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Programming Tips on imAEs Guidance Implementation

Yang Song, BeiGene, Inc.

ABSTRACT

Immune-mediated adverse events (imAEs) are predictable side effects of cancer immunotherapeutic clinical trials that occur due to the activation of the immune system. Characterizing, collecting, and reporting imAEs is crucial in evaluating the safety and efficacy of immunotherapies, and both the US Food and Drug Administration (FDA) and the Center for Drug Evaluation (CDE) of National Medical Products Administration (NMPA) have issued guidelines for their evaluation and reporting. This paper intends to interpret and compare FDA and CDE guidance and provide an overview of the process for identifying and analyzing imAEs, with a focus on the critical role of statistical programmers in this cross-functional collaboration. Additionally, this paper explores various considerations and offers some helpful programming tips.

INTRODUCTION

Cancer immunotherapeutic drugs, which modulate the endogenous immune system to produce an anticancer effect, have emerged as a promising treatment for a wide range of cancer types. These drugs have demonstrated both safety and efficacy and are becoming standard of care treatments for patients with hematologic and solid tumor malignancies. However, there are significant differences in the safety profile of immunotherapeutic drugs compared to traditional cytotoxic drugs or targeted small molecule drugs. Adverse events that are consistent with an autoimmune etiology should be evaluated as potential imAEs to guide patient management and inform drug labeling or investigator brochures. imAEs are specific concerns associated with cancer immunotherapeutic drugs, occurring due to increased activity of the immune system secondary to immune checkpoint blockade (Postow, 2018). These imAEs can involve any organ system and may occur during or after treatment (Naidoo, 2015).

Despite the potential benefits of cancer immunotherapeutic drugs, there are challenges associated with identifying and analyzing imAEs due to differences in clinical trial definitions and procedures. This may hinder the comprehensive analysis of safety data, limit the fully informed presentation of safety information in drug labeling, and impact patient safety. To address this, the FDA and CDE have issued technical guidelines that provide scientific recommendations for identifying and evaluating imAEs based on the mechanism of action and characteristics of cancer immunotherapeutic drugs. This will ensure consistency in the reporting and presentation of imAEs data across different clinical trial designs and inform the writing of relevant adverse reaction information in drug labeling.

FDA AND CDE GUIDANCE INTERPRETATION

FDA GUIDANCE

The FDA recommends a prospective approach for collecting and characterizing imAEs, requiring sponsors to prospectively design the protocol and CRF to capture relevant information and have an early discussion with the clinical review division before implementing a trial. The specific process of collecting and evaluating imAEs relevant safety data is as follows:

Identifying Potential imAEs

Sponsors should create a pre-specified list of potential imAEs using MedDRA terms, including Standardized MedDRA Queries (SMQs), to collect and characterize imAEs-related data. This list must be updated throughout the development program and should be included in relevant documents, such as protocol, investigator brochure, and safety analysis plan.

Protocol and CRF Considerations

The protocol should include instructions for evaluating AEs to assess immunological causality, descriptions of collecting imAEs-related data, and capturing information on potential imAEs for at least 90 days after the last dose of an immunotherapeutic drug.

Case report form (CRF) should include date of onset, CTCAE grade, action taken with study drug, outcome, concomitant medications (including steroids, other immunosuppressive drugs, and hormone replacement therapy) with doses and duration used to treat the potential imAEs and the ability to link it to the specific imAEs, date of resolution, baseline medical conditions, prior treatment history that may predispose a patient to experience an imAE, investigator's assessment of whether an AE is an imAE and the rationale behind the decision.

imAEs Classification

Sponsors should have a prespecified, systematic, and reproducible method for classifying imAEs to allow comparison across trials and development programs.

1. To make sure to accurately and fully capture and characterize imAEs-related data, sponsors should update and revise potential imAEs list timely.
2. Adverse events that were not prespecified can be added to the relevant imAEs category if it describes a similar medical concept. If the patient received steroids, other immunosuppressive drugs, and/or hormone replacement therapy and the sponsor assessed the AE to be an imAE considering the investigator's assessment and rationale.
3. Sponsors should document the rationale for their agreement or disagreement with the investigator's decision.

NDA or BLA Safety Data Considerations

For NDA or BLA, sponsor should provide a variable to show if an AE is in prespecified potential imAEs list, imAEs flag assessed by both investigator and sponsor, imAEs outcome, link between AE and CM domain, rechallenge information if appropriate. In the narrative safety part of NDA or BLA, sponsor should discuss whether AEs are imAEs and the rationale behind the decision.

Labeling Recommendations

For labeling, the guidance summarizes labeling recommendations on how to incorporate imAEs information into the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of labeling for cancer immunotherapeutic drugs.

CDE GUIDANCE

The CDE guidelines provide a comprehensive definition of imAEs and highlight medical considerations, including characteristics based on immune mechanisms and clinical manifestations. As most of the detailed medical considerations are not directly related to the daily work of programmers, they will not be further elaborated in this article. However, the parts that are relevant to programming work will be summarized and consolidated in the section of programming tips. The guidelines also outline a process for identifying and assessing imAEs, while encouraging sponsors to communicate with regulatory agencies promptly.

Process of imAEs Identification

When it comes to overall identification of imAEs, sponsors can develop a scientific process based on the study protocol and data collection. The current overall identification process for imAEs includes, but is not limited to, the following methods:

1. First, summarize all AEs, and then use a prospective process to filter and identify imAEs from the summary.

2. Based on the investigator's design, the sponsor should make a further adjudication of imAEs using a prospective process based on previous clinical trial experience.

3. Use predefined medical logic for computer program identification.

For grade 4 or 5 imAEs and unexpected severe grade 3 imAEs, it is necessary for the sponsor to conduct a detailed case-by-case review.

NDA or BLA Considerations

It is recommended to present the imAEs decisions made by the investigator and sponsor and provide a detailed evaluation process in submission materials, such as summary of clinical safety (SCS). For grade 4 or 5 imAEs, a reasonable explanation should be provided if there are inconsistencies in the decisions made by the investigator and sponsor.

Labeling Recommendations

The drug labeling should adopt the imAEs definition recommended by CDE, and adverse reactions based on imAEs identified by the sponsor should be summarized and presented in the ADVERSE REACTIONS section of the drug labeling.

COMPARISON BETWEEN FDA AND CDE GUIDANCE

In conclusion, there are several similarities and differences between FDA and CDE guidance. For a detailed comparison, please refer to the table provided below.

	FDA	**CDE**
File Name	Characterizing, Collecting, and Reporting Immune-Mediated Adverse Reactions in Cancer Immunotherapeutic Clinical Trials	抗肿瘤治疗的免疫相关不良事件评价技术指导原则
Version	2022-10 (draft)	2022-05-17
Scope	Cancer immunotherapeutic drugs	Chemical drugs, biological products
imAEs* Definition	imARs refers to adverse reactions that occurred in the context of exposure to a cancer immunotherapeutic drug and are consistent with the development of an autoimmune reaction and are not attributable to another cause.	irAEs: In clinical trials for anti-cancer drugs or therapies, adverse reactions of all grades that have been determined to be causally related to the immune mechanism.
Process	The FDA stresses the importance of prospective process and provides detailed guidance on how to collect imAEs-related data accurately and fully. 1. Identify potential imAEs with a pre-specified list. 2. Collect imAEs-related data with detailed requirements for protocol instructions and CRF variable inclusion. 3. Classify imAEs with a pre-specified, systematic, and reproducible method.	CDE places great importance on medical evaluation and monitoring of grade 4 or 5 imAEs and unexpected severe grade 3 imAEs. CDE provides 3 methods: 1. Summarize all AEs, and then use a prospective process to filter and identify imAEs from the summary. 2. Based on the investigator's design, the sponsor should make further imAEs adjudication. 3. Use predefined medical logic for computer program identification.

	FDA	CDE
Submission	In addition to the information mentioned above, the analysis datasets should include: a variable to show if an AE is in potential imAEs list, imAEs flag assessed by both investigator and sponsor, imAEs outcome, link between AE and CM domain, rechallenge information if appropriate. A discussion of the sponsor's assessment of whether AEs are imAEs and the rationale behind the decision.	The imAEs decisions made by the investigator and sponsor. A detailed imAEs evaluation process. A reasonable explanation should be provided if there are inconsistencies in the decisions made by the investigator and sponsor for grade 4 or 5 imAEs.
Drug Labeling	In the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections.	In the ADVERSE REACTIONS section.
Link	https://www.fda.gov/media/162341/download	https://www.cde.org.cn/main/att/download/91c0fd306e0963c1d379f3552623eb42

* Currently, there is no globally accepted standard definition or terminology for imAEs/irAEs/imARs. The FDA uses immune-mediated adverse reactions (imARs), while CDE uses immune-related adverse events (irAEs). In this article, since the US prescribing information (USPI) of all FDA approved immuno-oncology products uses imAEs, we will refer to these events as imAEs.

Table 1. Comparison Between FDA and CDE Guidance

THE PROCESS OF IDENTIFYING AND EVALUATING IMAES

This article provides an overview of BeiGene's imAEs identification and evaluation process for reference purpose only. This complicated process requires close collaboration across various departments and should be guided by relevant documents. This section will provide an overview of the content of these documents, although specific details cannot be disclosed due to confidentiality concerns. Additionally, this article will also outline the collaborative process among different departments, with a particular emphasis on the crucial role of the programming team.

INTRODUCTION OF IMAES RELATED DOCUMENTS

First, the sponsor needs a standard operating procedure (SOP), which is a methodology that offers comprehensive guidance for the general process of identifying and evaluating imAEs. According to the recommendations from both FDA and CDE, the sponsor needs a prespecified imAEs classification process (refer to as the imAEs identification charter) and a potential imAEs list (refer to as the imAEs company custom queries (CCQ) list). Since the SOP is for internal use only, the imAEs charter provides a more detailed description of the procedure for generating imAEs outputs, including the programmatic algorithmic method and the usage of the imAEs CCQ list for submission purpose. The imAEs CCQ list is used for the identification of imAEs preferred terms. Based on imAEs charter, the imAEs programming guidance is provided to internally guide the statistical programming work.

In addition to the documents mentioned above, the sponsor should also collect information on whether the patient received steroids, other immunosuppressive drugs, and/or hormone replacement therapy when assessing imAEs. Therefore, the utilization of WHODrug customized drug groupings (CDG) for classifying concomitant medications is recommended. Due to the inclusion of detailed instructions on imAEs-related drug grouping information in the programming guidance, this paper will not elaborate further on WHODrug CDG.

Summary of imAEs Related Documents

Please find below an introduction to the documents related to imAEs:

Document	Purpose	Owner	Submission
SOP	Outline the roles and responsibilities involved. Introduce the process for defining and maintaining relevant imAEs documents and provide guidance on how to implement these documents. Establish a standardized process for identifying and evaluating imAEs.	Safety Department	Not to submit
imAEs Identification Charter	Provide the detailed procedure of generating imAEs outputs. Provide the programming logic diagram of imAEs identification. Explain the specific usage of the CCQ list.	Safety Department	The medical writer will include this charter as an appendix to the CSR.
imAEs CCQ List*	List the preferred terms for each category of imAEs using the required MedDRA version.	Safety Department	Statistical programmers will include it as external data in the programming data package.
Programming Guidance	Provide programming specifications based on the imAEs identification charter. Provide some notes for specific scenarios. Describe how to filter WHODrug codes.	Statistical Programmer	Not to submit

* The preferred terms in the CCQ list should include all relevant MedDRA versions.

Table 2. Summary of imAEs Related Documents

Relationship of imAEs Related Documents

1. SOP is the highest-level document used to provide comprehensive guidance for the entire company in the process of identifying and evaluating imAEs.
2. The charter is the core document used for submission and includes a portion of the content or guidance from the other three documents.
3. Programming guidance and CCQ list are the foundational documents derived from the charter. Programming guidance provides detailed programming logic, and CCQ list is used for programming.
4. Both the charter and the CCQ list are used for submission.

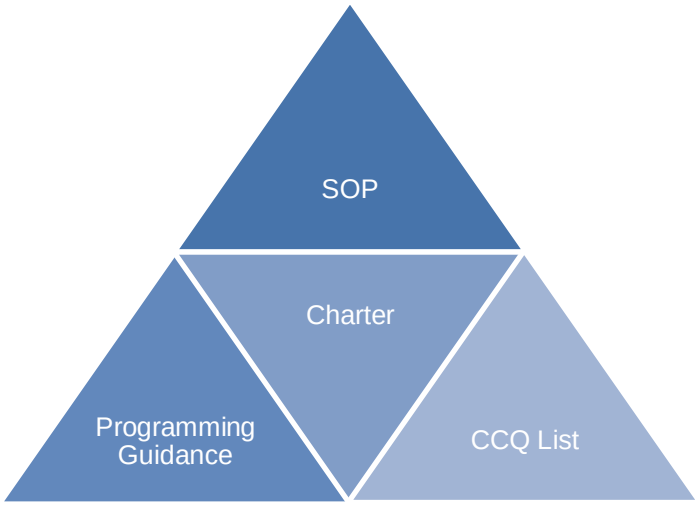

Figure 1. Relationship of imAEs Related Documents

CROSS-FUNCTIONAL PROCESS FOR IDENTIFYING AND EVALUATING IMAES

Flowchart for Identifying and Evaluating imAEs

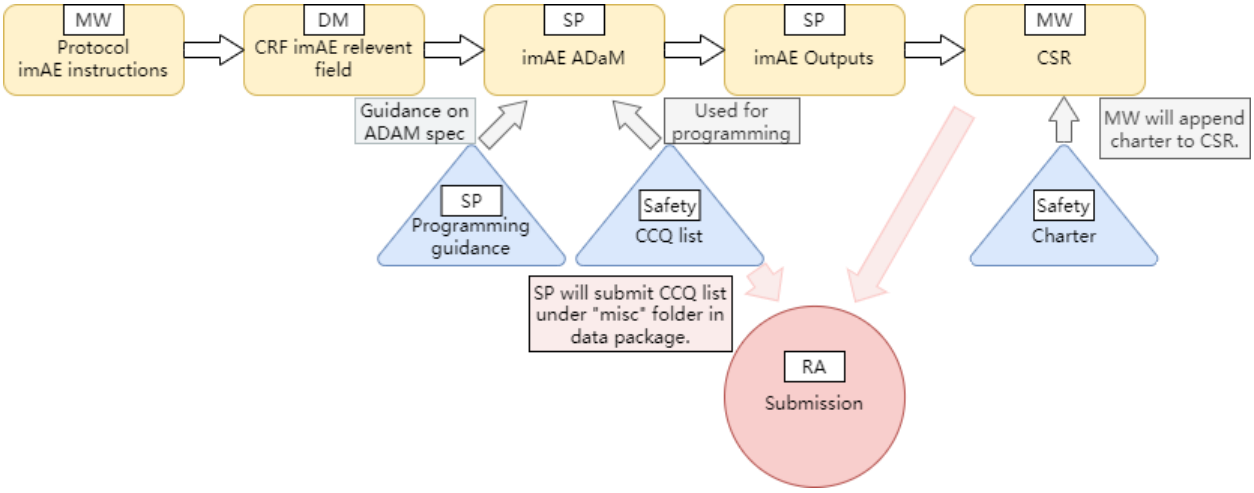

Figure 2. Flowchart for Identifying and Evaluating imAEs

The main challenge in identifying and evaluating imAEs is how to balance the filtering of potential imAEs list, selection based on specific concomitant medication use, and medical assessment using aggregated summary data. This process provides a more comprehensive CCQ list and includes considerations for concomitant medication in the programming guidance. Additionally, it integrates medical logic based on clinical experience into the computer program. The process provides a simplified and streamlined approach, eliminating the requirement for medical adjudication. The results identified by this process are highly robust, demonstrating excellent reproducibility across different clinical trials.

Key Roles in Identifying and Evaluating imAEs

The safety department is responsible for defining and maintaining SOP, charter, CCQ list and WHODrug CDG, as well as determining the appropriate timing for version updates and informing the team. They also document the imAEs methodology within the charter.

The statistical programmer (SP) utilizes the CCQ list, following programming guidance, to generate imAEs outputs. The CCQ list is included in the "misc" folder within the data package for submission. The SP should also establish and update programming guidance. Additionally, they engage in discussions with data management (DM) team on the relevant imAEs data that should be collected in CRF and contribute to the development of a standard CRF.

The medical writer (MW) is responsible for writing the section on imAEs in the protocol, drafting drug labeling, and appending imAEs charter to CSR. The data management team is responsible for the collection of imAEs-related data and the design of CRF. The regulatory affairs (RA) team is responsible for the submission of relevant documents.

Apart from the departments mentioned in the flowchart above, there are also many other departments involved in it. The medical coding team will help to periodically review the WHODrug CDG and inform the team if any invalid ATCs are found. The statisticians will assist in reviewing the programming guidance and provide some comments on the statistical analysis of imAEs. Medical monitors will help to review imAEs assessed by investigators. The clinical operation team assists in ensuring the feasibility of implementing the imAEs methodology in practical clinical trial operations.

PROGRAMMING TIPS

Based on the guidance, documents, and process mentioned above, this article summarizes some practical tips for daily programming work. Some of these tips are recommendations from FDA and CDE, while others are based on clinical experience.

AESI ANALYSIS

It can be particularly challenging to differentiate whether AEs are related to the immunotherapeutic drug, especially when overlapping toxicities are expected with other drugs or anticipated for the population under study. To facilitate causality assessment, the sponsor can increase surveillance for potential imAEs by defining them as adverse events of special interest (AESIs).

USE OF IMAES CCQ LIST

Consult the safety department to select the appropriate MedDRA version compatible with the database.

Please note that even without updates of MedDRA version, the imAEs CCQ list may still be undergoing continuous updates. Therefore, it is important to consistently follow the latest version of the CCQ list with the safety department.

TIPS FOR DATA COLLECTION

Relationship Between imAEs and TEAEs

CDE has stated that imAEs should be considered as part of TEAEs. Typically, the cut-off date for TEAEs is the last dose date + 28 or 30 days. However, it is important to note that some imAEs may have a delayed onset and occur several months after the administration of the study drug. In addition, the FDA recommends that data should be collected for at least 90 days after the last dose of an immunotherapeutic drug. Considering these factors, it is not recommended to use the end date of TEAEs as a cut-off for imAEs in clinical practice. Instead, it is suggested to have a longer observation period, such as the last treatment date + 90 days. This extended period will help to capture a wider range of potential imAEs and ensure that these events are adequately and fully recorded.

Concomitant Medication

If the patient received steroids, other immunosuppressive drugs, and/or hormone replacement therapy to manage an AE, sponsors should consider this AE as an imAE.

CRF should provide a field to link records between CM and AE domain.

It is suggested to separately collect the data regarding systemic corticosteroid usage in the CRF. In addition to the previously defined ATC code, the additional information obtained from CRF will ensure comprehensive and accurate data collection regarding systemic corticosteroid usage.

Action Taken

While corticosteroids and other immunosuppressive drugs are regularly used to manage imAEs, the absence of a history of immunosuppressive treatment for an AE does not preclude its characterization as an imAE, especially for low-grade imAEs that result in dose interruption.

AE Causality

FDA recommendation: When evaluating a potential imAE, it is essential to differentiate between the effects of the immunotherapeutic and effects not related to the immunotherapeutic. Therefore, from a programming perspective, it is highly necessary to consider the causality between AEs and immunotherapy drugs.

Investigator and Sponsor imAEs Decision

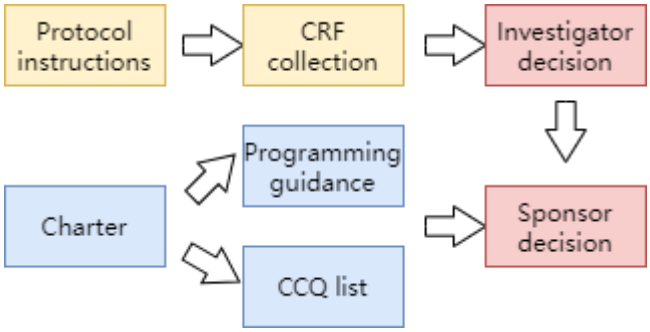

Figure 3. Investigator and Sponsor imAEs Identification Process

Any AE flagged by investigators as an imAE needs to be taken into consideration by the sponsor.

Sponsor should document the rationale if they agree or disagree with the investigator's decision.

For grade 4 or 5 imAEs, a reasonable explanation should be provided if there are inconsistencies in the decisions made by the investigator and sponsor.

TIPS FOR COMBINATION STUDY

In accordance with FDA guidance, potential imAEs should be collected for at least 90 days after the last dose of immunotherapeutic drug. In the case of a combination study, it is recommended to include any study drug rather than specifically focusing on the immunotherapeutic drug. This approach will facilitate a fair comparison between the two treatment arms and ensure consistency in the algorithm utilized for imAEs derivation throughout the study. Similarly, it is recommended to include any study drug, rather than just immunotherapeutic drug, when considering AE causality or AE action taken. We can include additional lines in the summary table, like imAEs related to immunotherapeutic drug and imAEs leading to immunotherapeutic drug discontinuation or interruption. This will provide specific information on immunotherapeutic drug while eliminating any potential noise.

When using a crossover design in clinical trials, it is recommended to present the imAEs separately in the CSR. Because the immunotherapy regimens and exposure time may differ between experimental arm and control arm.

CONCLUSION

In summary, the paper highlights the importance of accurately identifying and evaluating imAEs in cancer immunotherapeutic clinical trials. The FDA and CDE have issued guidelines for this purpose, emphasizing the need for comprehensive data collection and reporting. The paper provides interpretation and comparison of the FDA and CDE guidelines, outlining the process for identifying and analyzing imAEs. Statistical programmers play a crucial role in this cross-functional collaboration, and the paper also offers some programming tips for implementing relevant guidance. In general, the establishment and maintenance of standardized process, documentation, and collaboration among different departments are essential for effective imAEs identification.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Yang Song
BeiGene, Inc.
+86 13709826700
yang.song@beigene.com