

DS06

Navigating the Complexities of AESI:

A Centralized Approach to

Molecule-Level Management

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AESI: Adverse Event of Special Interest

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Xiaojing Zhu

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Agenda

- Introduction
- Overall Workflow
- AAG - A Standardized Dataset
- Version Control
- Conclusion
- Acknowledgements
- Q&A

Introduction

What is AESI?

Adverse Event of Special Interest (AESI)

- **AESI** is “An event (serious or non-serious) of **scientific and medical concern** specific to the **sponsor’s product or program**, for which **ongoing monitoring** and **rapid communication** by the **investigator to the sponsor** can be appropriate” (International Council for Harmonisation [ICH], 2022).
- **Defining groups of AESI** is a useful approach to **assess the safety profile** and **fulfills health authority requirements** in regulatory documents.

Introduction

Example of AESI Table

Medical Concept Category MedDRA Preferred Term	Treatment Group A (N = X)	Treatment Group B (N = X)
Medical Concept 1		
Total number of patients with at least one adverse event	X (X.X%)	X (X.X%)
Total number of events	X	X
Preferred Term 1	X (X.X%)	X (X.X%)
Preferred Term 2	X (X.X%)	X (X.X%)
.....		
Medical Concept 2		
Total number of patients with at least one adverse event	X (X.X%)	X (X.X%)
Total number of events	X	X
Preferred Term 1	X (X.X%)	X (X.X%)
Preferred Term 2	X (X.X%)	X (X.X%)
.....		

Introduction

Complexity of Managing AEsI Programming

Challenge 1: AEsI search strategies keep evolving.

- In a First-in-Human study, the clinical development team starts collecting basic information of AEsI in electronic case report forms (eCRF).
- As a molecule advances, 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.
- **MedDRA dictionary versions get updated** biannually.

Introduction

Complexity of Managing AESI Programming

Challenge 2: Implementing AESI definitions requires cross-functional collaboration.

- Typically, the clinical safety team is responsible for identifying which AESI groups to report, defining the search strategy of AESI groups in the MedDRA coding system, and managing its changes over time.
- **Communication between the clinical safety team and the data science team** is essential for accurate analysis and reporting.

Introduction

Complexity of Managing AESI Programming

Challenge 3: A large-scale molecule program adds complexity.

- As a fast-paced molecule program expands, communicating on a study-by-study basis can be inefficient and lead to inconsistencies across studies and documents.
- Within the molecule program, reporting AESI for different deliverables could require different versions of MedDRA dictionary or AESI definitions.
- Ensuring **consistency in 1) AESI definitions and 2) Reporting across different regulatory documents** within the molecule program is critical.

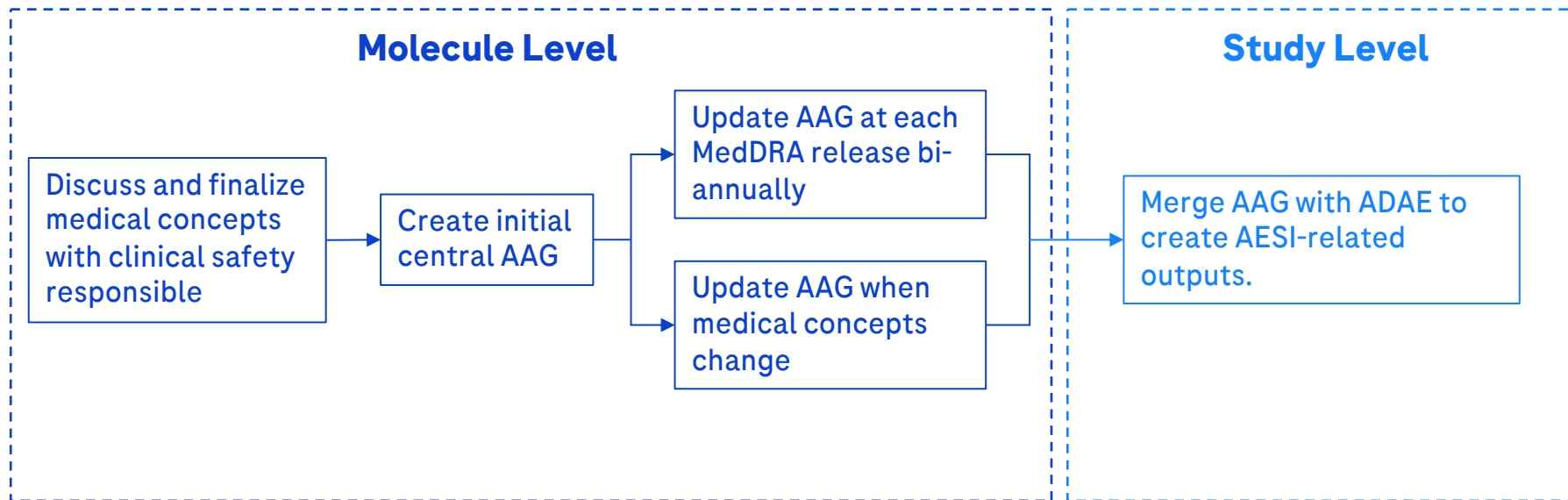
Overall Workflow

Our Approach of Centralizing AESI Programming

- We, a specialized team from the data science function, implement a **centralized AESI programming strategy** at the molecule level by
 - Participating in **all AESI-related discussions** with the function representatives from the clinical safety and regulatory
 - **Guiding study teams** for AESI-related programming activities at the study-level
 - Utilizing a **standardized dataset AAG** (Adverse Event Grouping Definition Dataset)
 - Adopting a **version control** strategy

Overall Workflow

Our Approach of Centralizing AESI Programming



AAG - A Standardized Dataset

Using AAG to Capture and Maintain the Search Strategy of AESI

■ Adverse Event Grouping Definition Dataset (AAG)

- AAG contains **definitions of AESI groups**, including both Standard MedDRA Query (SMQ) and Custom Query (CQ)
- **Traceability:** Track the **versions of both the MedDRA dictionary and AESI definitions**.
- **Automation:** Facilitate the **merging with ADAE** based on the value-level information.

AAG - A Standardized Dataset

Standard Specification of AAG

List of AAG variables

Variable Name	Variable Label	Description
SRCVAR	Variable on which Grouping is Based	The key variable in ADAE when merging with AAG For example, “AEDECOD”, “AEHLT”.
GRPTYPE	Grouping Definition Type	The type of grouping For example, 'SMQ' or 'CUSTOM'.
GRPID	Grouping Definition Identifier	The prefix of new ADAE variable names after merging AAG with ADAE For example, GRPID = ‘SMQ01’ leads to the creation of ADAE.SMQ01NAM and ADAE.SMQ01SC.
GRPNAME	Grouping Definition Name	The name of the medical concept For example, values under ADAE.SMQ01NAM or ADAE.CQ01NAM.

AAG - A Standardized Dataset

Standard Specification of AAG

List of AAG variables

Variable Name	Variable Label	Description
DICTVRSN	Grouping Def. Dictionary Version	The version of MedDRA dictionary For example, 'MedDRA v27.0'.
AESIVRSN	Grouping Def. Version	The version of AESI definition For example, 'AESI v1.1'.
TERMID	Grouping Def. Clause Dictionary Code	The dictionary code of the term For example, 10009887.
TERMNAME	Grouping Def. Clause Dictionary Term	The dictionary term For example, 'COLITIS'.
SCOPE	Scope of the Query	Expected only when GRPID is 'SMQ'. For example, 'BROAD' or 'NARROW'.

AAG - A Standardized Dataset

Value-level Data in AAG

Scenario 1: Match by Preferred Terms

- 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.

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism	10004889	Biopsy thyroid gland abnormal	BROAD
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism	10005830	Blood thyroid stimulating hormone abnormal	BROAD
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism			BROAD

AAG - A Standardized Dataset

Value-level Data in AAG



■ Scenario 1: Match by Preferred Terms

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism	10004889	Biopsy thyroid gland abnormal	BROAD
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism	10005830	Blood thyroid stimulating hormone abnormal	BROAD
AEDECOD	SMQ	SMQ01	Immune-Mediated Hypothyroidism			BROAD

⇐ Example AAG

USUBJID	AEDECOD	SMQ01NAM	SMQ01SC
10001	Biopsy thyroid gland abnormal	Immune-Mediated Hypothyroidism	BROAD
10001	Blood thyroid stimulating hormone abnormal	Immune-Mediated Hypothyroidism	BROAD
10001	<Some other AE>	Left as blank if not a match	Left as blank if not a match

New variables in ADAE after merging with AAG

⇐ Example ADAE
after merging with AAG

- If **ADAE.AEDECOD** matches **AAG.TERMNAME**, ADAE.SMQ01NAM gets populated as AAG.GRPNAME, and ADAE.SMQ01SC gets populated as ADAE.SMQ01SC.

AAG - A Standardized Dataset

Value-level Data in AAG

Scenario 2: Match by the High Level Term

- 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.

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
AEHLT	CUSTOM	CQ02	Immune-Mediated Colitis	10009888	Colitis (excl infective)	[Not applicable, leave blank]

AAG - A Standardized Dataset

Value-level Data in AAG



■ Scenario 2: Match by the High Level Term

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMD	TERMNAME	SCOPE
AEHLT	CUSTOM	CQ02	Immune-Mediated Colitis	10009888	Colitis (excl infective)	[Not applicable, leave blank]

⇐ Example AAG

USUBJID	AEDECOD	AEHLT	CQ02NAM
10001	Colitis	Colitis (excl infective)	Immune-Mediated Colitis
10002	Autoimmune colitis	Colitis (excl infective)	Immune-Mediated Colitis
10003	Immune-mediated enterocolitis	Colitis (excl infective)	Immune-Mediated Colitis

New variable in ADAE
after merging with AAG

⇐ Example ADAE after merging with AAG

- If **ADAE.AEHLT** matches **AAG.TERMNAME**, ADAE.CQ02NAM gets populated as AAG.GRPNAME.
- In case of multiaxiality (i.e. one PT being associated with multiple HLTs), only events under the primary path will be flagged.

AAG - A Standardized Dataset

Value-level Data in AAG

Scenario 3: Match by **all Preferred Terms under a High Level Term**

- 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.

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis	10009887	Colitis	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis	10009895	Colitis ischaemic	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis			[Not applicable, leave blank]

AAG - A Standardized Dataset

Value-level Data in AAG



■ Scenario 3: Match by all Preferred Terms under a High Level Term

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis	10009887	Colitis	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis	10009895	Colitis ischaemic	[Not applicable, leave blank]
AEDECOD	CUSTOM	CQ03	Immune-Mediated Colitis			[Not applicable, leave blank]

⇐ Example AAG

USUBJID	AEDECOD	AEHLT	CQ03NAM
10001	Colitis	Colitis (excl infective)	Immune-Mediated Colitis
10002	Colitis ischaemic	Colitis (excl infective)	Immune-Mediated Colitis

New variables in ADAE
after merging with AAG

⇐ Example ADAE
after merging with AAG

- If **ADAE.AEDECOD** matches **AAG.TERMNAME**, **ADAE.CQ03NAM** gets populated as **AAG.GRPNAME**.
- In case of multiaxiality, events under both primary and secondary paths will be flagged.

AAG - A Standardized Dataset



Value-level Data in AAG

Scenario 4: Match by all Preferred Terms associated with multiple groups

- 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.

	SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE
1	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012110	Defecation urgency	NARROW
2	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012735	Diarrhoea	NARROW
3	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea			NARROW
4	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009887	Colitis	[Not applicable, leave blank]
5	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009895	Colitis ischaemic	[Not applicable, leave blank]
6	AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea			[Not applicable, leave blank]

AAG - A Standardized Dataset

Value-level Data in AAG



■ Scenario 4: Match by **all Preferred Terms** associated with multiple groups

SRCVAR	GRPTYPE	GRPID	GRPNAME	TERMID	TERMNAME	SCOPE	⇐ Example AAG
AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012110	Defecation urgency	NARROW	
AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10012735	Diarrhoea	NARROW	
AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009887	Colitis	[Not applicable, leave blank]	
AEDECOD	CUSTOM	CQ04	Immune-Mediated Colitis + Noninfectious Diarrhoea	10009895	Colitis ischaemic	[Not applicable, leave blank]	

USUBJID	AEDECOD	CQ04NAM
10001	Defecation urgency	Immune-Mediated Colitis + Noninfectious Diarrhoea
10002	Diarrhoea	Immune-Mediated Colitis + Noninfectious Diarrhoea
10003	Colitis	Immune-Mediated Colitis + Noninfectious Diarrhoea
10004	Colitis ischaemic	Immune-Mediated Colitis + Noninfectious Diarrhoea

New variable in ADAE after merging with AAG

⇐ Example ADAE after merging with AAG

- If **ADAE.AEDECOD** matches **AAG.TERMNAME**, defined by all preferred terms under the narrow SMQ of “Noninfectious diarrhoea (SMQ)” or under the HLT of “Colitis (excl infective)”, **ADAE.CQ04NAM** gets populated as **AAG.GRPNAME**.

Version Control

Version Updates of MedDRA Dictionary

- The MedDRA dictionary is updated bi-annually, with new versions released in March and September.
- **Following the MedDRA version update, we up-version AAG, ensuring its alignment with the latest dictionary code, terms, and hierarchical structures.**

Version Control

Version Updates of MedDRA dictionary

- The **MedDRA version** is documented as the **first suffix** in the folder name containing the AAG dataset in the central library.

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

.....

- Additionally, the MedDRA version is captured as **a variable in AAG**.

Variable Name	Variable Label	Description
DICTVRSN	Grouping Def. Dictionary Version	The version of MedDRA dictionary For example, 'MedDRA v27.0'.

⇐ Recommend checking AAG.DICTVRSN against TS.TSVAL where PARAMCD is "AEDICT"

Version Control

Version Updates of AESI Search Strategy

- There are two scenarios where the AESI search strategies are 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 strategies require 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 strategies. In response, we release a new version of the AAG dataset based on the updated AESI search algorithms.

Version Control

Version Updates of AESI Search Strategy

- The **AESI version** is appended as the **second suffix** in the folder name storing the AAG dataset in the central library.

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

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- The AESI version is also documented as **a variable in AAG**.

Variable Name	Variable Label	Description
AESIVRSN	Grouping Def. Version	The version of AESI definition For example, 'AESI v1.1'.

Conclusion

- The centralized approach of AESI management enhances the **consistency and accuracy of safety reporting across regulatory documents and across studies** in a large molecule program.
- The standardized structure of AAG enables **automated data processing** and **reduces the maintenance efforts** at the study level.
 - Proper **version control** ensures **traceability and reproducibility** of analysis.
- The centralized approach for AESI programming could also be extended to manage centralized drug basket datasets.

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Reference

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Questions?

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