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Navigating the Complexities of AESI: A Centralized Approach to Molecule-Level Management

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ABSTRACT

Adverse Event of Special Interest (AESI) is an event, whether serious or non-serious, of scientific and medical concern specific to the sponsor's product or program, for which continuous monitoring and prompt communication by the investigator to the sponsor can be appropriate (International Council for Harmonisation [ICH], 2022). During the active development of an investigational medical product in clinical trials, the report of AESI supports the safety assessment and fulfills health authority requirements in regulatory documents. The search strategy of AESI changes over time with accumulated knowledge from evolving data. The implementation of AESI and its version control become challenging particularly in a large project across multiple indications with many ongoing trials. Support from cross-functional teams in a single study as well as the development team at indication or molecule level further adds complexity to the alignment and maintenance of AESI definitions. We will focus on how we address such challenges strategically with a centralized approach at a molecule level and enable the work with quality and effectiveness.

INTRODUCTION

During the pre-marketing phases of drug development, the ongoing evaluation of the drug safety aims to detect the safety signals early and form a good understanding of the safety profile of a medical product. The hierarchies in the MedDRA coding system alone are not sufficient in characterizing the safety profile; thus, defining groups of Adverse Events of Special Interest (AESI) is a useful approach in safety analysis and reporting. In a First-in-Human study, the clinical development team starts with collecting relevant information of AESI in electronic case report forms (eCRF) based on a general understanding of the mechanism of the drug. As a molecule advances from early-phase to late-phase development, the clinical safety team typically accumulates better understanding of the safety profile and aims to report the potential and/or identified risks of the drug systematically. Clear definitions of AESI enable the efficient summarization of AESI via statistical programming.

When a fast-paced molecule program expands across multiple pivotal studies, it becomes critical to ensure alignment on AESI definitions and consistency in reporting across different regulatory documents within the molecule program. Typically, the clinical safety team is responsible for identifying which AESI groups to report, defining the search strategy of the AESI groups in the MedDRA coding system, and managing its changes over time.

Communication and alignment between the clinical safety team and the data science team (including statistical programmers and statisticians) are essential for accurate analysis and reporting. Communicating on a study-by-study basis can not only be inefficient, but also lead to inconsistencies across studies and documents, resulting in difficulties in interpreting results.

We adopt a centralized approach in which a specialized team from the data science function participates in all AESI-related discussions with the function representatives from the clinical safety and regulatory. We, the statistical programmers sitting within the specialized data science team, are also responsible for implementing the centralized programming strategy and guiding study teams for AESI-related programming activities at the study-level.

In addition to the evolving nature of AESI definitions, challenges also arise when different regulatory documents require reporting different sets of AESI or when multiple deliverables are requested simultaneously but each

requiring different versions of the MedDRA dictionary or AESI definitions. To streamline the process, we utilize a version control strategy to support the dynamic selection of AESI groups for reporting.

OVERALL WORKFLOW

The process of the centralized approach is illustrated in Figure 1. We utilize a molecule-level Adverse Event Grouping Definition Dataset (AAG) to capture and maintain the search strategy of defined sets of AESI. The AAG is an intermediate dataset used to create MedDRA query variables in the Adverse Event Analysis Dataset (ADAE) (e.g. SMQzzNAM, CQzzNAM, etc.); however, AAG itself does not follow the currently defined CDISC-ADaM data structure. The downstream creation of AESI related outputs is not in scope of this article.

Figure 1. Centralized approach of managing AESI definitions

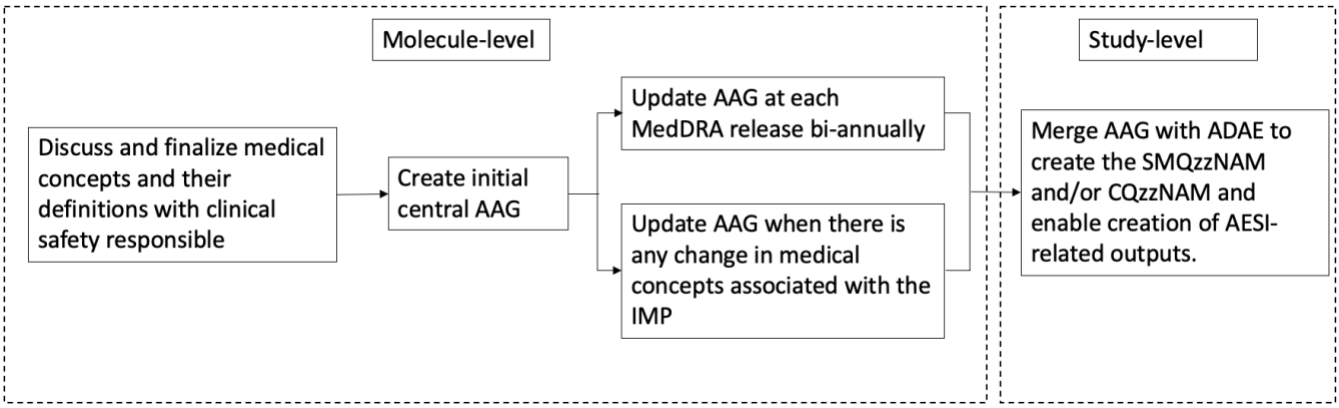

Figure 2. Structure of data storage under the centralized approach

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Central Library at Molecule Level
      └── Folder for AAG with <MedDRA version 1> and <AESI version 1>
            └── aag.sas7bdat
      └── Folder for AAG with <MedDRA version 1> and <AESI version 2>
            └── aag.sas7bdat
      └── Folder for AAG with <MedDRA version 2> and <AESI version 2>
            └── aag.sas7bdat
      ……
```

Table 1. Responsibilities of the teams

Responsibilities of the data science team centralizing AESI programming at the molecule level	Responsibilities of the data science team at the study level
● Deliver the AAG dataset as the single source of truth at the molecule level from a central library, ensuring AAG is shared across all studies under the same molecule with clear announcement and documentations. ● Following each bi-annual version update of the MedDRA dictionary, proactively update AAG. ● Between the up-versioning events of MedDRA dictionary, reactively implement any ad-hoc	● The statistical programming team directly accesses AAG from the central library, with a read-only right, without accessing the programs that create AAG. ● Based on the molecule standards, the statistical programming team directly incorporates AAG into the ADAE dataset to generate AESI outputs.

updates to the AESI search strategy, as per requests from the clinical safety team. ● Sharing AESI search strategy with study teams with view access for transparency.	● The statisticians review the MedDRA version, AESI version, and AESI outputs to ensure accurate analysis.

STANDARDIZED DATASETS

1. Standard Specification of Adverse Event Grouping Definition Dataset (AAG)

Centralized AAG holds the variables, to track the versions of both the MedDRA dictionary and AESI definitions for traceability, as well as to automate the programming process of merging with ADAE based on the value-level information provided in the AAG dataset. To facilitate illustrating the next section, we display the internal standard variables in AAG below (Roche Data Standards & Governance, 2024)

Table 2. Standardized specification of centralized AAG

Variable Name	*Variable Label*	*Type*	*Length*	*Codelist*	*Comments*
SRCVAR	Variable on which Grouping is Based	Char	8		This variable indicates the ADAE variable name which should be used as the key when merging with AAG. For example, “AEDECOD”, “AEHLT”.
GRPTYPE	Grouping Definition Type	Char	6		This variable defines the type of grouping. For example, 'SMQ' or 'CUSTOM'.
GRPID*	Grouping Definition Identifier	Num	8		This variable indicates the prefix of variable names to be used in ADAE when merging AAG with ADAE. For example, an input value of ‘SMQ01’ leads to the creation of ADAE.SMQ01NAM and ADAE.SMQ01CD.
GRPNAME	Grouping Definition Name	Char	200		This variable indicates the name of the medical concept, which gets populated as the values in the Query Names in ADAE, for example, ADAE.SMQzzNAM or ADAE.CQzzNAM.
DICTVRSN**	Grouping Def. Dictionary Version	Char	12		MedDRA dictionary version. For example, ‘MedDRA v27.0’.
AESIVRSN	Grouping Def. Version	Char	12		The version of AESI definition. For example, ‘AESI v1.1’.
TERMID	Grouping Def. Clause Dictionary Code	Char	21		This variable stores the dictionary code of the term.
TERMNAME	Grouping Def. Clause Dictionary Term	Char	200		This variable stores the dictionary term.
SCOPE	Scope of the Query	Char	6	BROAD/ NARROW	Expected only when GRPID is ‘SMQ’.

*AESI definitions often contain both Standard MedDRA Query (SMQ) and Custom Query (CQ). The MedDRA query variables in ADAE (i.e. SMQzzNAM, CQzzNAM) utilize the zero-padded 2-digit integers to indicate each SMQ or CQ of interest. We increment the two digits sequentially between SMQ and CQ variable names. These digits served as an indicator of the ID of the corresponding AESI definition, for example, SMQ01, CQ02, CQ03, SMQ04 sequentially. This approach also provides programming benefits when creating tables, such as the AESI summary. If a medical concept is removed at a certain point, we recommend not re-ordering the digits to maintain traceability and consistency.

**Over the course of the program development, AAG accumulates grouping definitions across multiple MedDRA versions. To ensure the correct application of the MedDRA dictionary version, check AAG.DICTVRSN against the value in TS.TSVAL where PARAMCD is "AEDICT" for consistency.

2. Value-level data in AAG

The definition of a medical concept can be based on specific hierarchies of the MedDRA dictionary, an existing Standard MedDRA Query (SMQ) or a combination of both. Table 3 illustrates four scenarios of how value-level data in AAG is constructed to support different search methods in ADAE.

Scenario 1: The medical concept "Immune-Mediated Hypothyroidism" is searched in ADAE by matching the ADAE preferred terms with the ones from the broad SMQ of "Hypothyroidism", as specified in AAG.

- The value-level data in AAG has one row per preferred term because the ADAE merging key is AEDECOD and AAG includes all preferred terms in the specified SMQ.

Table 3.1. Scenario 1: Example illustration of the AAG value-level data

SRCVAR	***GRPTYPE***	***GRPID***	***GRPNAME***	***TERMID***	***TERMNAME***	***SCOPE***
AEDECOD	SMQ	SMQzz	Immune-Mediated Hypothyroidism	10004889	BIOPSY THYROID GLAND ABNORMAL	BROAD
AEDECOD	SMQ	SMQzz	Immune-Mediated Hypothyroidism	10005830	BLOOD THYROID STIMULATING HORMONE ABNORMAL	BROAD
AEDECOD	SMQ	SMQzz	Immune-Mediated Hypothyroidism	….	….	BROAD

Scenario 2: The medical concept "Immune-Mediated Colitis" is searched in ADAE by identifying the ADAE High Level Term (HLT) of "Colitis (excl infective)", as specified in AAG.

- The value-level data in AAG has one row because the ADAE merging key is AEHLT, and this AESI searches only one HLT.

Table 3.2. Scenario 2: Example illustration of the AAG value-level data

SRCVAR	***GRPTYPE***	***GRPID***	***GRPNAME***	***TERMID***	***TERMNAME***	***SCOPE***
AEHLT	CUSTOM	CQzz	Immune-Mediated Colitis	10009888	Colitis (excl infective)	[Not applicable, leave blank]

Scenario 3: The medical concept "Immune-Mediated Colitis" is searched in ADAE by identifying all ADAE preferred terms under the HLT of "Colitis (excl infective)", as specified in AAG.

- The value-level data in AAG has multiple rows because the ADAE merging key is AEDECOD and AAG includes all preferred terms in the specified HLT.

Table 3.3. Scenario 3: Example illustration of the AAG value-level data

SRCVAR	*GRPTYPE*	*GRPID*	*GRPNAME*	*TERMID*	*TERMNAME*	*SCOPE*
AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis	10009887	COLITIS	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis	10009895	COLITIS ISCHAEMIC	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis	….	….	[Not applicable, leave blank]

Scenario 4: The medical concept "Immune-Mediated Colitis + Noninfectious Diarrhoea" is searched in ADAE by matching the ADAE preferred terms with the ones from the narrow SMQ of "Noninfectious diarrhoea (SMQ)" or by identifying all ADAE preferred terms under the HLT of "Colitis (excl infective)", as specified in AAG.

- Rows 1-3 list the preferred terms from narrow SMQ of "Noninfectious diarrhoea (SMQ)"
- Rows 4-6 list the preferred terms from HLT of "Colitis (excl infective)"

Table 3.4. Scenario 4: Example illustration of the AAG value-level data

	SRCVAR	*GRPTYPE*	*GRPID*	*GRPNAME*	*TERMID*	*TERMNAME*	*SCOPE*
1	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012110	DEFCATION URGENCY	NARROW
2	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012735	DIARRHOEA	NARROW
3	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	….	….	NARROW
4	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009887	COLITIS	[Not applicable, leave blank]
5	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009895	COLITIS ISCHAEMIC	[Not applicable, leave blank]
6	AEDECOD	CUSTOM	CQzz	Immune-Mediated Colitis + Noninfectious Diarrhoea	….	….	[Not applicable, leave blank]

VERSION CONTROL

1. Version updates of the MedDRA dictionary

The MedDRA dictionary is updated biannually, with new versions released in March and September. Each update incorporates revisions to terms and hierarchical structures to align with the latest regulatory standards.

The latest MedDRA version is implemented into the internal systems bi-annually in May and November, approximately two months after the official release, allowing for adequate time of internal testing and deployment.

Following the internal MedDRA version update, we revise the programs of the AAG dataset as needed, ensuring its alignment with the latest dictionary terms and hierarchical structures.

The MedDRA version is documented as the first suffix in the folder name containing the AAG dataset in the central library (Figure 2). Additionally, the MedDRA version is captured as a variable in the AAG dataset (Table 2).

2. Version updates of AESI search strategy

There are two scenarios where the AESI search strategy is updated, resulting in an update to the AESI version.

Scenario 1: Immediately following the MedDRA up-version, we proactively collaborate with the clinical safety team to assess whether the AESI search strategy requires any revision. Upon confirmation, we update the AAG dataset according to the latest AESI search algorithms.

Scenario 2: Between the two consecutive MedDRA up-versions, the clinical safety team may request ad-hoc updates to the AESI search strategy. In response, we release a new version of the AAG dataset based on the updated AESI search algorithms.

In both scenarios, the AESI version will be updated. The AESI version is appended as the second suffix in the folder name storing the AAG dataset in the central library (Figure 2), and it is also documented as a variable in the AAG dataset (Table 2).

CONCLUSIONS

The centralized approach of managing AESI definitions and implementation enhances the consistency of safety reporting across regulatory documents, particularly within large molecule programs involving numerous studies across multiple indications. The standardized structure of AAG enables automated data processing and reduces the maintenance efforts at the study level. Proper version control not only ensures traceability and reproducibility of analysis, but also provides flexibility in selecting appropriate MedDRA and AESI versions to meet various regulatory needs. Additionally, this approach mitigates the risk of incorrect AESI reporting due to large scale of the molecule program, lack of communication, or inexperience of programming staff. The centralized approach for AESI programming could also be extended to the management of centralized drug basket datasets.

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