Paper DS08

Company-Level End-to-End Therapeutic Area Data Standards Development – A Case Study Involving CRS and ICANS

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ABSTRACT

The development of therapeutic area data standards in the pharmaceutical industry requires ongoing enhancement, even in disease areas with existing regulatory guidelines. This paper addresses the agile expansion of company data standards, using Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) as examples. These toxicities are closely monitored both pre- and post- regulatory approval for cancer immunotherapies. By developing end-to-end data standards for CRS and ICANS and implementing them in applicable clinical trials, companies can more effectively optimize safety profile of new treatments, enhance data quality and interoperability, and ensure regulatory readiness. The proposed framework aims to guide the development of comprehensive data standards for these toxicities, offering insights for advancing oncology data standards.

1. INTRODUCTION

1.1 BACKGROUND ON THERAPEUTIC AREA STANDARDS

When discussing therapeutic area data standards, the "Therapeutic Area User Guides (TAUGs)" by the Clinical Data Interchange Standards Consortium (CDISC) often come to mind. The FDA has played an instrumental role in the development of these standards. In 2011, the Center for Drug Evaluation and Research (CDER) identified several therapeutic areas for further standardization, categorizing them into three tiers of priority [2]. The FDA collaborates with CDISC and the Critical Path Institute on the development of these standards, which involves initial development, internal and public reviews, and public release.

The question often arises: Does the FDA mandate the adoption of the CDISC TAUGs? According to the FDA's "Study Data Technical Conformance Guide" [3], CDISC TAUGs are not data standards themselves. Rather, they extend the foundational standards of CDISC (e.g., SDTM and ADaM) to represent data relevant to specific disease areas and should not be considered as official FDA guidance.

1.2 OVERVIEW AND ADOPTION CHALLENGES

Although TAUGs have significant potential to streamline data collection and accelerate research, their adoption across the industry has been limited due to several factors:

- **No position on data collection requirements**: TAUGs do not provide guidance on what data are needed for regulatory submission or approval.
- **Efficacy Focus**: Current TAUGs primarily support efficacy analyses, highlighting the need for additional standardization in safety data to broaden their applicability.
- **Emerging Therapies**: To remain relevant, TAUGs must continuously evolve alongside new therapeutic developments.
- **Revision Gaps**: The absence of updates after initial publication can hinder their applicability as scientific and regulatory landscapes change.

1.3 THERAPEUTIC AREA DATA STANDARD DEVELOPMENT IN PHARMACEUTICAL COMPANIES

Large pharmaceutical and biotechnology companies are at the forefront of developing therapeutic area data standards as extensions of their enterprise-level data frameworks. The motivations driving these developments include:

1. **Accumulated Experience**: Leveraging expertise gained in specific disease areas to inform company-level data standard development, thereby benefiting other compounds within the same category.
2. **Expanding into New Disease Areas**: Accelerating product development in therapeutic fields new to the company by incorporating data standards informed by external resources.
3. **Extensive Development Plans**: Ensuring the consistent application of industry guidelines through comprehensive company-level data standards, exemplified by the development of company data standards for implementing Immune-related Response Evaluation Criteria In Solid Tumors (iRECIST).

Given the challenges outlined earlier, company-level data standards offer a more agile and tailored approach to overcoming these obstacles. The subsequent sections will explore how the development of therapeutic area data standards for CRS and ICANs exemplifies this approach, detailing their creation and implementation within a corporate framework.

2. CASE STUDY: CRS AND ICANS

2.1 WHAT ARE CRS AND ICANS?

Cytokines are proteins that regulate inflammation and immune responses. CRS is condition that occurs when the immune system overreacts to a severe infection or immunotherapy, resulting in a sudden release of cytokines into the bloodstream that can damage organs and healthy tissue.

Immune effector cell-associated neurotoxicity syndrome (ICANS), often referred to as neurotoxicity (NT), frequently occurs alongside or following CRS. It is considered a neurological manifestation of CRS.

2.2 CRS AS A MAJOR SAFETY CONCERN IN CANCER IMMUNOTHERAPIES

Shah D et al reviewed the CRS events across the three predominant classes of immunotherapy - CAR-T, bi-specific T-cell engager, and immune checkpoint inhibitors and concluded that CRS remains a significant side effect requiring characterization, management, and mitigation during the development of novel immunotherapies [5].

Due to the risks of CRS and NT, currently approved autologous CAR-T cell immunotherapies are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). These products all carry a boxed warning for the potential risks of CRS and NT [6].

For bi-specific T-cell engagers, the FDA approved three products recently: Teclistamab, Tarlatamab, and Epcoritamab-bysp (Epkinly), each of which includes a boxed warning about CRS and NT [7, 8, 9].

The FDA Office of Oncologic Drug (OOD) specified adverse event analysis data for CRS and neurological toxicities (NT) in its Standard Safety Data Requests published in 2021 [10].

Establishing comprehensive data standards for CRS and ICANS is crucial for advancing the development of new immunotherapies. Specifically, this involves collecting relevant data to assess CRS and ICANS risks associated with new therapies, representing both collected and derived data in accordance with CDISC format, and analyzing the data to address key clinical and safety questions. These standards will assist pharmaceutical companies and regulatory agencies in evaluating the benefit-risk profiles of these therapies and ensuring data comparability within the same category.

3. FRAMEWORK FOR CRS AND ICANS DATA STANDARDS

When developing end-to-end data standards for CRS and ICANS, it is recommended to follow these steps:

1. Identify the clinical and safety questions to address.
2. Specify statistical analyses for various purposes.
3. Define data collection requirements.
4. Address key questions related to SDTM mapping.
5. Design ADaM datasets.

3.1 CLINICAL AND SAFETY QUESTIONS TO ADDRESS

The development of data standards should revolve around key clinical and safety queries:

- **Risk Identification**: Defining and reporting CRS and ICANS events.
- **Risk Characterization**: Understanding the incidence, severity, duration, and occurrence of CRS and ICANS events
- **Risk Management Strategies**: Developing prophylactic and treatment measures.
- **Exposure-Response Relationships**: Exploring correlations between dose regimens / exposure levels and associated risks.

- **Regulatory Requirements**: Ensuring adherence to guidelines and addressing specific regulatory requests.
- **Patient Risk Factors**: What patient-level factors increase the likelihood of these adverse events?

By systematically addressing these questions, we aim to build a comprehensive understanding of the clinical and safety aspects surrounding CRS and ICANS risks. This framework will serve as a foundation for developing robust data standards.

3.2 DATA COLLECTION STANDARDS

3.2.1 Defining CRS and ICANS, and Grading Systems

1. Defining CRS and ICANS

The importance of a standardized approach to defining and capturing Cytokine Release Syndrome (CRS) is underscored by Stewart M et al [11], given the overlapping symptoms and temporal association of CRS with other clinical conditions.

The American Society for Transplantation and Cellular Therapy (ASTCT) defines CRS as:
"A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction" [4].

For ICANS, the ASTCT defines it as:
"A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells". Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema" [4].

The grading systems for CRS and ICANS, published by ASTCT, are now widely adopted across the biopharmaceutical industry.

2. Evolving Guidelines and Practice

Stewart's paper highlights that while existing CRS guidelines and grading systems are mostly based on clinical experience with CAR-T cell therapies, they may eventually require revisions as more data emerge from novel cancer immunotherapies and broader clinical experience. Despite these advancements, Stewart notes that adopting a *uniform* comprehensive data collection approach for CRS risks may not always be practical.

Instead, Stewart proposes a strategy where the level of comprehensive data collection depends on an investigational product's initial CRS risk assessment:

- L**ow or no CRS risk**: Initial safety monitoring may involve only standard AE reporting without upfront cytokine or biomarker data collection, until clinical evidence later suggests a potential CRS risk.
- H**igh CRS risk**: A dedicated clinical and safety monitoring plan is necessary from the onset, requiring a specific case report form (CRF) to capture associated signs and symptoms.

These tailored data collection approaches allow flexibility and resource optimization while ensuring sufficient monitoring based on a product's risk profile.

3. Focus on High-Risk Scenarios

The recommendations following focus on scenarios where there is a high risk with CRS and ICANS.

3.2.2 Adverse Event CRF

In the paper by Stewart M. et al. [11], it is proposed to capture adverse events (AEs) such as fever, elevated liver function tests (LFTs), or seizure separately while linking them to the overarching CRS event. This approach allows for nuanced analysis of CRS across affected organ systems, such as hepatic, renal, or neural systems, and offers flexibility to either report all events separately or consolidate CRS-related data into a single AE entry. A similar approach should be taken for adverse events related to ICANS.

It is important to note that while individual AEs are graded using the CTCAE (Common Terminology Criteria for Adverse Events), CRS and ICANS events are graded using the ASTCT system. These grades should be recorded in distinct data fields within the AE CRF to maintain clarity.

Some companies may opt for a simplified approach, capturing only the CRS event in the AE CRF and omitting linked individual AEs. However, this practice risks losing critical data, which could be essential for applying future CRS diagnostic or grading criteria.

Additionally, recording precise start and end times for CRS and ICANS events is crucial, as these events often occur shortly after immunotherapy administration, necessitating more accurate tracking than standard AEs.

3.2.3 CRF for Signs and Symptoms of CRS

As stated in section 3.2.1, in high CRS risk scenarios, a separate CRF is required to collect pre-specified clinical signs and symptoms of CRS with a clear linkage to the CRS event recorded in the AE CRF. These signs and symptoms may include:

- **General symptoms:** Fever, chills, nausea, fatigue, headache, diarrhea, vomiting, and rigors.
- **Vital sign abnormalities:** Hypotension, hypoxia, tachycardia.

For each symptom, the following details should be documented:

- Start and end times.
- Ongoing status.
- CTCAE grade and ASTCT grade.
- Specific interventions, e.g., vasopressors for hypotension or nasal cannula oxygen therapy for hypoxia.

Such detailed data facilitate cross-verification with CRS event records in the AE CRF, allowing for improved characterization of individual CRS events. A similar approach should be used for ICANS, with a separate CRF to collect the relevant details.

3.2.4 CRS Pre-treatment and Concomitant Anti-cytokine Therapy

Additional data on concomitant medications (e.g., tocilizumab, corticosteroids, vasopressors, oxygen therapy) and specific interventions (e.g., oxygen delivery methods, mechanical interventions, IV fluids) must be captured and linked to the corresponding CRS event and CRS signs and symptoms. This linkage is critical, as CRS grading often depends on these interventions.

3.2.5 Vital Signs, Laboratory Data and Biomarkers

Standard vital sign assessments should include body temperature, pulse, blood pressure, and oxygen saturation. For higher-resolution monitoring, wearable devices might be considered to provide real-time vital sign data, especially for high-risk patients. The topic of whether and how to link data collected from wearable devices with CRFs remains to be addressed.

In severe CRS cases, additional laboratory tests, including cytokine biomarkers, may be required. These data deepen insights into CRS pathophysiology and contribute to more effective management strategies.

3.3 SDTM DATA STANDARD

This paper does not aim to provide a detailed discussion on the SDTM data standard as it relates to CRS and ICANS, as the data collected for these conditions generally fall within existing domains such as AE/SUPPAE, CM/SUPPCM, CE/SUPPCE, and VS/SUPPVS. However, there are a few important considerations for effective implementation:

1. **Differentiate data for regulatory and for internal use**: The company-level data standard for CRS/ICANS should specify which data will be submitted for regulatory purposes and which will not be submitted, being used solely for internal event-level review.
2. **Design standard CRFs with SDTM mapping in consideration**: Identify the relevant SDTM domains during CRF development, and structure the CRF to collect data in a way that aligns with the SDTM data model, ensuring seamless mapping later.
3. **Represent linkage of related records**: The relationship between records mapped to different SDTM domains must be accurately represented using SUPPxx datasets or the RELREC data. This ensures coherence, traceability, and cross-reference.

3.4 ADAM DATA STANDARD

The adverse event analysis dataset for CRS and NT (Neurotoxicity) is outlined in the FDA Office of Oncological Drug (OOD) Standard Safety Data Requests v1.3, published in February 2021 [10]. While included, this dataset specification is not as widely adopted as some other dataset specifications in the document. Consequently, statistical programmers in the oncology therapeutic area may have several clarifying questions, such as:

1. What analyses are intended to be supported by this analysis dataset?
2. Do all the listed variables fit within a single ADaM-compliant dataset, and what would be its structure?

3.4.1 Intended Analyses on CRS and NT

From the author's perspective, the intended analyses include:

1. Subject incidence of CRS and NT: Analyze the incidence rate of CRS and NT for the entire study and by treatment periods. As oncology treatments are often administered by cycle, summaries of subject incidence may also be performed by cycle.

2. Characteristics of individual CRS and NT events: Summarize the characteristics of individual CRS and NT events, such as toxicity grade, maximum toxicity grade, time to event, and duration of event. Summaries may be conducted overall and by treatment period and cycle. It is important to consider variations in analyses due to differences in handling multiple events occurring in the same time interval for the same subject.

3. Medications and procedures for CRS and NT events: Summarize the medications and procedures employed in treating CRS and NT events.

3.4.2 Recommended ADaM datasets on CRS and NT

Based on the intended analyses described, multiple ADaM datasets are recommended for CRS and NT, alongside the standard ADAE dataset that includes all adverse events. These datasets should support various analyses while ensuring traceability from SDTM to ADaM.

A. ADAE Dataset

- **Description:** Contains all AE records sourced from the AE domain using the OCCDS structure. Events of special interest are flagged using SMQzzNAM or CQzzNAM (MedDRA or custom query), with CRS and NT events specifically identified by different CQxxNAM flags.

- Analytical Support:
    - Subject incidence of CRS or NT and its subset such as serious events, grade 3 and above events, events resulting in treatment interruption or discontinuation, and events treated with anti-cytokine medication

B. ADCRSNT Dataset

- **Description:** A subset of ADAE, beginning with records identified as CRS or NT and involving derivations such as:
    - **Timing Variables:** Derive the treatment period and cycle for each CRS/NT event onset.
    - **Event Collapsing:** Address any rules for collapsing multiple events within a time interval and add derived records as needed, flagging them appropriately.

- Analytical Support:
    - Summary of event rate
    - Functioning as the intermediate dataset for ADCRSSUM

C. ADCRSSUM or ADAESUM

- **Description:** Derived from ADCRSNT, this dataset follows Basic Data Structure (BDS) to facilitate summaries of CRS and NT across the entire study and within smaller intervals like periods and cycles.
    - **Parameters (PARAM) and AVAL:** Include endpoints such as time to first CRS/NT event, duration of CRS/NT event, and maximum CTCAE grade of CRS/NT.
    - **Timing variables (AVISIT or AEVLINT):** Capture intervals such as "Overall", "Period xx", and "Cycle zz". This dataset contains one record per subject per time interval per parameter, based on collapsed records from the ADCRSNT dataset.

- **Analytical Support:** Enables comprehensive summaries over varying study intervals.

D. ADCE Dataset?
From the author's standpoint, the ADCE dataset is rarely needed for analysis and is not recommended for inclusion in this context.

A paper by Xi J. et al. [12] discusses their experience with CRS and NT analysis data during submission preparation and regulatory review for two CAR-T compounds. While the FDA Office of Oncological Drug (OOD) safety data standard request was not explicitly mentioned, their experiences align with the author's understanding of FDA expectations for this type of analysis data.

Additionally, Xi J. [12] reported submitting supplementary datasets for CRS and NT events per FDA request to facilitate the review of their submission package. Notably, these datasets were not CDISC-compliant, suggesting that the FDA's request may reflect an ad hoc need to address gaps in the sponsor's original submission package. For example, one such dataset, ADAE2, replaced NT events with their corresponding signs and symptoms, potentially reflecting differences in capturing CRS and NT events in their studies—likely corresponding to Approach 1 for CRS and Approach 2 for NT, as explained in Section 3.2.2 of this paper.

These observations underscore the following recommendations:

1. Seek FDA input early in the development of company-level CRS and NT data standards, clearly explaining the entire process—from CRF design to analysis dataset preparation and statistical analysis—to ensure alignment with their expectations.

2. Interact with the FDA review division during pivotal trial planning and submission meetings to ensure mutual understanding of submission data expectations.

3.5 TFLS

Refer to Section 3.4 for the intended analyses typically performed on CRS and ICANS.

In addition to standard TFLs, some companies have developed advanced visualization tools that allow users to explore and analyze CRS and ICANS dynamically. These tools offer convenient functionalities such as filtering, data sorting, and selective display of subject characteristic variables in the visualizations. This dynamic approach facilitates pattern identification, treatment group comparison, and a deeper understanding of events.4.

As CRS and ICANS data accumulate from multiple studies, statistical models can be applied to identify risk factors associated with these conditions. These models are instrumental in enhancing CRS management during clinical trials and in post-marketing settings, guiding interventions, and improving patient safety.

CONCLUSION

Developing data standards for safety topics presents unique challenges compared to efficacy analysis. Key challenges include:

1. Comprehensive Data Collection: Safety data must be collected not only for planned analyses included in the Clinical Study Report (CSR) and submission datasets, but also for purposes such as patient-level safety monitoring and compound-level safety signal detection.
2. Adherence to Standards: Safety data not intended for pre-specified analysis or submission datasets often suffer for reduced motivation for standardization. This can lead to inconsistencies and varied data quality.
3. Emergent Safety Topics: For emerging safety issues, it may initially be unclear what data components should be captured and how data collection should be optimally structured, adding complexity to the standardization process.
4. Flexibility in Analysis: Compared to efficacy data, the analysis of safety data often affords more flexibility to sponsors. While this flexibility is valuable, it can diminish the push for strict data standardization.

By addressing these challenges, the development of robust data standards for safety topics, such as CRS and ICANS, supports the advancement of new treatments and enhances patient safety.

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