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Optimizing ISS Analysis for Multi-Indication Submissions

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ABSTRACT

The Integrated Summary of Safety (ISS) is a critical component of regulatory submissions, particularly when addressing multiple indications for a single compound. This paper outlines key considerations for optimizing ISS preparation, focusing on data pooling strategies, harmonization of controlled terminologies, coding dictionaries as well as managing simultaneous ISS submissions for different indications. From the perspective of statistics programming, pooling at the Analysis Data Model (ADaM) level is advocated due to its efficiency in leveraging standardized datasets, minimizing redundant derivations, and accelerating the generation of tables, listings, and figures (TLFs) under tight timelines. Harmonization components align with the FDA's Study Data Technical Conformance Guide, ensuring consistent terminologies and coding dictionaries, such as MedDRA and WHODRUG, across studies. Two operational models—separate versus centralized pooling—are compared in the context of simultaneous submissions, highlighting the advantages of a centralized approach in ensuring analytical consistency and operational efficiency. By addressing these challenges, this paper explores a potential framework for streamlining ISS preparation across diverse indications, enhancing methodological consistency, and efficiently meeting regulatory requirements.

INTRODUCTION

The Integrated Summary of Safety (ISS) is a vital component of the Common Technical Document (CTD) required for regulatory submissions of new drug applications. It provides a comprehensive overview of the safety profile of a pharmaceutical compound by integrating data across multiple clinical studies. As the pharmaceutical industry increasingly pursues compounds intended for multiple indications, the complexity of preparing ISS submissions has grown significantly. This evolution introduces challenges in data standardization, terminology harmonization, coding consistency, and the efficient handling of overlapping studies.

Traditional approaches to ISS preparation often treat each indication as a standalone effort. However, this can lead to redundancy, inconsistency in data derivations, and increased resource demands—especially when timelines are compressed and datasets are extensive. Moreover, regulatory expectations emphasize the need for uniform and harmonized safety reporting across studies and populations, regardless of study design variations.

This paper explores practical strategies to optimize ISS development for compounds with multiple therapeutic indications. It discusses the merits of pooling data at the Analysis Data Model (ADaM) level, approaches for controlled terminology and treatment harmonization, and methods to manage coding dictionary up version. Particular attention is given to a comparison of two operational models for managing simultaneous ISS submissions – using separate versus centralized pooled approaches, and their respective impacts on resource efficiency and analytical consistency.

Through this exploration, a potential framework is proposed to streamline ISS preparation, aligns with regulatory requirements, and improves the overall efficiency of ISS preparation for multi-indication drug submissions.

POOLING STRATEGY

In clinical trials, pooling data from multiple studies is essential for preparing an Integrated Summary of Safety (ISS). Two primary strategies are commonly used: pooling based on SDTM or ADaM datasets. Both approaches are acceptable, each with its own advantages and disadvantages, and the choice depends on specific study requirements.

In practice, the decision depends on evaluating which pooling level is simpler, more feasible, and requires fewer additional derivations. In the scenarios under discussion, pooling at the ADaM level appears to be

the more appropriate approach based on a thorough assessment of feasibility and derivation complexity.

1. When the individual studies pooled for the ISS originate from a single sponsor compound, with ADaM datasets conforming to CDISC standards and consistent derivation rules established during study design. Pooling at the ADaM level enhances efficiency by eliminating redundant derivation efforts.

2. While some ISS analyses require new derivations, most can be addressed using existing ADaM datasets, with only minor components needing derivation from SDTM data.

3. Multiple ISS submissions for different indications are being prepared concurrently, each with stringent timelines. Since ADaM datasets are readily available with most derivations completed, pooling at the ADaM level significantly reduces the time required to generate tables, listings, and figures (TLFs).

Figure 1 shows the working flow for pooling individual studies at the ADaM level.

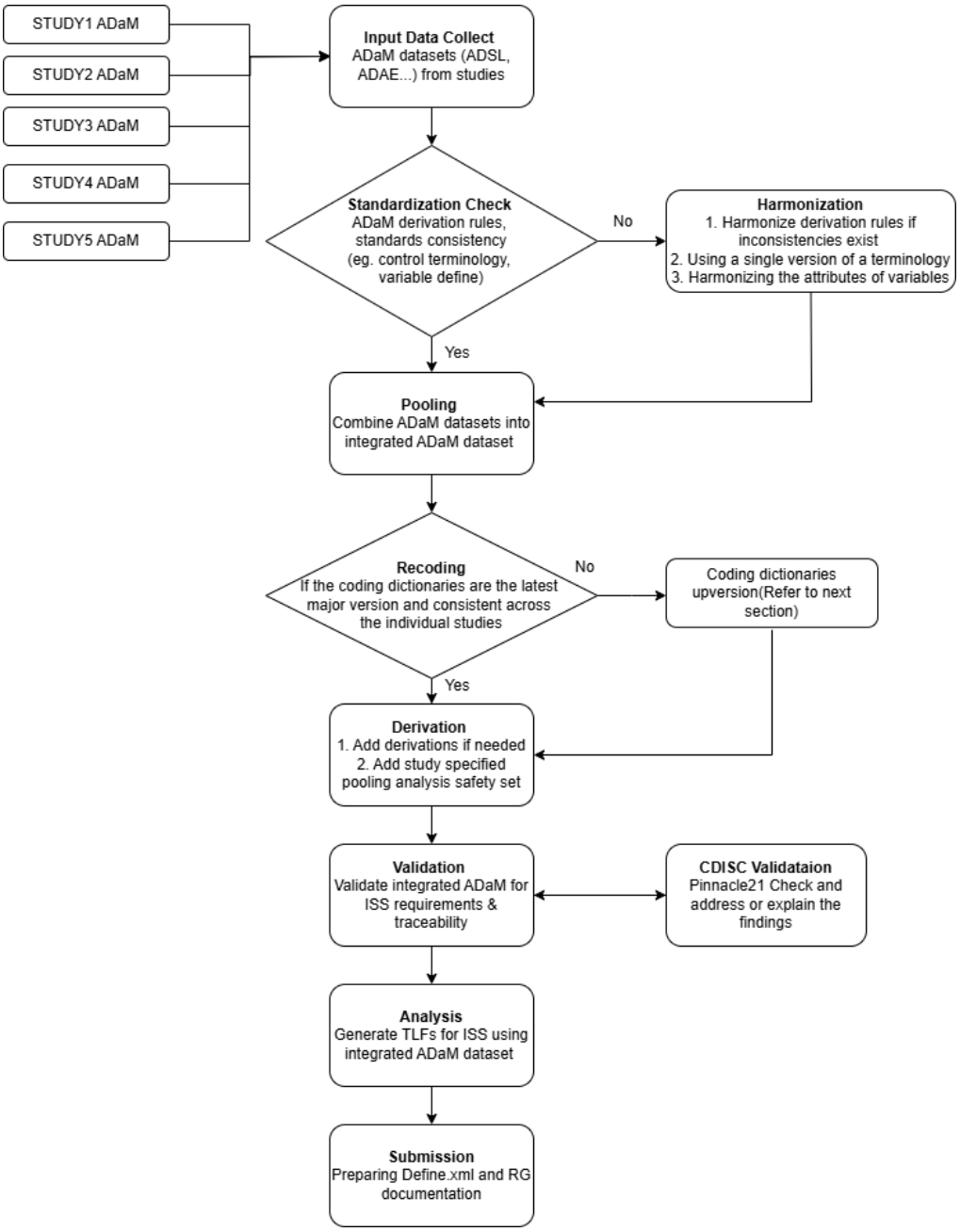

Figure 1. Working flow for pooling at ADaM level

HARMONIZATION AND DERIVATION

CONTROLLED TERMINOLOGIES AND IG HARMONIZATION

Since individual studies may use different versions of controlled terminologies and CDISC implementation guide (IG), the ISS pooling process aims to ensure a consistent codelist for programming and a more standardized approach to the presentation and comparison of statistical results across multiple studies. Therefore, a single version of both the controlled terminology and the implementation guide should be used throughout the process.

To achieve this, the process follows the FDA's Study Data Technical Conformance Guide, as referenced below:

"Regardless of the specific versions used for individual studies, pooled analyses (e.g., for an ISS) should be conducted using a single version of a terminology. The current version should be used at the time that data across studies are pooled. It is also acceptable to use the most recent major version of a terminology if it describes the data well."

TREATMENT VARIABLES HARMONIZATION

Across individual studies, treatment values may be recorded using different descriptions, requiring standardization to a unified format.

For example, treatment values such as "Test Drug A 50mg", "Trial Medicine A 50mg," and "Drug A 50mg" should all be standardized to "Drug A 50mg" for the TRT01A variable.

POOLING SAFETY SET DERIVATION

Placebo-controlled safety set

The placebo-controlled safety set will include participants from the randomized, placebo-controlled phases of individual studies, irrespective of indication, to provide robust comparative safety data for the study drug versus placebo.

Drug-treated safety set

The drug-treated pooled safety set will encompass all participants treated with the study drug across all studies, regardless of indication, to deliver a comprehensive overview of safety data across all indications.

Specific populations:

To assess safety data for each indication, data from completed or unblinded individual studies for the same indication will be pooled.

To assess safety data for the pediatric population, pediatric participants from completed or unblinded individual studies, regardless of indication, will be pooled.

Pooling analyses may also be conducted for different dose groups or distinct disease types to support targeted safety evaluations.

CODING DICTIONARIES UPVERSION

Another important consideration is the versioning of the coding dictionaries. Since ISS incorporates a number of studies in the same compound, including completed, terminated, or ongoing studies, the version of the coding dictionaries used for each study may be different. According to FDA's Study Data Technical Conformance Guide,

"To avoid potential confusion or incorrect results, the preparation of the adverse event dataset for the ISS should include MedDRA terms from the most current version of MedDRA at the time that data across studies are pooled. It is also acceptable to use the most recent major version of MedDRA if it describes the data well. The reason for an ISS based on a single version of MedDRA is that reviewers often analyze adverse events across studies, including the use of Standardized MedDRA Queries."

The same requirement should also be implemented to the WHODRUG dictionary. The common method for recoding is by pooling all individual studies datasets (ADAE, ADMH, ADCM…), then medical coding team perform the up-version coding according to lowest level term (LLTCD) for MedDRA and drug record number (RECNO), sequence number 1 (SEQ1) and sequence number 2 (SEQ2) for WHODRUG.

In the implementation of the project, it is necessary to account for the time required for recoding, as well as whether the data cutoff timing falls near the release date of a new dictionary version. If the data cutoff

date is right after the release date, then medical coding team should be informed to pause the upgrade to new version and use the agreed version in study data standardization plan (SDSP).

SIMULTANEOUS ISS SUBMISSION ACROSS DIFFERENT INDICATIONS

When preparing to submit ISS for different indications within the same compound simultaneously, several considerations must be addressed.

SAFETY DATABASE ACROSS INDICATIONS:

For different indications of the same compound, each ISS submission may include some overlapping individual studies, along with a distinct pivotal study. As shown in Table 1, Studies 1, 2, and 3 are individual studies included in both the ISS pools for Indications C and D. Study 4 serves as the pivotal study for the Indication C ISS pool and will be unblinded and incorporated into the integrated safety database at the time of the data cut.

Indications	Studies	Indication C ISS Pool	Indication D ISS Pool
A	Study 1	Y	Y
A	Study 2	Y	Y
B	Study 3	Y	Y
C	Study 4	Y (Pivotal)	Y
D	Study 5		Y (Pivotal)

Table 1 Safety database for each indication pool

Figure 2 illustrates the overall timeline for all individual studies related to the same compound. Study 4 will have data cut prior to Study 5. Therefore, by the time the data cut for Study 5 is performed, Study 4 will already be unblinded and included in the Indication D ISS safety database.

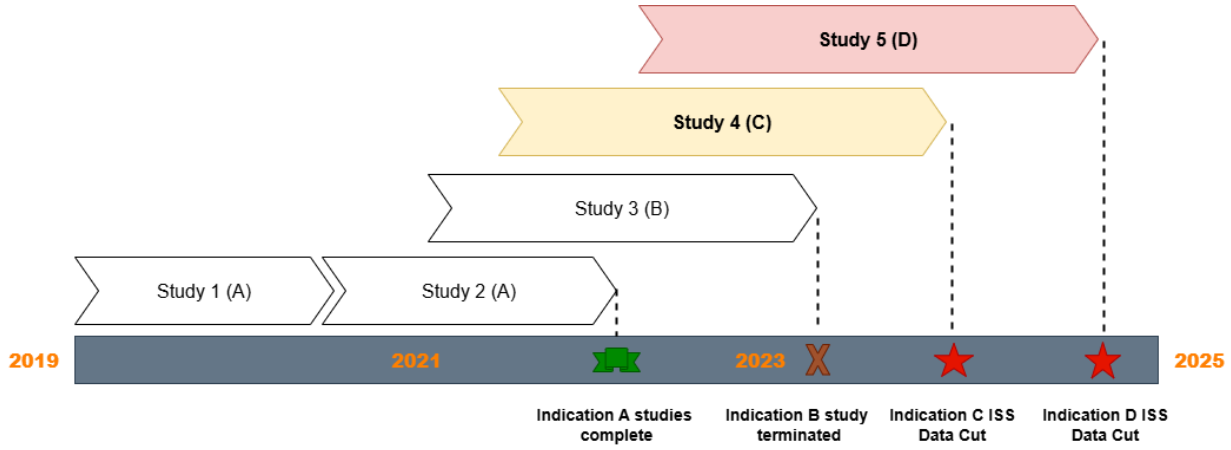

Figure 2 The overall timeline for the studies in the same compound

MANAGING MULTI-INDICATION ISS WITH SHORT SUBMISSION INTERVALS

Given the brief interval between the two ISS submissions and the substantial overlap of individual studies, engaging the same team for both submissions is a strategic and efficient choice. This ensures methodological consistency in data handling, statistical analysis, and result interpretation, thereby minimizing the potential for discrepancies or mismatches between the common part of the different indication ISS and eliminating redundant efforts.

When beginning the pooling of ADaM datasets, there are two approaches to consider.

Approach 1: Separate Pool by Indication

The first approach is to create two separate pooled metadata, ADaM and TLF programs, for each indication and maintain them independently in different working triplets (Figure 3).

This approach can be explored as a method to manage datasets and programs separately by indication, enabling independent maintenance.

The main advantage of this method is that it prepares 2 separate components which are ready for submission without any further modification for each indication. It also enables easier program adjustments without the need for conditional handling of derivation rules in response to indication-specific ISS requests or updates.

However, this approach presents some notable disadvantages. It requires to maintain two sets of metadata and programming files, thereby increasing the need for resources on the team. Given that most of the pooling logic and derivation rules are the same across indications, there exists a substantial potential that modifications or updates from the study team may necessitate implementation across both ISS analyses. If an update is implemented in one indication's ISS analysis but inadvertently omitted in the other, such discrepancies can be hard to detect—even with double programming.

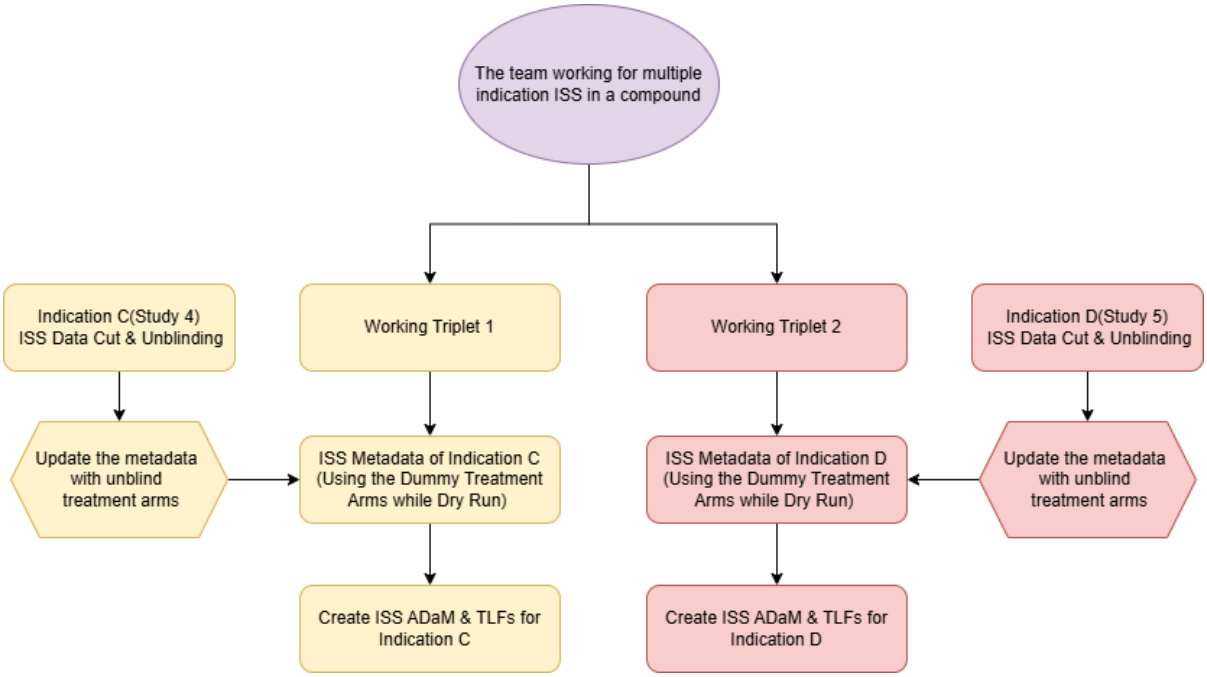

Figure 3 Workflow for separate pool for each indication

Approach 2: Centralized Pool Across Indications

As an alternative, creating centralized metadata and programs within the same working triplet can mitigate the risk of such inconsistencies. This approach involves developing metadata, ADaM datasets and outputs through centralized programs by applying shared derivation rules for both indications and implementing indication-specific variables as needed. This ensures that updates or adjustments are captured consistently across both ISS analyses, maintaining the integrity and completeness of the ADaM dataset and outputs.

From a methodological perspective, an important consideration arises: the centralized metadata encompasses information from all individual studies, including Study 5, which serves as the pivotal study for Indication D ISS. Consequently, during the preparation of submission packages for Indication C ISS,

all Study 5-related information must be systematically excluded from the metadata. This operational step allows the programming team to proceed with the submissions process for Indication C within the designated environment (Working Triplet 1), utilizing the centralized analytical programs. Figure 4 illustrates the workflow of centralized pooling across multiple indications.

An additional methodological benefit emerges in the context of parallel compound-level milestone deliverables (such as Safety Management Team activities - SMT and Development Safety Update Report - DSUR), which frequently coincide with the ISS preparation timeline. In such scenarios, given that the results are generated at compound-level, centralized metadata and programs offer significant advantages, as the latest versions can be directly utilized across working triplets without redundant copy-paste operations, ensuring consistency and efficiency.

To support blinded data handling during the preparation phase, some ongoing studies with blinded treatment arms, referred to as dummy treatment arms, are incorporated into the centralized ADaM datasets and TLFs. For Indication C ISS, the treatment arms are updated in both the metadata and the ADaM dataset after the data cut for Study 4 and subsequent unblinding, this ensures that the safety data accurately reflects the actual treatment assignments.

Subsequently, for Indication D, the ISS data cut for Study 5 was conducted, with a similar unblinding process applied to Study 5's treatment arms in the metadata and ADaM dataset. Through adopting this structured approach, the potential for timeline compression is enhanced, helping to alleviate pressure from a tight timeline.

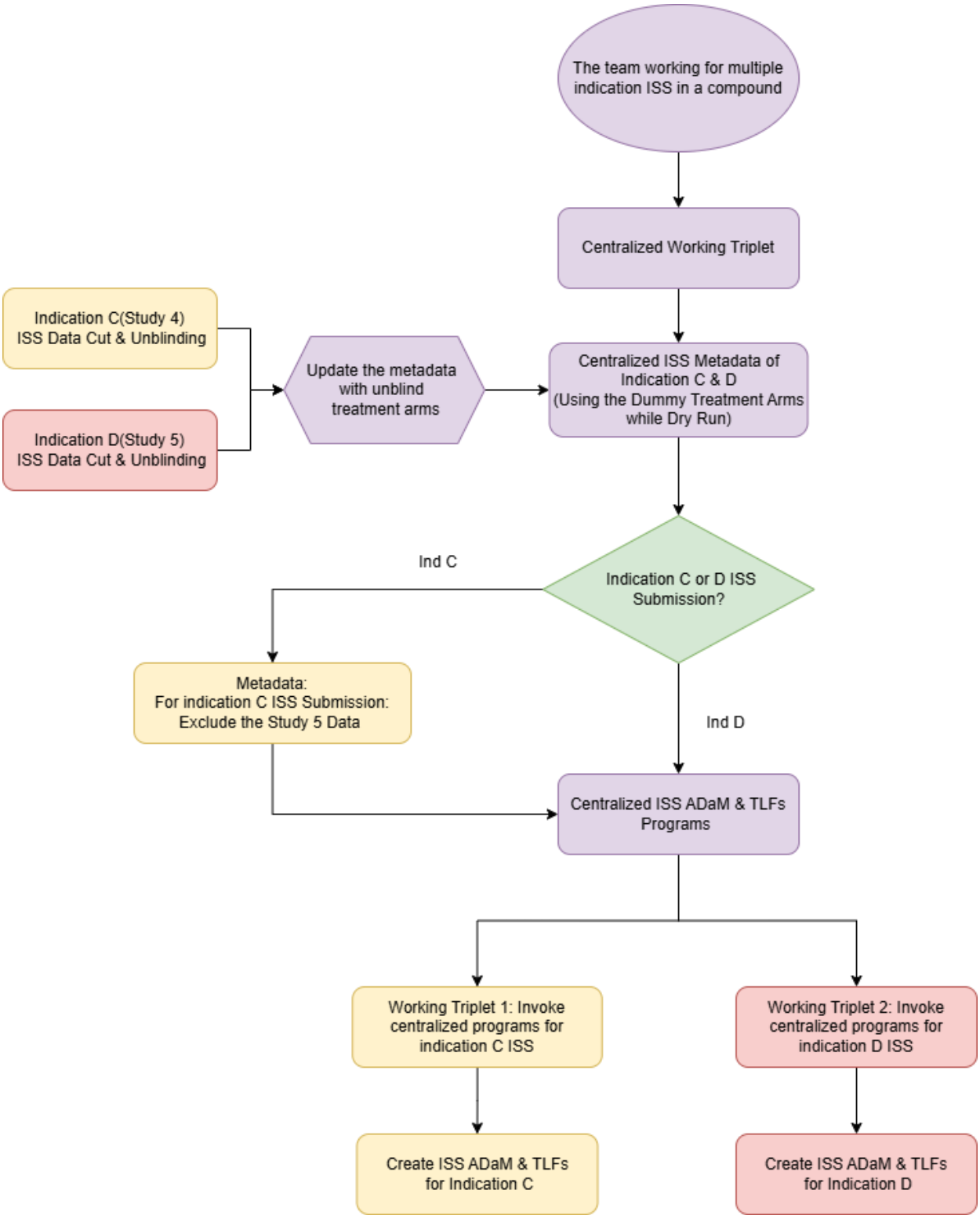

Figure 4 Workflow for centralized pool across indications

CONCLUSION

Preparing an Integrated Summary of Safety (ISS) for multiple indications often leads to the exploration of strategic data pooling, harmonization, and submission management. Pooling at the ADaM-level emerges as a practical option to streamline safety analyses by leveraging standardized datasets, minimizing redundant derivations, and meeting tight timelines. Harmonizing controlled terminologies and coding dictionaries ensures consistency per FDA guidance. When managing simultaneous submissions, a centralized approach may help reduce discrepancies and optimizes resources. Together, these elements form a promising framework for enhancing precision, efficiency, and compliance in multi-indication ISS submissions.

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