR | Standard Toxicity Grade | Char | * | Perm | AE.AETOXGR |
| AETOXGRN | Standard Toxicity Grade (N) | Num | * | Perm | Code AETOXGR to numeric Low toxicity should correspond to low value |
| ATOXGR | Analysis Toxicity Grade | Char | * | Perm | Toxicity grade for analysis. May be based on AETOXGR or an imputed or assigned value. May change case of text, such as from all uppercase in AETOXGR to mixed case in ATOXGR. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|-----------------------------------|------|------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| ATOXGRN | Analysis Toxicity Grade (N) | Num | * | Perm | Code ATOXGR to numeric Low toxicity should correspond to low value |
| TOXGGRy | Pooled Toxicity Grade Group y | Char | * | Perm | Pooled grouping of toxicity grade for analysis. |
| TOXGGRyN | Pooled Toxicity Grade y (N) | Num | * | Perm | Code of TOXGGRy to numeric Low toxicity should correspond to low value |
| AEACN | Action Taken with Study Treatment | Char | (ACN) | Perm | AE.AEACN |

* Indicates variable may be subject to sponsor-defined controlled terminology. Values in parenthesis are the names of CDISC Controlled Terminology codelists.

4.1.9 MedDRA Query Variables

Standardized MedDRA Queries (SMQs) are becoming increasingly common in clinical trial safety evaluations, particularly when known or suspected safety issues are associated with experimental compounds. In addition, Customized Queries (CQs) are often used to modify an SMQ or identify AEs of special interest through grouping of MedDRA terms. The following variables are used to identify SMQs and CQs, where the ‘zz’ indicates a number starting with 01 for each SMQ or CQ of interest. This ordering can be based on importance or some other sponsor-defined criteria. It is recommended that the ordering be consistent across studies within a development program, but it is recognized that there may be situations where this is not possible or practical.

Table 4.1.9.1 Standardized MedDRA Query Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|----------------|------|------------------------------|------|--|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| SMQzzNAM | SMQ zz Name | Char | | Cond | The standardized MedDRA query’s name. Would be blank for terms that are not in the SMQ. Therefore this variable could be blank if none of the terms within the SMQ are present in the dataset. Conditional on whether SMQ analysis is done. |

| ADAE – Adverse Event Analysis Dataset | | | | | |
|---------------------------------------|--------------------------|------|------------------------------|------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| SMQzzCD | SMQ zz Code | Num | | Perm | The standardized MedDRA queries number code. |
| SMQzzSC | SMQ zz Scope | Char | BROAD, NARROW | Cond | The search strategy for SMQs can be narrow or broad. The preferred terms that are narrow in scope have high specificity for identifying events of interest while the broad terms have high sensitivity. By definition, all narrow terms are also considered within the broad score. Therefore, to summarize all broad terms, terms with either narrow OR broad would be considered. Will be null for terms that do not meet the criteria. Conditional on whether SMQ analysis is done. |
| SMQzzSCN | SMQ zz Scope (N) | Num | 1, 2 | Perm | Will be null for terms that do not meet the criteria. |
| CQzzNAM | Customized Query zz Name | Char | | Cond | The customized query (CQ) name or name of the AE of special interest category based on a grouping of MedDRA terms. Would be blank for terms that are not in the CQ. Conditional on whether CQ analysis is done. Examples: “DERMATOLOGICAL EVENTS”, “CARDIAC EVENTS”, “IARS (INFUSION ASSOCIATED REACTIONS)” |

4.1.10 Original or Prior Coding Variables

The suite of variables used for the primary analysis are described in section 4.1.2. Variables described here are those from original (or prior) analyses, and not used directly for analysis from this data set.

Keeping multiple sets of mapping variables is not common, but there are a couple instances where it might be helpful:

- When a study is mapped to one version of MedDRA or other mapping dictionary for an interim analysis and another for final analysis
- When studies using different version of MedDRA or other mapping dictionary are pooled together for an integrated analysis

The variables described below provide traceability to original (or prior) analysis(es). The suffix “y” represents an integer [1-9] corresponding to a previous version. Include the dictionary name and version as part of the metadata for each variable.

These variable names at this time are recommendations only. There is an ADaM sub-team currently working on integration, and this group may create different naming conventions for that type of analysis.

Table 4.1.10.1 Original or Prior MedDRA Coding Variables

| ADAE – Adverse Event Analysis Dataset | | | | | |
|--|-----------------------------------|-------------|---|-------------|---|
| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
| DECDORGy | PT in Original Dictionary y | Char | MedDRA | Perm | Original preferred term coding of AE.AETERM using MedDRA or other dictionary version X.X. |
| BDSYORGy | SOC in Original Dictionary y | Char | MedDRA | Perm | Original body system coding of AE.AETERM using MedDRA or other dictionary version X.X. |
| HLGTORGy | HLGT in Original Dictionary y | Char | MedDRA | Perm | Original HLGT coding of AE.AETERM using MedDRA or other dictionary version X.X. |
| HLTORGy | HLT in Original Dictionary y | Char | MedDRA | Perm | Original HLT coding of AE.AETERM using MedDRA or other dictionary version X.X. |
| LLTORGy | LLT in Original Dictionary y | Char | MedDRA | Perm | Original LLT coding of AE.AETERM using MedDRA or other dictionary version X.X. |
| LLTNORGy | LLT Code in Original Dictionary y | Char | MedDRA | Perm | Original LLT code of AE.AETERM using MedDRA or other dictionary version X.X. |

4.2 Other Metadata

Because the AE structure does not use parameters, there is no need for Parameter Value-Level Metadata.

The other type of ADaM metadata is the Analysis Results Metadata, which may be included for analysis of AEs. (see ADaM v2.1 [1] for more details).

5. Example 1: Analysis of Treatment Emergent Adverse Events

The basic summary of adverse event frequencies described in section 12.2.2 (and located in section 14.3.1) of ICH Guideline E3 [7] report should be used to display frequencies in treatment and control groups.

This example displays a simple summary of all treatment emergent adverse events. The example is based on a two treatment parallel design study. The display summarizes (1) the number of subjects in each treatment group in whom any adverse event was experienced and (2) the rate of occurrence in each treatment group.

5.1 Analysis Display Example Layout

Table 5.1.1 Example of Summary of Treatment Emergent Adverse Events²

Table 14.2.7.1

Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Analysis Population: Safety

| | Treatment A | Treatment B |
|---|--------------------|--------------------|
| SYSTEM ORGAN CLASS | (N = xxx) | (N = xxx) |
| Preferred Term | n (%) | n (%) |
| Number of subjects reporting at least one adverse event | x (x.x) | x (x.x) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| At least one event | x (x.x) | x (x.x) |
| Anaemia | x (x.x) | x (x.x) |
| ... | x (x.x) | x (x.x) |
| CARDIAC DISORDERS | | |
| At least one event | x (x.x) | x (x.x) |
| Angina pectoris | x (x.x) | x (x.x) |
| Coronary artery disease | x (x.x) | x (x.x) |
| Ventricular tachycardia | x (x.x) | x (x.x) |
| Myocardial infarction | x (x.x) | x (x.x) |
| Ventricular fibrillation | x (x.x) | x (x.x) |
| ... | x (x.x) | x (x.x) |
| <Other SOCs and PTs> | | |

Page 1 of x

N = Safety subjects, i.e., subjects who received at least one dose of study drug
n = Number of subjects reporting at least one treatment emergent adverse event
% = $n / N * 100$

Adverse events are presented by descending frequency within Treatment B
System organ classes and preferred terms are coded using MedDRA version x.x.

² The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

5.2 Sample ADAE Variable Metadata

Table 5.2.1 Example of ADAE Variable Metadata

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|-------------------------------------|---------------|----------------|-----------------------------|---|
| ADAE | STUDYID | Study Identifier | text | \$3 | | AE.STUDYID |
| ADAE | USUBJID | Unique Subject Identifier | text | \$11 | | AE.USUBJID |
| ADAE | AESEQ | Sequence Number | integer | 3.0 | | AE.AESEQ |
| ADAE | AETERM | Reported Term for the Adverse Event | text | \$200 | | AE.AETERM |
| ADAE | AEDECOD | Dictionary-Derived Term | text | \$200 | MedDRA | AE.AEDECOD MedDRA Version 11.1 |
| ADAE | AEBODSYS | Body System or Organ Class | text | \$200 | MedDRA | AE.AEBODSYS MedDRA Version 11.1 |
| ADAE | TRTEMFL | Treatment Emergent Analysis Flag | text | \$1 | Y | If ADSL.TRSDT <= ASTDT<=(ADSL.TRTEDT +14) then TRTEMFL='Y' |
| ADAE | PREFL | Pre-treatment Flag | text | \$1 | Y | If ASTDT < ADSL.TRSDT then PREFL='Y' |
| ADAE | FUPFL | Follow-up Flag | text | \$1 | Y | If ASTDT > ADSL.TRTEDT+14 then FUPFL='Y' |
| ADAE | AESTDTC | Start Date/Time of Adverse Event | text | \$10 | | AE.AESTDTC |
| ADAE | ASTDT | Analysis Start Date | integer | yymmdd10. | | <Sponsor will insert derivation here> |
| ADAE | ASTDTF | Analysis Start Date Imputation Flag | text | \$1 | (DATEFL) | If start date is completely missing or missing the year then ASTDTF='Y' Else if start date has month missing then ASTDTF='M' Else if start date has day missing then ASTDTF='D' |
| ADAE | AEENDTC | End Date/Time of Adverse Event | text | \$10 | | AE.AEENDTC |
| ADAE | AENDT | Analysis End Date | integer | yymmdd10. | | <Sponsor will insert derivation here> |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|-----------------------------------|---------------|----------------|---|---|
| ADAE | AENDTF | Analysis End Date Imputation Flag | text | \$1 | (DATEFL) | If end date is completely missing or missing the year then AENDTF='Y' Else if end date has month missing then AENDTF='M' Else if end date has day missing then AENDTF='D' |
| ADAE | AESER | Serious Event | text | \$1 | (YN) | AE.AESER |
| ADAE | APHASE | Phase | text | \$15 | PRE-TREATMENT TREATMENT FOLLOW-UP | If ASTDT<ADSL.TRSDT, then APHASE='PRE-TREATMENT' Else if ASTDT > ADSL.TRSDT + 14 days then APHASE='FOLLOW-UP', Else APHASE='TREATMENT' |
| ADAE | AESEV | Severity/Intensity | text | \$25 | (AESEV) | AE.AESEV |
| ADAE | ASEV | Analysis Severity/Intensity | text | \$25 | Mild Moderate Severe | If AE.AESEV='MILD' then ASEV='Mild' Else if AE.AESEV='MODERATE' then ASEV='Moderate' Else if AE.AESEV is equal to 'SEVERE' or Severity/Intensity is missing then ASEV='Severe' |
| ADAE | ASEVN | Analysis Severity/Intensity (N) | integer | 1.0 | 1, 2, 3 | Map ASEV to ASEVN in the following manner: 'Mild' = 1 'Moderate' = 2 'Severe' = 3 |
| ADAE | AEREL | Causality | text | \$25 | NOT RELATED UNLIKELY RELATED POSSIBLY RELATED PROBABLY RELATED DEFINITELY RELATED | AE.AEREL |
| ADAE | RELGR1 | Pooled Causality Group 1 | text | \$25 | Not Related Related | If AE.AEREL is equal to 'NOT RELATED' or 'UNLIKELY RELATED' then RELGR1='Not Related' Else if AE.AEREL is equal to 'POSSIBLY RELATED' or 'PROBABLY RELATED' or 'DEFINITELY RELATED' or Causality is missing then RELGR1='Related' |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|---------------------------------------|---------------|----------------|-----------------------------|--|
| ADAE | RELGR1N | Pooled Causality Group 1 (N) | integer | 1.0 | 0, 1 | Map RELGR1 to RELGR1N in the following manner: 'Not Related' = 0 'Related' = 1 |
| ADAE | SAFFL | Safety Population Flag | text | \$1 | Y,N | ADSL.SAFFL |
| ADAE | AOCCFL | 1st Occurrence of Any AE Flag | text | \$1 | Y | Subset ADAE to Treatment Emergent Adverse Events (TRTEMFL='Y') Sort by Subject (USUBJID), Analysis Start Date (ASTDT), and Sequence Number (AESEQ) and flag the first record (set AOCCFL='Y') within each Subject |
| ADAE | AOCCSFL | 1st Occurrence of SOC Flag | text | \$1 | Y | Subset ADAE to Treatment Emergent Adverse Events (TRTEMFL='Y') Sort by Subject (USUBJID), System Organ Class (AEBODSYS), Analysis Start Date (ASTDT), and Sequence Number (AESEQ) and flag the first record (set AOCCSFL='Y') within each Subject and SOC |
| ADAE | AOCCPFL | 1st Occurrence of Preferred Term Flag | text | \$1 | Y | Subset ADAE to Treatment Emergent Adverse Events (TRTEMFL='Y') Sort by Subject (USUBJID), System Organ Class (AEBODSYS), Preferred Term (AEDECOD) Analysis Start Date (ASTDT), and Sequence Number (AESEQ) and flag the first record (set AOCCPFL='Y') within each Subject, SOC, and PT |
| ADAE | TRTA | Actual Treatment | text | \$6 | Drug A Drug B | ADSL.TRT01A |
| ADAE | TRTAN | Actual Treatment (N) | integer | 1.0 | 1, 2 | ADSL.TRT01AN Drug A = 1 Drug B = 2 |
| ADAE | TRTSDT | Date of First Exposure to Treatment | integer | yymmdd10. | | ADSL.TRTSDT |
| ADAE | TRTEDT | Date of Last Exposure to Treatment | integer | yymmdd10. | | ADSL.TRTEDT |
| ADAE | AGE | Age | integer | 3.0 | | ADSL.AGE |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|--------------------|---------------|----------------|-----------------------------|---------------------|
| ADAE | AGEGR1 | Pooled Age Group 1 | text | \$4 | <65, >=65 | ADSL.AGEGR1 |
| ADAE | SEX | Sex | text | \$1 | (SEX) | ADSL.SEX |
| ADAE | RACE | Race | text | \$41 | (RACE) | ADSL.RACE |

5.3 Sample ADAE Data

Table 5.3.1 is an illustration of the adverse events analysis dataset (ADAE) defined above. The ADAE dataset illustrated in this example was designed to support some standard subsets and/or classifications of treatment emergent adverse events including seriousness, severity, and relationship to study drug. The example describes some of the key variables and records that would be included in the dataset.

Key points to note in the example are:

1. The producer of the dataset chose to use record level actual treatment variable (TRTA) populated with the same value across all rows in the dataset rather than subject level treatment variable (TRT01A). For a parallel design either TRTA or TRT01A could be used as the actual treatment identifier. The producer interpreted TRTA as the treatment associated with the record for analysis display purposes and populated the pre-treatment records with treatment even though subjects had not yet received treatment at that time.
2. Variables such as AESEQ, AETERM, and AESTDTC are copied in from SDTM AE domain to provide data point traceability.
3. Variables such as AEBODSYS, AEDECOD, AESER, AESEV, and AEREL are copied in from the SDTM AE domain for analysis purposes.
4. ASTDT is the AE timing variable used for analysis. Other timing variables such as AENDT/ASTDTF/AENDTF/AESTDTC/AEENDTC/TRTSDT/TRTEDT are supportive variables for metadata traceability.
5. The addition of ASEV and RELGR1 allow for the imputation of missing severity and grouping and imputation of Relationship to Study Drug as specified in the Statistical Analysis Plan.
6. The Occurrence Flags (AOCCzzFL) are permissible. The main purpose of these flags is to facilitate data point traceability between records in the dataset and unique counts in the summary displays. In addition if a Time to Event (TTE) Analysis is built off of Adverse Events, the flags provide a crucial link between the summary records in the TTE BDS and the source of the records in ADAE. If the producer of the ADAE dataset has standard programs in place to summarize unique counts of events then they may chose not to create these flags.
7. The core variables of AGE, AGEGR1, SEX, and RACE are included in ADAE to facilitate subgroup analyses.

Table 5.3.1 Sample ADAE Data

| Row | STUDYID | USUBJID | AESEQ | AETERM | AEDECOD | AEBODSYS | TRTEMFL | PREFL | FUPFL |
|-----|---------|-------------|-------|-------------------------------|----------------------|--|---------|-------|-------|
| 1 | XYZ | XYZ-001-001 | 1 | HEADACHE | Headache | Nervous system disorders | | Y | |
| 2 | XYZ | XYZ-001-001 | 2 | CHRONIC BACK PAIN | Back pain | Musculoskeletal and connective tissue disorders | | Y | |
| 3 | XYZ | XYZ-001-001 | 3 | NOSE BLEEDING RIGHT NOSTRIL | Epistaxis | Respiratory, thoracic and mediastinal disorders | | Y | |
| 4 | XYZ | XYZ-001-001 | 4 | PROBLEMS OF HYPOTENSION | Hypotension | Vascular disorders | Y | | |
| 5 | XYZ | XYZ-001-001 | 5 | HEADACHE | Headache | Nervous system disorders | Y | | |
| 6 | XYZ | XYZ-001-001 | 6 | HEADACHE | Headache | Nervous system disorders | Y | | |
| 7 | XYZ | XYZ-001-001 | 7 | LOOSE STOOL | Diarrhoea | Gastrointestinal disorders | Y | | |
| 8 | XYZ | XYZ-001-001 | 8 | ABDOMINAL DISCOMFORT | Abdominal discomfort | Gastrointestinal disorders | Y | | |
| 9 | XYZ | XYZ-001-001 | 9 | DIARRHEA | Diarrhoea | Gastrointestinal disorders | Y | | |
| 10 | XYZ | XYZ-001-001 | 10 | ABDOMINAL FULLNESS DUE TO GAS | Abdominal distension | Gastrointestinal disorders | Y | | |
| 11 | XYZ | XYZ-001-001 | 11 | NAUSEA (INTERMITTENT) | Nausea | Gastrointestinal disorders | Y | | |
| 12 | XYZ | XYZ-001-001 | 12 | WEAKNESS | Asthenia | General disorders and administration site conditions | Y | | |
| 13 | XYZ | XYZ-001-001 | 13 | HEADACHE | Headache | Nervous system disorders | Y | | |
| 14 | XYZ | XYZ-001-001 | 14 | HEADACHE | Headache | Nervous system disorders | Y | | |
| 15 | XYZ | XYZ-001-001 | 15 | HYPOTENSIVE | Hypotension | Vascular disorders | Y | | |
| 16 | XYZ | XYZ-001-001 | 16 | HEADACHE | Headache | Nervous system disorders | | | Y |

| Row | AESTDTC | ASTDT | ASTDTF | AEENDTC | AENDT | AENDTF | AESER | APHASE | AESEV | ASEV | ASEVN |
|-----|------------|------------|--------|------------|------------|--------|-------|---------------|----------|----------|-------|
| 1 | 2006-01 | 2006-01-01 | D | 2006-01-22 | 2006-01-22 | | N | PRE-TREATMENT | MILD | Mild | 1 |
| 2 | 2006-01-21 | 2006-01-21 | | 2006-01-28 | 2006-01-28 | | N | PRE-TREATMENT | MODERATE | Moderate | 2 |
| 3 | 2006-01-22 | 2006-01-22 | | 2006-01-22 | 2006-01-22 | | N | PRE-TREATMENT | MILD | Mild | 1 |
| 4 | | 2006-01-23 | Y | | 2006-05-15 | Y | N | TREATMENT | MILD | Mild | 1 |

| Row | AESTDTC | ASTDT | ASTDTF | AEENDTC | AENDT | AENDTF | AESER | APHASE | AESEV | ASEV | ASEVN |
|-----|------------|------------|--------|------------|------------|--------|-------|-----------|----------|----------|-------|
| 5 | 2006-01-24 | 2006-01-24 | | 2006-01 | 2006-01-31 | D | N | TREATMENT | MODERATE | Moderate | 2 |
| 6 | 2006-02 | 2006-02-01 | D | 2006-02-05 | 2006-02-05 | | N | TREATMENT | SEVERE | Severe | 3 |
| 7 | 2006-03-05 | 2006-03-05 | | 2006-03-06 | 2006-03-06 | | N | TREATMENT | | Severe | 3 |
| 8 | 2006-03-05 | 2006-03-05 | | 2006 | 2006-05-15 | M | N | TREATMENT | MODERATE | Moderate | 2 |
| 9 | 2006-03-17 | 2006-03-17 | | 2006-03-18 | 2006-03-18 | | N | TREATMENT | MODERATE | Moderate | 2 |
| 10 | 2006-03-17 | 2006-03-17 | | 2006-03-19 | 2006-03-19 | | N | TREATMENT | MILD | Mild | 1 |
| 11 | 2006-04-20 | 2006-04-20 | | 2006-04-22 | 2006-04-22 | | N | TREATMENT | MILD | Mild | 1 |
| 12 | 2006-05-17 | 2006-05-17 | | 2006-05-20 | 2006-05-20 | | N | TREATMENT | MILD | Mild | 1 |
| 13 | 2006-05-20 | 2006-05-20 | | 2006-05-22 | 2006-05-22 | | N | TREATMENT | MILD | Mild | 1 |
| 14 | 2006-05-23 | 2006-05-23 | | 2006-06-27 | 2006-06-27 | | N | TREATMENT | MILD | Mild | 1 |
| 15 | 2006-05-21 | 2006-05-21 | | 2006-05-25 | 2006-05-25 | | Y | TREATMENT | SEVERE | Severe | 3 |
| 16 | 2006-06-01 | 2006-06-01 | | 2006-06-01 | 2006-06-01 | | N | FOLLOW-UP | MILD | Mild | 1 |

| Row | AEREL | RELGR1 | RELGR1N | SAFFL | AOCFL | AOCCSFL | AOCCPFL | TRTA | TRTAN | TRTSDT | TRTEDT |
|-----|--------------------|-------------|---------|-------|-------|---------|---------|--------|-------|------------|------------|
| 1 | NOT RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 2 | NOT RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 3 | NOT RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 4 | POSSIBLY RELATED | Related | 1 | Y | Y | Y | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 5 | PROBABLY RELATED | Related | 1 | Y | | Y | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 6 | PROBABLY RELATED | Related | 1 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 7 | DEFINITELY RELATED | Related | 1 | Y | | Y | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 8 | DEFINITELY RELATED | Related | 1 | Y | | | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 9 | DEFINITELY RELATED | Related | 1 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 10 | DEFINITELY RELATED | Related | 1 | Y | | | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 11 | PROBABLY RELATED | Related | 1 | Y | | | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 12 | POSSIBLY RELATED | Related | 1 | Y | | Y | Y | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 13 | UNLIKELY RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |

| Row | AEREL | RELGR1 | RELGRIN | SAFFL | AOCCFL | AOCCSFL | AOCCPFL | TRTA | TRTAN | TRTSDT | TRTEDT |
|-----|------------------|-------------|---------|-------|--------|---------|---------|--------|-------|------------|------------|
| 14 | UNLIKELY RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 15 | UNLIKELY RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |
| 16 | UNLIKELY RELATED | Not Related | 0 | Y | | | | Drug A | 1 | 2006-01-23 | 2006-05-15 |

| Row | AGE | AGEGR1 | SEX | RACE |
|-----|-----|--------|-----|-------|
| 1 | 54 | <65 | M | ASIAN |
| 2 | 54 | <65 | M | ASIAN |
| 3 | 54 | <65 | M | ASIAN |
| 4 | 54 | <65 | M | ASIAN |
| 5 | 54 | <65 | M | ASIAN |
| 6 | 54 | <65 | M | ASIAN |
| 7 | 54 | <65 | M | ASIAN |
| 8 | 54 | <65 | M | ASIAN |
| 9 | 54 | <65 | M | ASIAN |
| 10 | 54 | <65 | M | ASIAN |
| 11 | 54 | <65 | M | ASIAN |
| 12 | 54 | <65 | M | ASIAN |
| 13 | 54 | <65 | M | ASIAN |
| 14 | 54 | <65 | M | ASIAN |
| 15 | 54 | <65 | M | ASIAN |
| 16 | 54 | <65 | M | ASIAN |

6. Example 2: Analysis of Hemorrhages (SMQ) among Treatment Emergent Adverse Events by Sex

This example demonstrates how to incorporate SMQs into an AE analysis data set. In this example, an SMQ for hemorrhages is being used. This particular SMQ is hierarchical with only narrow-scope terms, including terms referring to different types of hemorrhage, hematoma, bleeding, etc. (for a full description of SMQs one may refer to the Maintenance and Support Services Organization (MSSO's) Introductory Guide for Standardized MedDRA Queries [8]).

Key points to note in the example are:

1. The exact name of the SMQ being used in this example is "Haemorrhages (SMQ)". This precise terminology is used throughout the example.
2. As mentioned above, this particular SMQ contains only narrow scope terms. However, in order to illustrate best practice, the scope is also specified when a reference is made to the SMQ. Although redundant in this particular case, it is important to show which scope is being used when providing SMQ-based summaries since the scope can often have a profound effect on the percent of subjects who meet certain SMQ criteria.

6.1 Analysis Display Example Layouts

Table 6.1.1 Example of Summary of Haemorrhages (SMQ) (Narrow Scope) Adverse Events by Sex and Actual Treatment Group³

Table 14.2.7.3

Summary of Haemorrhages (SMQ) (Narrow Scope) Adverse Events by Sex and Actual Treatment Group
Analysis Population: Safety

| Preferred Term | Treatment Group n (%) | | | |
|--|-----------------------|------------------|--------------------|------------------|
| | B (N=447) | | A (N=455) | |
| | Females (N=281) | Males (N=166) | Females (N=297) | Males (N=158) |
| Any Haemorrhages (SMQ) (Narrow Scope) Event | 36 (12.8) | 48 (28.9) | 26 (8.8) | 31 (19.6) |
| Cerebral haemorrhage | 11 (3.9) | 15 (9.0) | 6 (2.0) | 13 (8.2) |
| Conjunctival haemorrhage | 0 | 1 (0.6) | 0 | 0 |
| Ecchymosis | 1 (0.4) | 0 | 0 | 0 |
| Epistaxis | 0 | 1 (0.6) | 0 | 0 |
| Extradural haematoma | 1 (0.4) | 0 | 1 (0.3) | 1 (0.6) |
| Gastrointestinal haemorrhage | 10 (3.6) | 4 (2.4) | 8 (2.7) | 6 (3.8) |
| Haematuria | 1 (0.4) | 2 (1.2) | 0 | 3 (1.9) |
| Haemoptysis | 1 (0.4) | 1 (0.6) | 0 | 0 |
| Haemorrhage | 1 (0.4) | 2 (1.2) | 0 | 0 |
| Infusion site haemorrhage | 1 (0.4) | 4 (2.4) | 2 (0.7) | 2 (1.3) |
| Melaena | 0 | 0 | 0 | 1 (0.6) |
| Petechiae | 0 | 1 (0.6) | 0 | 0 |
| Subarachnoid haemorrhage | 14 (5.0) | 24 (14.5) | 12 (4.0) | 11 (7.0) |
| Subdural haematoma | 2 (0.7) | 2 (1.2) | 0 | 0 |

³ The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

Figure 14.2.7.1
 Mosaic Plot of Hemorrhagic (SMQ) Preferred Terms by Sex and Actual Treatment Group
 Analysis Population: Safety

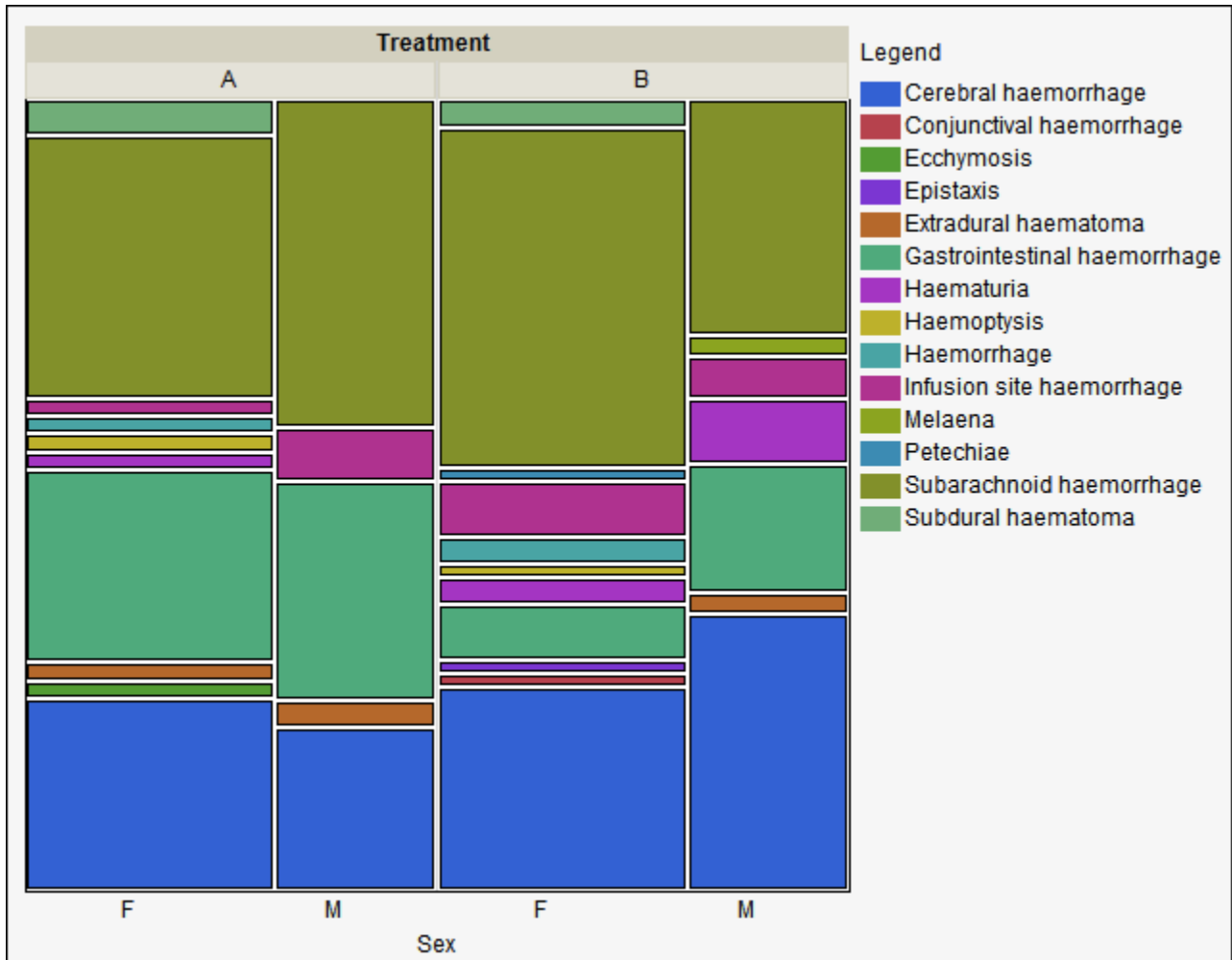


Figure 6.1.1 Example of Mosaic Plot of Haemorrhages (SMQ) (Narrow Scope) Preferred Terms by Sex and Actual Treatment Group⁴

⁴ The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

Figure 14.2.7.2

Hemorrhagic (SMQ) Preferred Terms Sorted by Relative Risk

Analysis Population: Safety Population

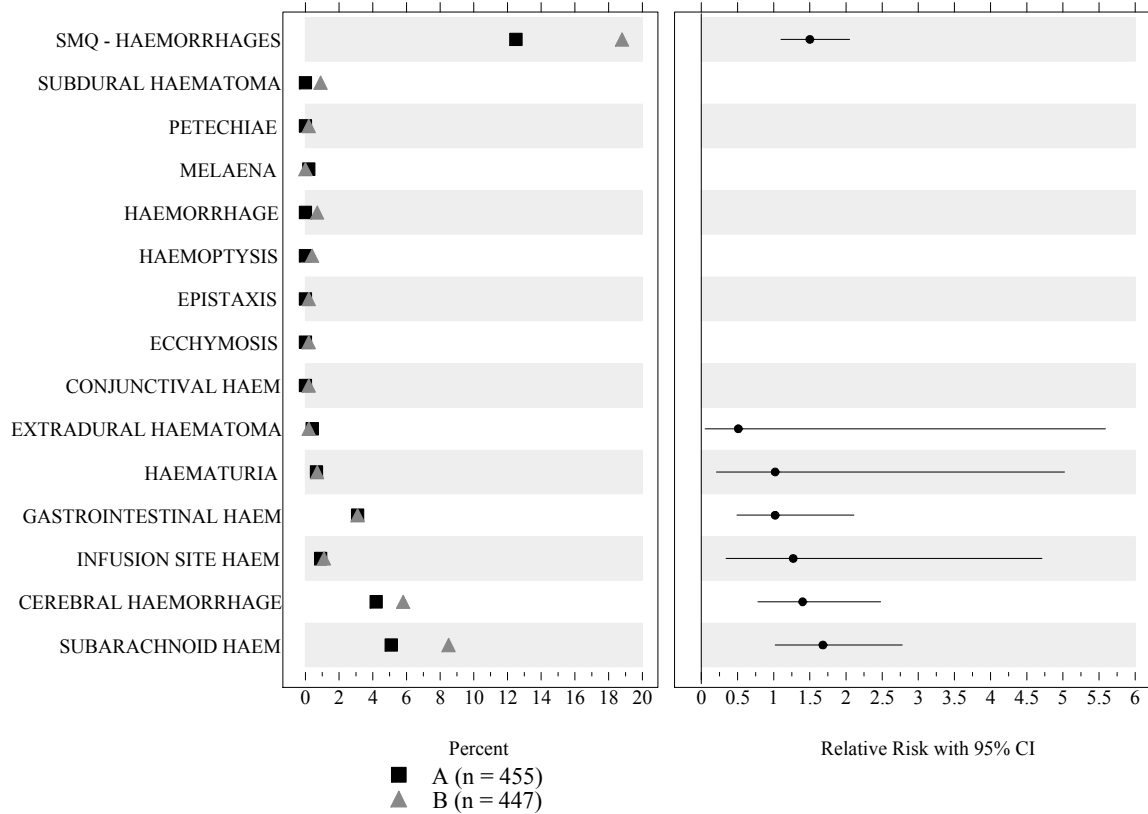


Figure 6.1.2 Example of Haemorrhages (SMQ) (Narrow Scope) Preferred Terms Sorted by Relative Risk⁵

⁵ The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

6.2 Sample ADAE Variable Metadata

In Table 6.2.1 below, four variables relate to our primary SMQ of interest (hemorrhage terms), SMQ01CD, SMQ01NAM, SMQ01SC, and SMQ01SCN. The ‘01’ indicates that this is the first SMQ and subsequent SMQs or subSMQs would be sequenced accordingly. Note that this ordering can be based on importance or some other sponsor-defined criteria. The first two of these variables, SMQ01CD and SMQ01NAM contain the numeric code and name for the SMQ from the MedDRA dictionary. The next two variables, SMQ01SC and SMQ01SCN, are character and numeric variables, respectively, that indicate not only whether or not the given AE meets the criteria for the given SMQ, but also whether the term meets the SMQ’s broad or narrow scope (the ‘SC’ suffix is for “scope”).

Table 6.2.1 Example of ADAE Variable Metadata

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|-------------------------------------|---------------|----------------|-----------------------------|---|
| ADAE | USUBJID | Unique Subject Identifier | Text | \$6 | | ADSL.USUBJID |
| ADAE | AETERM | Reported Term for the Adverse Event | Text | \$200 | | AE.AETERM |
| ADAE | AEDECOD | Dictionary-Derived Term | Text | \$200 | MedDRA | AE.AEDECOD |
| ADAE | AEBODSYS | Body System or Organ Class | Text | \$200 | MedDRA | AE.AEBODSYS |
| ADAE | ASTDT | Analysis Start Date | Integer | yymmdd10. | | <Sponsor will insert derivation here> |
| ADAE | AEPTCD | Preferred Term Code | integer | 8.0 | | AE.AEPTCD |
| ADAE | SMQ01CD | SMQ 01 Code | integer | 8.0 | | SMQ01CD=20000039 if the AEPTCD is included in this SMQ. |
| ADAE | SMQ01NAM | SMQ 01 Name | Text | \$200 | | SMQ01NAM='Haemorrhage terms (excl laboratory terms) (SMQ)' if the AEPTCD is included in this SMQ. |
| ADAE | SMQ01SC | SMQ 01 Scope | Text | \$6 | BROAD, NARROW | For this given SMQ, all scopes are Narrow. |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|------------------|---------------|----------------|-----------------------------|--|
| ADAE | SMQ01SCN | SMQ 01 Scope (N) | integer | 1.0 | 1, 2 | Map SMQ01SC to SMQ01SCN in the following manner: Broad = 1 Narrow = 2. |

6.3 Sample ADAE Data

Table 6.3.1: Sample ADAE Data Showing SMQ Variables

| Row | USUBJID | AETERM | AEDECOD | AEBODSYS | ASTDT | AEPTCD | SMQ01CD | SMQ01NAM | SMQ01SC | SMQ01SCN |
|-----|---------|----------------------------|---------------------|---|------------|----------|----------|---|---------|----------|
| 1 | 0092017 | SCLERAL BLEED RIGHT EYE | Scleral haemorrhage | Eye disorders | 2009-06-09 | 10050508 | 20000039 | Haemorrhage terms (excl laboratory terms) (SMQ) | NARROW | 2 |
| 2 | 0112012 | BRUISING OF LEFT UPPER ARM | Contusion | Injury, poisoning and procedural complications | 2008-08-27 | 10050584 | 20000039 | Haemorrhage terms (excl laboratory terms) (SMQ) | NARROW | 2 |
| 3 | 0112012 | BRUISING TO LEFT WRIST | Contusion | Injury, poisoning and procedural complications | 2007-08-22 | 10050584 | 20000039 | Haemorrhage terms (excl laboratory terms) (SMQ) | NARROW | 2 |
| 4 | 0112013 | NAUSEA | Nausea | Gastrointestinal disorders | 2010-06-16 | 10028813 | | | | |
| 5 | 0112014 | NOSE BLEEDING | Epistaxis | Respiratory, thoracic and mediastinal disorders | 2009-11-22 | 10015090 | 20000039 | Haemorrhage terms (excl laboratory terms) (SMQ) | NARROW | 2 |

| Row | USUBJID | AETERM | AEDECOD | AEBODSYS | ASTDT | AEPTCD | SMQ01CD | SMQ01NAM | SMQ01SC | SMQ01SCN |
|-----|---------|-----------|-----------|---|------------|----------|----------|---|---------|----------|
| 6 | 0122006 | EPISTAXIS | Epistaxis | Respiratory, thoracic and mediastinal disorders | 2009-11-06 | 10015090 | 20000039 | Haemorrhage terms (excl laboratory terms) (SMQ) | NARROW | 2 |

7. Example 3: Analysis of Peripheral Sensory Neuropathy (PSN) Adverse Events by Severity and Cumulative Dose Exposure

Some institutions and organizations use standardized coding guidelines for reporting of adverse events. Examples of such standardized scales are [NCI (National Cancer Institute) and ACTG (Antiviral therapeutic area)]. These scales may be based upon variables as collected on AE CRFs, such as a grading scheme based upon severity [AESEV/AESEVN]. Other guidelines may be so objective that some variables, for example, drug relatedness [AEREL/AERELN] are not captured.

In this example the adverse event analysis dataset is used to summarize the frequency of peripheral sensory neuropathy (PSN) by cumulative dose exposure in an oncology study. In this study PSN was reported on the CRF at each cycle and at each 6-month follow-up visit, using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.03 [9] Peripheral sensory neuropathy (MedDRA v12.0 Code = 10034620):

- Grade 0 = None;
- Grade 1 = Asymptomatic; loss of deep tendon reflexes or paresthesia;
- Grade 2 = Moderate symptoms; limiting instrumental ADL;
- Grade 3 = Severe symptoms; limiting self care ADL;
- Grade 4 = Life-threatening consequences; urgent intervention indicated;
- Grade 5 = Death.

As a result of using this means of reporting, the PSN events reported in this module were all coded to ‘paresthesia’.

7.1 Analysis Display Example Layout

Table 7.1.1 Example of Summary of Cumulative Dose Quartiles to First Onset for PSN by Severity Grade⁶

Table 14.2.7.4

Summary of cumulative dose quartiles to first onset for PSN by severity grade

Analysis population: Intent-to-treat

| Cumulative dose | Number of patients Exposed | PSN grade | | | |
|--|----------------------------|--|--|--|--|
| | | Number (%) of patients with grade \geq 1 | Number (%) of patients with grade \geq 2 | Number (%) of patients with grade \geq 3 | Number (%) of patients with grade 4 or 5 |
| Total number of patients with PSN | | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| 1 st quartile (3 cycles) | N | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| 2 nd quartile (6 cycles) | N | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| 3 rd quartile (9 cycles) | N | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| 4 th quartile (12 cycles) | N | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Median cumulative dose to first onset (mg/m ²) | | X | X | X | X |

⁶ The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

7.2 Sample ADAE Variable Metadata

Table 7.2.1: Sample ADAE Variable Metadata for selected variables

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|----------------------------------|---------------|----------------|--|---|
| ADAE | USUBJID | Unique Subject Identifier | Text | \$7 | | ADSL.USUBJID |
| ADAE | ITTFL | Intent-to-Treat Population Flag | Text | \$1 | Y,N | ADSL.ITTFL |
| ADAE | AEDECOD | Dictionary-Derived Term | Text | \$200 | MedDRA | AE.AEDECOD |
| ADAE | AETOXGR | Standard Toxicity Grade | Text | \$25 | 1, 2, 3, 4, 5 | AE.AETOXGR |
| ADAE | AETOXGRN | Standard Toxicity Grade (N) | integer | 1.0 | 1, 2, 3, 4, 5 | Code AE.AETOXGR to numeric |
| ADAE | DOSECUM | Cumulative Study Drug Dose | Float | 6.2 | | Total all values of EX.EXDOSE for the subject up to the start of the AE. |
| ADAE | DOSECUMU | Cumulative Study Drug Dose Units | Text | \$2 | mg | EX.EXDOSU |
| ADAE | DOSCMGR1 | Cumulative Dose Group 1 | integer | \$12 | Quartile 1 Quartile 2 Quartile 3 Quartile 4 | Missing if DOSECUM=0, else DOSCMGR1 = Quartile 1 if DOSECUM is in the 1 st Quartile, Quartile 2 if in the 2 nd Quartile, Quartile 3 if in the 3 rd Quartile and Quartile 4 if in the 4 th Quartile. |

7.3 Sample ADAE Data

Key points to note in the example are:

1. This is a simple example to only illustrate the cumulative dose variables that can be added to ADAE. It does not include additional variables that would also be needed for analysis like a flag to indicate the first occurrence for PSN.
2. Row 3 and 7 include two patients who had no dose of study drug at the time of PSN and would not be included in the table.

Table 7.3.1: Sample ADAE Data Showing Cumulative Dose Variables

| Row | USUBJID | ITTF1 | AEDECOD | AETOXGR | AETOXGRN | DOSECUM | DOSECUMU | DOSCMGR1 |
|-----|---------|-------|-------------|---------|----------|---------|----------|------------|
| 1 | 101-002 | Y | PARESTHESIA | 3 | 3 | 247.06 | mg | Quartile 1 |
| 2 | 101-003 | Y | PARESTHESIA | 2 | 2 | 674.02 | mg | Quartile 3 |
| 3 | 101-005 | Y | PARESTHESIA | 1 | 1 | 0 | mg | |
| 4 | 101-006 | Y | PARESTHESIA | 2 | 2 | 900.00 | mg | Quartile 4 |
| 5 | 101-008 | Y | PARESTHESIA | 4 | 4 | 493.30 | mg | Quartile 2 |
| 6 | 101-010 | Y | PARESTHESIA | 3 | 3 | 894.29 | mg | Quartile 4 |
| 7 | 101-012 | Y | PARESTHESIA | 1 | 1 | 0 | mg | |

8. Example 4: Analysis of Treatment Emergent Adverse Events in a Cross-over Interaction Study

This example is a phase I, open-label, three periods cross-over study. Subjects are treated for 7 days within each period with a 7-day wash-out between periods. In each period, subjects are to receive one of 3 treatments (A, B, or A + B combined) in order of the sequence they are randomized to. Treatment emergent AEs were defined as AEs that occurred or worsened from the start of the treatment period through 72 hours after the end of the treatment period. Non-treatment emergent AEs were those that occurred before the first treatment period or more than 72 hours after the end of the treatment period until the start of the next treatment period. Post-treatment emergent AEs were those that occurred more than 72 hours after the last treatment period.

8.1 Analysis Display Example Layout

Table 8.1.1 Example of Summary of Treatment Emergent AEs by System Organ Class and Preferred Term and Treatment Group⁷

Table 14.2.7.5

Summary of Treatment Emergent AEs by System Organ Class and Preferred Term and Treatment Group
Analysis Population: Safety

| SYSTEM ORGAN CLASS Preferred Term | Treatment A (N = xxx) | | Treatment B (N = xxx) | | Treatment A + B (N = xxx) | |
|--------------------------------------|--------------------------|---------------|--------------------------|---------------|------------------------------|---------------|
| | n (%) | No. of events | n (%) | No. of events | n (%) | No. of events |
| Any TEAE | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| GASTROINTESTINAL DISORDER | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Nausea | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Constipation | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Vomiting | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Diarrhoea | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| INFECTIONS AND INFESTATIONS | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Pharyngitis | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| NERVOUS SYSTEM DISORDERS | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Headache | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Dizziness | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| Syncope | x (x.x) | x | x (x.x) | x | x (x.x) | x |
| <Other SOCs and PTs> | | | | | | |

TEAE = treatment emergent adverse event

N = Safety subjects, i.e., subjects who received at least one dose of study drug in that particular period

n = Number of subjects reporting at least one treatment emergent adverse event

% = $n / N * 100$

Adverse events are presented by descending frequency of SOC and PT within SOC within Treatment A+B

System organ classes and preferred terms are coded using MedDRA version x.x.

⁷ The style of the display of the results of an analysis will be determined by the sponsor. The example is intended to illustrate content not appearance.

8.2 Sample ADAE Variable Metadata

Table 8.2.1: Sample ADAE Variable Metadata for selected variables

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|-------------------------------------|---------------|----------------|---|---|
| ADAE | USUBJID | Unique Subject Identifier | Text | \$7 | | ADSL.USUBJID |
| ADAE | TRTA | Actual Treatment | Text | \$13 | Treatment A Treatment B Treatment A+B | ADSL.TRT01A if in the 1 st period, ADSL.TRT02A if in the 2 nd period, or ADSL.TRT03A if in the 3 rd period |
| ADAE | TRTAN | Actual Treatment (N) | Integer | 1.0 | 1, 2, 3 | Code TRTA to numeric. Treatment A = 1 Treatment B = 2 Treatment A+B = 3 |
| ADAE | SAFFL | Safety Population Flag | Text | \$1 | Y,N | ADSL.SAFFL |
| ADAE | AEBODSYS | Body System or Organ Class | Text | \$200 | MedDRA | AE.AEBODSYS |
| ADAE | AEDECOD | Dictionary-Derived Term | Text | \$200 | MedDRA | AE.AEDECOD |
| ADAE | ASTDTM | Analysis Start Date/Time | Integer | Datetime. | | Converting AE.AESTDTC from character ISO8601 format to numeric date format, applying sponsor defined imputation rules. |
| ADAE | ASTDTF | Analysis Start Date Imputation Flag | text | \$1 | (DATEFL) | The level of imputation done for the start date (D if day was imputed, M if month was imputed, or Y if year was imputed). |
| ADAE | ASTTMF | Analysis Start Time Imputation Flag | text | \$1 | (TIMEFL) | The level of imputation done for the start time (H if hour was imputed, M if minutes were imputed). |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|----------------------------------|---------------|----------------|---|---|
| ADAE | TRTEMFL | Treatment Emergent Analysis Flag | Text | \$1 | Y | If ADSL.TR01SDTM LE ASTDTM LE (ADSL.TR01EDTM+72 hours) or ADSL.TR02SDTM LE ASTDTM LE (ADSL.TR02EDTM+72 hours) or ADSL.TR03SDTM LE ASTDTM LE (ADSL.TR03EDTM+72 hours) then TRTEMFL=Y |
| ADAE | PREFL | Pre-treatment Flag | Text | \$1 | Y | If TRTEMFL ^= 'Y' and FUPFL ^= 'Y' then PREFL='Y' |
| ADAE | FUPFL | Follow-up Flag | Text | \$1 | Y | if ASTDTM GT (ADSL.TR03EDTM+72 hours) then FUPFL='Y' |
| ADAE | ASTDY | Analysis Start Relative Day | Integer | 3.0 | | Date portion of ASTDTM- date portion of ADSL.TR01SDTM+1 day if date portion of ASTDTM is on or after date portion of TR01SDTM, else date portion of ASTDTM- date portion of ADSL.TR01SDTM if date portion of ASTDTM precedes date portion of TR01SDTM |
| ADAE | EPOCH | Epoch | Text | \$200 | RUN-IN, FIRST TREATMENT, FIRST WASHOUT, SECOND TREATMENT, SECOND WASHOUT, THIRD TREATMENT, THIRD WASHOUT, FOLLOW-UP | AE.EPOCH |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|---|---------------|----------------|---|--|
| ADAE | APHASE | Phase | Text | \$50 | RUN-IN, FIRST TREATMENT, FIRST WASHOUT, SECOND TREATMENT, SECOND WASHOUT, THIRD TREATMENT, THIRD WASHOUT, FOLLOW-UP | If AESDTM < ADSL.TR01SDTM then APHASE='RUN-IN', else if ADSL.TR01SDTM LE AESDTM LE (ADSL.TR01EDTM+72 hours) then APHASE ='FIRST TREATMENT', else if (ADSL.TR01EDTM+72 hours) < AESDTM < ADSL.TR02SDTM then APHASE ='FIRST WASHOUT', etc. |
| ADAE | APERIOD | Period | Integer | 1.0 | 1, 2, 3 | If TR01SDTM LE ASTDTM LE (TR01EDTM+72 hours) then APERIOD=1, else if TR02SDTM LE ASTDTM LE (TR02EDTM+72 hours) then APERIOD=2, else if TR03SDTM LE ASTDTM LE (TR03EDTM+72 hours) then APERIOD=3 |
| ADAE | APERIODC | Period (C) | Text | \$50 | PERIOD 01, PERIOD 02, PERIOD 03 | If APERIOD=1 then APERIODC='PERIOD 01', else if APERIOD=2 then APERIODC='PERIOD 02', else if APERIOD=03 then APERIODC='PERIOD 03' |
| ADAE | TR01SDTM | Datetime of First Exposure in Period 01 | Integer | Datetime. | | ADSL.TR01SDTM |
| ADAE | TR01EDTM | Datetime of Last Exposure in Period 01 | Integer | Datetime. | | ADSL.TR01EDTM |
| ADAE | TR02SDTM | Datetime of First Exposure in Period 02 | Integer | Datetime. | | ADSL.TR02SDTM |
| ADAE | TR02EDTM | Datetime of Last Exposure in Period 02 | Integer | Datetime. | | ADSL.TR02EDTM |
| ADAE | TR03SDTM | Datetime of First Exposure in Period 03 | Integer | Datetime. | | ADSL.TR03SDTM |

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|--------------|---------------|--|---------------|----------------|-----------------------------|---------------------|
| ADAE | TR03EDTM | Datetime of Last Exposure in Period 03 | Integer | Datetime. | | ADSL.TR03EDTM |

8.3 Sample ADAE Data

Table 8.3.1 is an illustration of the adverse events analysis dataset (ADAE) defined above.

Key points to note in the example are:

1. The SDTM variable EPOCH was kept for traceability and to illustrate the differences between this variable and APHASE and APERIOD.
2. Treatment start and end datetimes for each period were kept and used to calculate APERIOD and TRTEMFL. Another option would have been to use ADSL variables relating to period start and end datetimes (APxxSDTM and APxxEDTM). However, if different periods for efficacy and safety were defined this latter option wouldn't work.
3. The producer of the dataset chose to populate APERIOD as an analysis period where the wash-out and follow-up period were not populated for APERIOD. The same applied for the record level actual treatment variable (TRTA) which was left missing for records not associated with a treatment. However, this is left up to the sponsor.
4. Row 5 indicates an AE that occurs in the follow-up EPOCH, is post-treatment emergent and not related to any analysis period or treatment.
5. Row 8 indicates an AE that occurs in the follow-up EPOCH but within the third treatment phase and analysis period and associated with treatment A+B.

Table 8.3: Sample ADAE Data

| Row | USUBJID | TRTA | TRTAN | SAFFL | AEBODSYS | AEDECOD | ASTDTM | ASTDTF | ASTTMF | TRTEMFL | PREFL | FUPFL |
|-----|---------|------|-------|-------|-----------------------------|--------------|------------------|--------|--------|---------|-------|-------|
| 1 | 101-001 | A | 1 | Y | GASTROINTESTINAL DISORDERS | VOMITING | 05MAY08:16:00:00 | | M | Y | | |
| 2 | 101-001 | B | 2 | Y | INFECTIONS AND INFESTATIONS | PHARYNGITIS | 16MAY08:06:42:00 | | | Y | | |
| 3 | 101-001 | A+B | 3 | Y | NERVOUS SYSTEM DISORDERS | HEADACHE | 01JUN08:15:30:00 | | | Y | | |
| 4 | 101-001 | A+B | 3 | Y | NERVOUS SYSTEM DISORDERS | CONSTIPATION | 02JUN08:07:15:00 | | | Y | | |
| 5 | 101-001 | | | Y | INFECTIONS AND INFESTATIONS | ORAL HERPES | 07JUN08:08:00:00 | | | | | Y |
| 6 | 101-002 | | | Y | VASCULAR DISORDERS | HYPOTENSION | 25MAY08:13:20:00 | | | | Y | |
| 7 | 101-002 | A+B | 3 | Y | NERVOUS SYSTEM DISORDERS | HEADACHE | 27MAY08:22:10:00 | | | Y | | |
| 8 | 101-002 | A+B | 3 | Y | NERVOUS SYSTEM DISORDERS | HEADACHE | 02JUN08:22:10:00 | | | Y | | |

| Row | ASTDY | EPOCH | APHASE | APERIOD | APERIODC | TR01SDTM | TR01EDTM | TR02SDTM |
|-----|-------|------------------|------------------|---------|-----------|------------------|------------------|------------------|
| 1 | 5 | FIRST TREATMENT | FIRST TREATMENT | 1 | PERIOD 01 | 01MAY08:10:05:00 | 07MAY08:09:10:10 | 15MAY08:08:15:00 |
| 2 | 16 | SECOND TREATMENT | SECOND TREATMENT | 2 | PERIOD 02 | 01MAY08:10:05:00 | 07MAY08:09:10:00 | 15MAY08:08:15:00 |
| 3 | 32 | THIRD TREATMENT | THIRD TREATMENT | 3 | PERIOD 03 | 01MAY08:10:05:00 | 07MAY08:09:10:00 | 15MAY08:08:15:00 |
| 4 | 33 | THIRD TREATMENT | THIRD TREATMENT | 3 | PERIOD 03 | 01MAY08:10:05:00 | 07MAY08:09:10:00 | 15MAY08:08:15:00 |
| 5 | 38 | FOLLOW-UP | FOLLOW-UP | | | 01MAY08:10:05:00 | 07MAY08:09:10:00 | 15MAY08:08:15:00 |
| 6 | 26 | SECOND WASHOUT | SECOND WASHOUT | | | 30APR08:12:05:00 | 06MAY08:08:32:00 | 14MAY08:11:55:00 |
| 7 | 28 | THIRD TREATMENT | THIRD TREATMENT | 3 | PERIOD 03 | 30APR08:12:05:00 | 06MAY08:08:32:00 | 14MAY08:11:55:00 |
| 8 | 34 | FOLLOW-UP | THIRD TREATMENT | 3 | PERIOD 03 | 30APR08:12:05:00 | 06MAY08:08:32:00 | 14MAY08:11:55:00 |

| Row | TR02EDTM | TR03SDTM | TR03EDTM |
|-----|------------------|------------------|------------------|
| 1 | 21MAY08:10:30:00 | 20MAY08:13:50:00 | 03JUN08:07:20:00 |
| 2 | 21MAY08:10:30:00 | 29MAY08:13:50:00 | 03JUN08:07:20:00 |
| 3 | 21MAY08:10:30:00 | 29MAY08:13:50:00 | 03JUN08:07:20:00 |

| Row | TR02EDTM | TR03SDTM | TR03EDTM |
|-----|------------------|------------------|------------------|
| 4 | 21MAY08:10:30:00 | 29MAY08:13:50:00 | 03JUN08:07:20:00 |
| 5 | 21MAY08:10:30:00 | 29MAY08:13:50:00 | 03JUN08:07:20:00 |
| 6 | 20MAY08:08:10:00 | 26MAY08:15:40:00 | 01JUN08:09:13:00 |
| 7 | 20MAY08:08:10:00 | 26MAY08:15:40:00 | 01JUN08:09:13:00 |
| 8 | 20MAY08:08:10:00 | 26MAY08:15:40:00 | 01JUN08:09:13:00 |

9. References

1. Analysis Data Model (ADaM) version 2.1
<http://www.cdisc.org/adam>
2. Analysis Data Model (ADaM) Implementation Guide version 1.0
<http://www.cdisc.org/adam>
3. Study Data Tabulation Model Implementation Guide (SDTMIG) V3.1.2 and Amendment 1 to the Study Data Tabulation Model (SDTM) v1.2 and the SDTM Implementation Guide: Human Clinical Trials V3.1.2
<http://www.cdisc.org/sdtm>
4. International Conference of Harmonization E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf
5. International Conference of Harmonization E9 “Statistical Principles for Clinical Trials”
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
6. Medical Dictionary for Regulatory Activities (MedDRA)
<http://www.meddramsso.com/>
7. International Conference of Harmonization E3 “Structure and Content of Clinical Study Reports”
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf
8. Standardised MedDRA Queries (SMQs)
http://www.meddramsso.com/subscriber_smq.asp
9. National Cancer Institute Common Toxicity (NCI CTC) version 4.03
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14.xls

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