Paper PP20

End-to-End Workflow for CDISC Estimand Framework in Clinical Trials:
Translating Complex Intercurrent Event Definitions into Submission-Ready ADaMs & TLGs

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Abstract

This abstract presents an **end-to-end workflow for implementing the CDISC estimand framework** in a late phase nephrology trial, with a focus on regulatory submission readiness. The primary challenge addressed is translating complex estimand definitions, particularly those involving intercurrent events (ICEs), into ADaM-compliant analysis datasets and outputs. Our statistical programming team collaborated proactively with statisticians, data standards experts, and study teams to align data collection, analysis plans, and programming early in trial execution. Key activities included defining ICE traceability, utilizing standard internal R packages, and designing TLG templates in anticipation of regulatory submissions. This integrated strategy minimized rework, ensured consistency across endpoints, and supported efficient generation of efficacy analyses. This workflow serves as a practical model for data science teams implementing new concepts and guidance to generate robust, submission-ready deliverables.

1. Introduction & Context

The ICH E9(R1) Addendum introduced the estimand framework to ensure alignment across trial objectives, design, data collection, and analysis methods. The workflow in below sections demonstrates practical implementation of estimand framework guidance in CDSIC data standards (SDTM and ADAM).

Our primary goal was to translate complex estimand definitions, particularly those involving Intercurrent Events (ICEs), into submission-ready ADaM analysis datasets (e.g., ADICE, ADLB, ADEFF) in regards endpoints such as UPCR (Urine Protein-to-Creatinine Ratio - Primary Endpoint) and eGFR (Secondary Endpoint) change from baseline.

ICEs are defined as events occurring post-treatment initiation that impact the interpretation or existence of the clinical measurement of interest. Strategies for handling ICEs include **Hypothetical**, **Treatment Policy**, and **Composite** approaches[3]. Table 1 provides the formal definition of these 3 strategies, while Table 2 illustrates their application to study's Primary Estimand for UPCR.

Table 1. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest

Handling Strategy	Definition
Hypothetical	To estimate the treatment effect in the hypothetical situation where the intercurrent event did not occur. The treatment effect is estimated as if the intercurrent event had not occurred.
Composite	The intercurrent event is incorporated into the outcome definition, and participants who experience the intercurrent event are assigned to a particular outcome value (e.g., responder v.s non-responder)
Treatment Policy	The intercurrent event is considered part of the treatment strategy, so outcomes are used regardless of whether the intercurrent event occurred or not.

Table 2. Primary Estimand Strategy and Data Handling Rules

ICE Example	Handling Strategy	Detailed Data Handling Rule
ICE01 - Start of protocol-prohibited corticosteroids or immunosuppressive treatment	**Hypothetical**	Data until occurrence of composite ICE will be imputed under MNAR (treatment arm) and MAR (placebo)
ICE02 - Start of other protocol-prohibited therapy		Data until occurrence of composite ICE will be imputed under MAR
ICE03 - Treatment discontinuation	**Treatment Policy**	All data on and after the ICE will be included; No imputation on missing data.
ICE04 - Death	**Composite**	Data on and after the ICE will be imputed with 95th percentile of worst change observed in all participants, plus random error
ICE05 - Receipt of Kidney Replacement Therapy (KRT)		

2. Workflow Implementation: Challenges & Solutions

The core of our implementation involved establishing the **ADICE (Intercurrent Events Analysis Dataset)**, structured as an Occurrence Data Structure (OCCDS) class in line with PHUSE ADaM Implementation guidelines[1,2]. The key challenges and their respective solutions are detailed below.

A. Complexity and Novelty of the Estimand Framework

- **Challenge:** The team lacked experience and established internal standards for implementing the novel estimand framework, specifically the ADICE dataset.
- **Solution:** We proactively aligned data structures and specifications across Biostatistics, Data Standard Governance (DSG), and the PHUSE White Paper. The framework leverages the existing ADaM Implementation Guide (ADAMIG) and OCCDSIG, utilizing a standard company template. Implementation is further documented in the Analysis Data Reviewer's Guide (ADRG) for the filing package.

B. Study-Specific ICE Complications (e.g., Protocol-Prohibited Medications)

- **Challenge:** ICEs related to protocol-prohibited corticosteroids and other medications required complex handling, specifically the identification of dosage and duration criteria, leading to intensive data cleaning requirements and the need for clear definition of the specific prohibited medication list.
- **Solution:** At the data collection level, we prioritized the data cleaning efforts for the protocol-prohibited medication data collected through the concomitant medication form. At the ADaM level, we derived standard ADCM (Concomitant Medications Analysis Dataset) by working with a coding specialist to derive specific drug basket flag variables, and added the intermediate dataset ADCMSUM (Corticosteroids Summary Analysis) . ADCM and ADCMSUM were used as inputs in ADICE (Intercurrent Events Analysis Dataset) to support the derivation of protocol-prohibited medication intercurrent events.

C. Data Processing and Traceability

- **Challenge:** Ensuring efficient processing and transparent linkage between Intercurrent Event (ICE) occurrences and the final safety and efficacy analysis results.
- **Solution:** At the data collection level, we minimized the data quality risk for study specific ICEs by implementing dedicated CRF from/fields (e.g., patients had Kidney Replacement Therapy) and providing site clear CRF completion guidance to prevent "hidden" ICEs. At the ADaM level, we leveraged the **ADICE** dataset to consolidate ICE information to ensure traceability and manage the complexity of different ICE strategies (Hypothetical, Treatment Policy, Composite), a comprehensive set of key flagging variables were implemented in ADaM BDS datasets (e.g., **ADEFF**) to flag data points impacted by ICEs due to priority rules (when patient encounters multiple ICEs) and ensure traceability back to the ADICE record. Section 4 explains these flagging variables and programming considerations in detail.

D. Regulatory Submission Readiness

- **Challenge:** Ensuring all ADaM datasets and analytical outputs were fully compliant and ready for regulatory filing.
- **Solution:** We are collaborating closely with the Data Standard Governance (DSG) team. This involved a detailed review of the ADICE data structure and variable naming conventions, the pre-specification and design of **TLG templates**, and adherence to best practices for documenting estimand elements in the **ADRG**.

3. Illustration of Estimand Implementation Workflow

Table 3 illustrates the process for generating the primary estimand estimate for UPCR, highlighting the steps taken at the analysis dataset level (ADICE/ADEFF) and the TLG (Tables, Listings, and Graphs) level. The detailed implementation examples are discussed in the next section.

Table 3. Implementing the Primary Estimand (Estimand 01)

Step 1: ADaM Dataset Preparation	Step 2: ICE Handling and Imputation (TLG Level)
A. Data Aggregation: Get all records for 24-hour UPCR from ADLB.	**D. Imputation (MNAR/MAR):** Use an imputation package to impute data with MNAR after ICE01 (prohibited corticosteroids/immunosuppressive treatment) and MAR for the rest of the missing data simultaneously.
B. ICE Identification (ADICE): Consolidate all relevant ICEs (Hypothetical, Composite, Treatment Policy) and define ICE priority rules (e.g., ICE04/05 > ICE01 > ICE02 > ICE03).	**E. Composite Imputation:** Extract the imputed object from the *imputation* (e.g., rbmi) package and impute data with the 95th percentile of worst change observed + random error after ICE04 (Death) or ICE05 (Receipt of KRT), whichever is earlier.
C. Datapoint Flagging (ADEFF): Populate missing visits with NA and planned dates. Flag records after ICEs using ICC/ICE flags (e.g., `ICC1S`, `ICE01S`, etc.).	**F. Estimation:** Run the MMRM model on the imputed dataset, repeating steps D-F 1000 times, and summarize the results using Rubin's rule.

4. End-to-End Implementation of the Primary Estimand

This section presents two subject-level scenarios to illustrate the end-to-end data flow for the primary estimand using ADICE and downstream ADaM datasets. Scenario #1 demonstrates sequential intercurrent events occurring at distinct visits, while Scenario #2 focuses on overlapping intercurrent events occurring at the same visit. Together, these examples highlight how estimand-specific flagging, prioritization rules, and imputation strategies interact to produce analysis-ready datasets.

4.1 Scenario #1: A subject experiences three intercurrent events at three different timepoints

Table 4. Simplified ADICE dataset structure example for the Primary Estimand. ADICE serves as the central data structure that captures intercurrent event timing, classification, and estimand handling strategies, enabling consistent and traceable downstream derivations and serving as source information for regulatory requests for ICEs analysis. This table represents a scenario where one patient in the treatment arm experiences intercurrent event 02 at Week 37, intercurrent event 01 at Week 53, and intercurrent event 04 at Week 77.

USUBJID	ADECOD1	ASTDT	EST01STP	VISIT	ASEQ
10001	ICE02	2024-09-03	Hypothetical	Week 37	1
10001	ICE01	2024-10-03	Hypothetical	Week 53	2
10001	ICE04	2025-01-15	Composite	Week 77	3

ADECOD1 = Analysis Dictionary Derived Term, ASTDT = Analysis Start Date, EST01STP = Planned Handling Strategy for Estimand 01

Table 5. Implementation of the 'Impact by event type (ICCyS)' variable in ADEFF. Inclusion of ICCyS variables in ADEFF enables record-level tracking of intercurrent event impact directly within the efficacy analysis dataset. ICC1S through ICC5S variables allow the earliest affected record to be identified by the first occurrence where the relevant ICCyS flag is populated. For each subject:

1. The intercurrent event impact is derived by identifying the earliest intercurrent event date (ASTDT) for each event category (i.e. ICE01, ICE02). In this implementation, ICE categories (e.g., ICE01, ICE02) map directly to ICCyS variables, where y corresponds to the ICE category number.
2. Once an intercurrent event occurs, all efficacy records in ADEFF with assessment dates (ADT) on or after the event date are flagged (by populating ICCyS) as impacted.
3. The corresponding ICCyS variable is populated with the sequence number from ADICE (ADICE.ASEQ) of the earliest intercurrent event of that category.

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1S	ICC2S	ICC3S	ICC4S	ICC5S
10001	TEST01	Observed date	Baseline	1.2					
10001	TEST01	Planned date*	Week 13	NA*					
10001	TEST01	Observed date	Week 25	1.4					
10001	TEST01	Observed date	Week 37	2.3		1			
10001	TEST01	Observed date	Week 53	2.1	2	1			
10001	TEST01	Planned date*	Week 77	NA*	2	1		3	

*In this scenario, the patient has no Week 13 or Week 77 visits. Missing visits will use the planned visit date as the analysis date (based on study-specific visit windowing) and analysis values will be set to NA

Table 6. Implementation of the 'Impact by event type by estimand (ICCyEzzF)' and 'Impact by estimand (ICEzzS)' variables in ADEFF.

The ICCyEzzF variables indicate whether a datapoint is impacted by a specific intercurrent event for a given estimand, which is based on both the occurrence of the event and the estimand's data handling strategy:

- ICC1E01F represents the impact of ICE category 1 on Estimand 1
- Because ICE01 is handled using a hypothetical strategy for Estimand 1, ICC1E01F is set to "Y" for all records where ICC1S is populated; otherwise, set to null
- The same logic applies to ICC2E01F, ICC3E01F, ICC4E01F, and ICC5E01F, using ICC2S through ICC5S respectively, while also accounting for the estimand-specific handling strategy.
- If an intercurrent event is handled under a treatment policy strategy for a given estimand, the corresponding ICCyEzzF flag is not set to "Y," even if the ICCyS flag is populated, as the event does not impact data usage for that estimand

The ICEzzS variable summarizes whether a datapoint is impacted by one or more intercurrent events for a specific estimand, and, if so, identifies which intercurrent event has priority:

- Evaluates the estimand-specific ICCyEzzF flags and applies predefined priority rules when multiple intercurrent events affect the same datapoint
- The selected intercurrent event is recorded using the corresponding ICCyS value. ICEzzS identifies records that require imputation for a given estimand and ensures consistent handling of overlapping intercurrent events
    - For example, ICE01S represents the consolidated intercurrent event impacting a datapoint for Estimand 1
    - Derived using ICC1E01F through ICC5E01F in combination with ICC1S through ICC5S, applying the predefined ICE priority rules. (ICE 4=5 > 1 > 2 > 3)

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1E01F	ICC2E01F	ICC3E01F	ICC4E01F	ICC5E01F	ICE01S
10001	TEST01	Observed date	Baseline	1.2						
10001	TEST01	Planned date*	Week 13	NA						
10001	TEST01	Observed date	Week 25	1.4						
10001	TEST01	Observed date	Week 37	2.3		Y				1
10001	TEST01	Observed date	Week 53	2.1	Y	Y				2
10001	TEST01	Planned date*	Week 77	NA	Y	Y		Y		3

ICE01S consistently identifies the single intercurrent event that drives data handling and imputation for each record under Estimand 1. This variable is populated with the ADICE.ASEQ number of the corresponding ICE:

- At Week 37, ICE01S is populated with value 1 (ICC2S = 1) because ICE02 is the first intercurrent event that impacts Estimand 1 under a hypothetical strategy, and no higher-priority events apply at that time
- At Week 53, ICE01S is populated with value 2 (ICC1S = 2) because ICE01 also impacts Estimand 1 and has higher priority than ICE02 according to the predefined hierarchy
- At Week 77, ICE01S is populated with value 3 (ICC4S = 3) because a composite intercurrent event (ICE04/05) occurs, which has the highest priority and therefore supersedes all previously occurring intercurrent events.

Table 7. Handling of hypothetical intercurrent events using ICCyS, ICCyEzzF, ICEzzS

1. Records occurring after an intercurrent event that impacts the primary estimand are set to missing (AVAL = NA), as indicated by ICE01S being populated.
2. For subjects in the treatment arm, records impacted by ICE01 (identified by ICC1S) are designated for MNAR imputation in accordance with the hypothetical strategy defined for Estimand 01.
    a. MNAR imputation is applied only to records occurring after ICE01, and no additional intercurrent event priority rules are considered at this stage.
    b. If a subject were not in the treatment arm, these same records would instead remain eligible for MAR imputation.
3. All remaining missing values are imputed under a MAR assumption.
    a. This includes missing records resulting from other intercurrent events, regardless of priority, as well as missing data not associated with any intercurrent event.
4. MAR and MNAR imputations are performed simultaneously, and the resulting completed dataset is extracted as the intermediate RBMI imputed dataset for Estimand 01.

As a result, Estimand 01 produces a mixed MAR/MNAR imputed dataset that reflects hypothetical handling of selected intercurrent events while retaining observed data elsewhere.

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1E01F	ICC2E01F	ICC4E01F	ICE01S
10001	TEST01	Observed date	Baseline	1.2				
10001	TEST01	Planned date*	Week 13	NA				
10001	TEST01	Observed date	Week 25	1.4				
10001	TEST01	Observed date	Week 37	NA		Y		1
10001	TEST01	Observed date	Week 53	NA	Y	Y		2
10001	TEST01	Planned date*	Week 77	NA	Y	Y	Y	3

Colour-coding legend for AVAL imputation values: MAR (due to occurrence of intercurrent events 02, 04, 05 for a patient in any arm, or intercurrent event 01 for a patient not in the treatment arm); MAR (due to missing data); MNAR (due to occurrence of intercurrent event 01 for a patient in the treatment arm)

Table 8. Handling of composite intercurrent events using ICCyS, ICCyEzzF, ICEzzS

1. For Estimand 01, records are evaluated to identify the earliest occurrence of intercurrent events handled under a composite strategy (ICE04 or ICE05)
    a. Uses the corresponding ICC4S and ICC5S indicators.

2. Once the earliest composite intercurrent event is identified for a subject, all subsequent efficacy records are considered impacted by the composite strategy
    a. No need to evaluate other intercurrent events at this stage.
3. Data occurring after the composite intercurrent event are imputed using a worst-case approach
    a. Imputation uses 95th percentile of the worst observed change across all participants with added random error.
4. The MMRM analysis is then performed on the resulting imputed dataset
    a. Repeated across 1,000 imputations, starting from the intermediate RBMI dataset.
5. Final estimates used in the TLGs are obtained by combining results across imputations using Rubin's rules.

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1E01F	ICC2E01F	ICC4E01F	ICE01S
10001	TEST01	Observed date	Baseline	1.2				
10001	TEST01	Planned date*	Week 13	Imputed MAR value				
10001	TEST01	Observed date	Week 25	1.4				
10001	TEST01	Observed date	Week 37	Imputed MAR value		Y		1
10001	TEST01	Observed date	Week 53	Imputed MNAR value	Y	Y		2
10001	TEST01	Planned date*	Week 77	95th percentile imputation	Y	Y	Y	3

Table 8 illustrates a single example of an ADEFF dataset generated after imputation for Estimand 01, reflecting one realization from the set of 1,000 multiply imputed datasets produced under the composite intercurrent event strategy. All intercurrent events have already been evaluated, prioritized, and applied prior to this step, and the values shown represent the final analysis-ready efficacy data for this specific imputation.

4.2 Scenario #2: A subject experiences four intercurrent events at two timepoints

Scenario #2 demonstrates how the proposed ADICE-based framework handles multiple intercurrent events occurring at the same visit, including events governed by different estimand strategies. While Scenario #1 illustrates sequential intercurrent events over time, this scenario focuses on resolving concurrent intercurrent events and illustrates how predefined priority rules ensure a single, consistent estimand-specific handling decision for all subsequent efficacy data.

Table 9. Simplified ADICE dataset structure example. Represents a scenario where one patient experiences intercurrent events 03, 01, and 04 at Week 25, as well as intercurrent event 05 at Week 77.

USUBJID	ADECOD1	ASTDT	EST01STP	VISIT	ASEQ
10002	ICE03	2024-08-05	Treatment policy	Week 25	1
10002	ICE01	2024-08-05	Hypothetical	Week 25	2

10002	ICE04	2024-08-05	Composite	Week 25	3
10002	ICE05	2025-09-01	Composite	Week 77	4

ADECOD1 = Analysis Dictionary Derived Term, ASTDT = Analysis Start Date, EST01STP = Planned Handling Strategy for Estimand 01

Table 10. **Handling of multiple intercurrent events on efficacy data for Estimand 01**
This table illustrates how multiple intercurrent events occurring at the same visit (ICE03, ICE01, and ICE04 at Week 25) and a later composite event (ICE05 at Week 77) are evaluated for Estimand 01. Although several intercurrent events are present, application of the predefined priority rules results in a composite intercurrent event impacting all efficacy records from Week 25 onwards. As a result, post-event values are consistently handled using the composite strategy, demonstrating how ADICE-derived flags resolve overlapping intercurrent events and drive estimand-specific data handling at the subject level.

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1E01F	ICC3E01F	ICC4E01F	ICC5E01F	ICE01S
10002	TEST01	Observed date	Baseline	1.2					
10002	TEST01	Planned date*	Week 13	Imputed MAR value					
10002	TEST01	Observed date	Week 25	95th percentile imputation	Y		Y		3
10002	TEST01	Observed date	Week 37	95th percentile imputation	Y		Y		3
10002	TEST01	Observed date	Week 53	95th percentile imputation	Y		Y		3
10002	TEST01	Planned date*	Week 77	95th percentile imputation	Y		Y	Y	3

5. Comparative Implementation of the Secondary Estimand

To illustrate how the same standardized data framework supports multiple estimands, this section presents the implementation of Estimand 02 for the same subject example (Subject 10001) used in Section 4. While the underlying ADICE structure remains unchanged, differences in intercurrent event handling strategies lead to distinct estimand-specific flags, data inclusion decisions, and imputation outcomes. This example demonstrates how ADICE enables flexible yet traceable translation of protocol-defined estimands into analysis-ready datasets.

Table 11. Simplified ADICE dataset structure example for Estimand 02
This table presents the ADICE records for a single subject under Estimand 02:

- ICE02 and ICE01 are handled under a treatment policy strategy (rather than hypothetical strategy)
- ICE04 is handled under a composite strategy (consistent across both estimands)

Compared with Estimand 01, earlier intercurrent events do not trigger data exclusion or hypothetical imputation, resulting in observed efficacy data being retained until the composite intercurrent event at Week 77.

USUBJID	ADECOD1	ASTDT	EST02STP	VISIT	ASEQ
10001	ICE02	2024-09-03	Treatment policy	Week 37	1
10001	ICE01	2024-10-03	Treatment policy	Week 53	2
10001	ICE04	2025-01-15	Composite	Week 77	3

ADECOD1 = Analysis Dictionary Derived Term, ASTDT = Analysis Start Date, EST02STP = Planned Handling Strategy for Estimand 02

Table 12. Handling of multiple intercurrent events on efficacy data for Estimand 02

This table displays the corresponding estimand-specific flags and efficacy records:

- Since ICE02 and ICE01 are handled using a treatment policy strategy for Estimand 02, the ICC1E02F and ICC2E02F flags do not impact data usage
  - Observed values at Weeks 37 and 53 are retained.
- Only ICE04, which is handled under a composite strategy, impacts the estimand and results in worst-case imputation for subsequent records.
- This contrasts with Estimand 01, where earlier intercurrent events triggered hypothetical imputation and altered the post-baseline trajectory.

USUBJID	PARAMCD	ADT	AVISIT	AVAL	ICC1E02F	ICC2E02F	ICC4E02F	ICE02S
10001	TEST01	Observed date	Baseline	1.2				
10001	TEST01	Planned date*	Week 13	Imputed MAR value				
10001	TEST01	Observed date	Week 25	1.4				
10001	TEST01	Observed date	Week 37	2.3				
10001	TEST01	Observed date	Week 53	2.1				
10001	TEST01	Planned date*	Week 77	95th percentile imputation			Y	3

Across the presented examples, Estimand 01 and Estimand 02 differ not in data structure but in how intercurrent events are handled through estimand-specific flagging and prioritization. While ADICE consistently captures the timing and classification of intercurrent events, the ICCyS and ICCyEzzF variables translate these events into estimand-aligned data usage rules, determining whether post-event data are retained, excluded, or imputed. Under Estimand 01, intercurrent events handled using hypothetical or composite strategies frequently trigger imputation, with prioritization rules resolving overlapping events and ultimately governing the imputation method applied. In contrast, Estimand 02 applies treatment policy strategies to most intercurrent events, allowing observed data to be retained until a composite event occurs. These differences result in distinct imputation patterns and analysis inputs despite identical underlying data, illustrating how estimands formally define the clinical question of interest and directly shape downstream statistical handling through transparent, traceable flagging logic.

6. Submission-ready TLG Template

The structured efficacy analysis dataset enabled us to generate the complex multiple imputation analysis using an in-house-built R package. Following internal implementation guidance for TLGs and collaborating with biostatisticians, we designed a template for efficacy analysis for each estimand and endpoint. For example, the MMRM efficacy analysis template for our primary estimand and primary endpoint is shown below:

```
Primary Estimand: Change from Baseline in UPCR through Week 37
Analysis Population: Efficacy analysis set
```

Visit Statistics	Placebo (N=nnn)	Treatment (N=nnn)
Week xx		
n	XXX	XXX
Adjusted Mean (SE)	XXX.XX (XX.XXX)	XXX.XX (XX.XXX)
95% CI	(XXX.XX, XXX.XX)	(XXX.XX, XXX.XX)
Difference in Adjusted Mean (SE)		XXX.XX (XX.XXX)
95% CI		(XXX.XX, XXX.XX)
Percent Reduction (%)		XX.X%
P-value (MMRM)		X.XXXX
………		
Week xx		
n	XXX	XXX
Adjusted Mean (SE)	XXX.XX (XX.XXX)	XXX.XX (XX.XXX)
95% CI	(XXX.XX, XXX.XX)	(XXX.XX, XXX.XX)
Difference in Adjusted Mean (SE)		XXX.XX (XX.XXX)
95% CI		(XXX.XX, XXX.XX)
Percent Reduction (%)		XX.X%
P-value (MMRM)		X.XXXX

[Footnotes]

7. Conclusion and Lessons Learned

The implementation of the estimands framework using data standards is feasible and beneficial. By adopting an integrated, end-to-end strategy, we were able to successfully translate complex estimand definitions and challenging ICE handling strategies into ADaM-compliant datasets (ADCMSUM/ADICE/ADEFF).

This practical model supports the generation of submission-ready deliverables and enables efficient analysis generation for complex Estimand Framework for future trials.

Key Lessons Learned:

- **Proactive Collaboration:** Cross-functional collaboration with statisticians and data standards experts early in the process is crucial for minimizing rework and ensuring alignment.
- **Standardization:** The proposed ADICE structure and the use of flagging variables provide the necessary traceability and structure required for downstream TLG programming and regulatory requests.
- **Consistency:** The framework promotes harmonisation between statisticians, clinicians, and statistical programmers, ensuring alignment from the protocol stage through to final analysis.

References

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