PharmaSUG China 2026 - Paper DS152-2026

Making Composite Endpoints Work: An ADaM Programming Approach to Sustained Remission

Qing Xue, Fen Wu, Shuo Zhang, Peixuan Wang, Novartis

ABSTRACT

Composite and sustained binary endpoints are common in Phase III trials but are difficult to implement because they combine multiple clinical concepts, longitudinal rules, missing data handling, and estimand requirements. This paper presents a layered ADaM programming framework for deriving sustained remission endpoints in an ADEFF dataset. The approach separates derivation into component-level rules, visit-level composite flags, and final sustained endpoints while incorporating time-aware logic and estimand-aligned handling of missing data and intercurrent events. The framework improves traceability, reviewability, validation efficiency, and reuse, and it can be applied to other complex longitudinal composite endpoints.

This paper presents a layered ADaM programming framework for deriving sustained remission endpoints in an ADEFF data set. The method separates derivation into component-level rules, visit-level composite flags, and final sustained endpoints, while incorporating time-aware logic and estimand-aligned handling of missing data and intercurrent events. This design improves traceability, reviewability, validation efficiency, and reuse. Although illustrated with sustained remission, the approach is applicable to other complex longitudinal composite endpoints.

INTRODUCTION

Composite efficacy endpoints are widely used in clinical trials because they often provide a more clinically meaningful measure of treatment success than any single variable alone. However, programming these endpoints can be challenging, as they rely on multiple component criteria, data from different source data sets, visit-based rules, and careful handling of missing data and intercurrent events, all within the context of the estimand framework. In many cases, the greatest difficulty lies not in deriving the final endpoint itself, but in constructing a clear and traceable path from source observations to intermediate components and ultimately to the composite outcome.

Sustained remission is a good example of this complexity. It requires several conditions to be established and maintained over time, often across multiple visits and clinical assessments. This paper presents a practical approach to implementing sustained remission as a multi-layer composite endpoint. It describes a step-by-step derivation process, discusses common challenges such as visit selection and missing data handling, and shares lessons learned that may help programmers develop other complex composite efficacy endpoints in a structured and reviewable way.

CLINICAL AND STATISTICAL DEFINITION

Sustained remission is a layered, time-dependent endpoint. In this example, a subject must achieve remission at Week 12 and maintain that status through Week 52 without qualifying disease activity or treatment failure. Complete sustained remission adds an additional layer by requiring maintenance of inflammatory marker control from Week 12 to Week 52. The definitions below are best understood as a sequence of decision steps.

Remission at Week 12

Remission at Week 12 is the first decision point in the overall endpoint structure. It establishes whether the subject has achieved the required disease control status at Week 12. In operational terms, Week 12 remission requires no escape or rescue treatment before Week 12, no PMR (polymyalgia rheumatica) signs or symptoms at Week 12 that trigger escape or rescue treatment, and no new GCA (giant cell arteritis) diagnosis at Week 12 requiring escape or rescue treatment. If all required conditions are met, remission at Week 12 is achieved. If all required component conditions are met, the subject is classified as being in remission at Week 12. If any component indicates relapse, remission at Week 12 is not achieved.

This endpoint is important because it serves as the entry criterion for the later sustained remission assessment. A subject cannot be in sustained remission without first meeting the Week 12 remission definition.

Sustained Remission at Week 52

Sustained remission extends the Week 12 assessment into a longitudinal endpoint. The subject must first be in remission at Week 12. After that, remission must be maintained through Week 52. This means there must be no subsequent evidence of disease activity that meets failure criteria during the follow-up period. In practice, this includes recurrence of PMR signs or symptoms requiring escape or rescue treatment, a new diagnosis of GCA requiring treatment change, or another treatment failure event defined by the analysis rules.

The key concept is time dependency. Sustained remission is not based only on status at Week 52. Instead, it reflects the absence of qualifying failure events throughout the entire interval from Week 12 to Week 52. Therefore, the endpoint depends on both an initial milestone and continued maintenance over time.

Complete Sustained Remission at Week 52

Complete sustained remission adds another layer to sustained remission. A subject must first satisfy the sustained remission definition. In addition, inflammatory marker control must also be maintained over time. This includes no ESR (erythrocyte sedimentation rate) elevation to 40 mm/hr or higher at two consecutive scheduled visits and hsCRP (high sensitivity C reactive protein) remaining normalized below 10 mg/L without elevation to 10 mg/L or higher at two consecutive scheduled visits.

Obviously, this endpoint is more restrictive than sustained remission because it combines clinical maintenance with laboratory stability across multiple visits. It is therefore a longitudinal composite of both symptom-based and biomarker-based evidence. The use of consecutive scheduled visits makes the endpoint explicitly dependent on repeated observations over time rather than isolated abnormal values.

Component-Based Decomposition and Composite Endpoint Structure

Sustained remission and complete sustained remission are composite, time-dependent endpoints, programming them as a single rule is difficult to validate and explain. To improve traceability, derivation was organized as a layered framework in the ADEFF data set.

Component- based Endpoint Decomposition

The first step was to decompose the endpoint into clinically meaningful components, each with its own source data, analysis window, relapse rule, and missing data handling. Components were derived independently at the visit level before being combined into composite endpoints.

This decomposition converts a high-level clinical definition into a stepwise programming problem that can be validated transparently from source data to final endpoint.

Table 1 Component Definitions Used in Composite Sustained Remission Endpoints

Component	Description	Source Data	Analysis Window	Relapse Rule
ESCRES	Escape or rescue treatment	FACE/DS	Baseline to Week 8	Any escape or rescue treatment reported
SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	FACE	Week 12 to Week 52	Symptom recurrence with escape/rescue treatment
GCADIA	New diagnosis of GCA requiring escape/rescue treatment	FACE	Week 12 to Week 52	New GCA diagnosis with escape/rescue treatment
ELVESR	Elevated ESR (≥ threshold for consecutive visits)	ADLB	Week 12 to Week 52	Threshold exceeded for ≥2 consecutive visits
ELVCRP	Elevated CRP (≥ threshold for consecutive visits)	ADLB	Week 12 to Week 52	Threshold exceeded for ≥2 consecutive visits

From Components to Composite Response Flags

The component flags were then combined into visit-level composite response flags as summarized in Table 4.

- REFL (Clinical Remission Flag) was defined as response in all required clinical components (GCADIA, ESCRES, SIGSYM).
- CREFL (Complete Clinical Remission Flag) extended REFL by additionally requiring biomarker normalization, as indicated by ELVESR and ELVCRP.

Derivation of Final Sustained Endpoints

Final endpoints were derived by applying sustained logic across visits:

- SRE52FL (Sustained Remission at Week 52) evaluates whether a subject who achieved clinical remission (REFL) maintained that response continuously from Week 12 through Week 52.
- CSRE52FL (Complete Sustained Remission at Week 52) applies the same sustained logic but requires complete remission (CREFL).

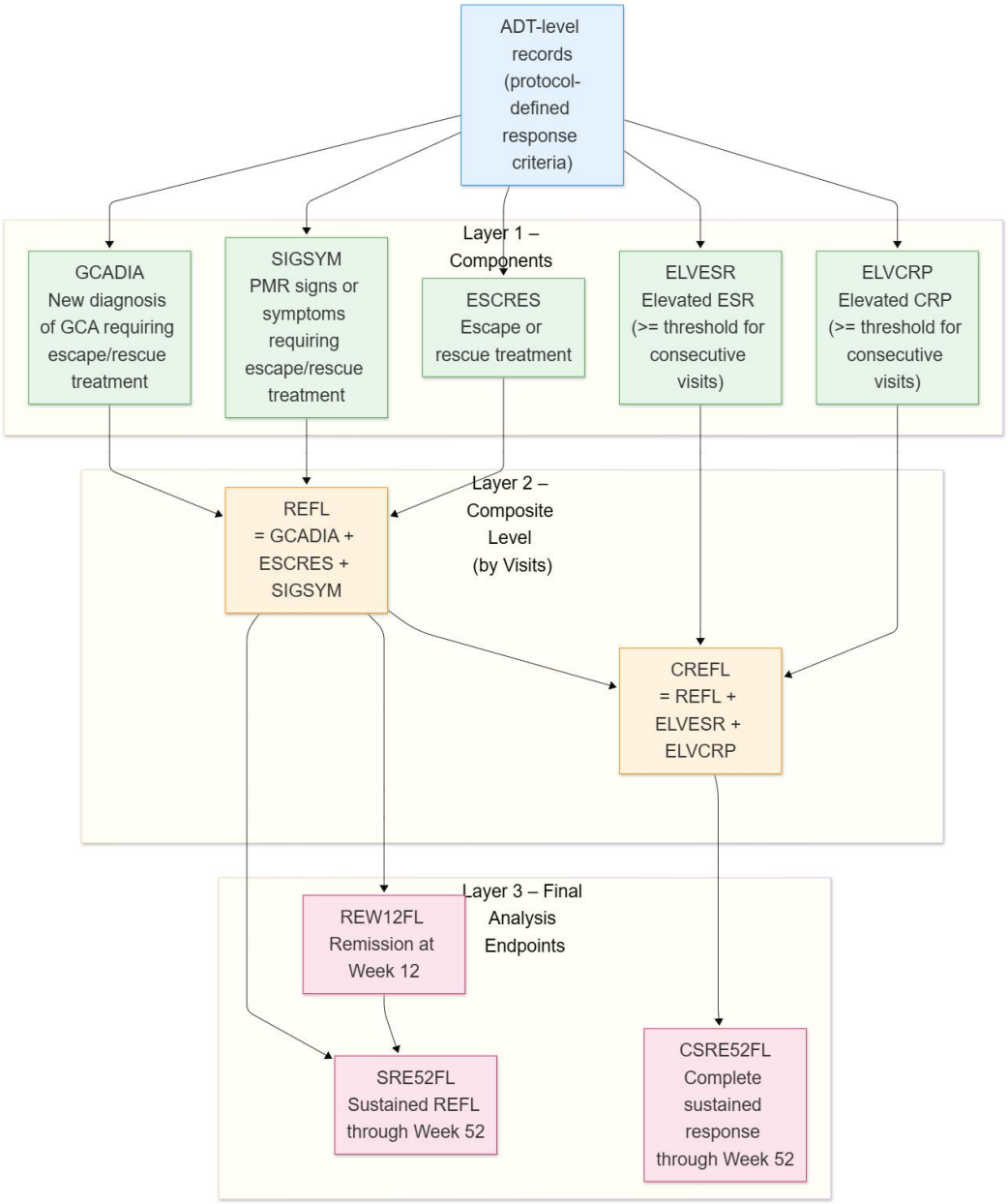
Table 2 Summary of Layered Endpoint Derivation

Layer	Endpoint Variable	Input Variables	Logic Summary

Composite	REFL	GCADIA, ESCRES, SIGSYM	REFL = 'Y' if all required clinical symptom components are 'N'; otherwise REFL='N'
Composite	CREFL	REFL, ELVESR, ELVCRP	CREFL = 'Y' if REFL = 'Y' and all required biomarker components are 'N'; otherwise REFL='N'
Final endpoint	REW12FL	REFL, sustained response indicators	REW12FL = 'Y' if REFL = 'Y' and response is sustained through Week 12
Final endpoint	SRE52FL	REFL, sustained response indicators	SRE52FL = 'Y' if REFL = 'Y' and response is sustained through Week 52
Final endpoint	CSRE52FL	CREFL, sustained response indicators	CSRE52FL = 'Y' if CREFL = 'Y' and complete response is sustained through Week 52

The relationships among these layers are summarized visually in Figure 1, which shows the derivation flow from component-level event flags to visit-level composite remission flags and final sustained endpoints. This overview provides the conceptual link between the endpoint structure described above and the detailed programming logic presented in the following sections.

Figure 1. Layered derivation of composite and final endpoints in ADEFF



This stepwise strategy creates a clear dependency chain from components to final endpoints, reduces duplicated logic, and improves traceability, validation efficiency, and reuse.

VISIT WINDOWS AND MULTIPLE ASSESSMENTS

Why Visit Windows Are Needed

After the endpoint structure is defined, the next step is to align source records to a common analysis timeline. Visit windows support this alignment by mapping assessments, treatments, and laboratory results across domains and enabling consistent evaluation of time-dependent rules.

They also support consistent evaluation of time-dependent rules by mapping records to common analysis visits across domains.

Component-Driven Selection Strategy

Although all components are aligned to analysis visit windows, record-selection rules differ by component. Clinical event components prioritize capturing relapse, whereas laboratory components represent status closest to the planned visit.

Worst-Case Selection for Clinical Event Components (SIGSYM and GCADIA)

For clinical disease-activity components such as SIGSYM and GCADIA, a worst-case rule is applied within each visit window.

All assessments within a window are reviewed together:

- If any assessment indicates relapse, the visit-level result is set to Relapse.
- Only if all assessments indicate remission is the visit-level result set to Remission.

When assigning the analysis date (ADT):

- If all assessments indicate relapse, the earliest assessment date is selected to represent the onset of relapse.
- If all assessments indicate remission, the latest assessment date is selected to represent continued disease control.
- If both relapse and remission assessments are present, the relapse assessment is retained, and the earliest relapse date is selected.

This rule captures relapse at the earliest meaningful time while allowing remission to reflect the latest confirmation within the window.

Target-Aligned Selection for Laboratory Components (ELVESR and ELVCRP)

For laboratory-based components, ELVESR (ESR elevation) and ELVCRP (CRP elevation), the objective is to represent biomarker status as close as possible to the planned visit timing. Therefore, within each visit window, the laboratory record closest to the target analysis day is selected prior to further evaluation.

Unlike clinical components, a single elevated value does not immediately constitute abnormity. Instead, these components are evaluated using consecutive-visit logic, where abnormity is defined only when the elevation threshold is met for the required number of consecutive analysis visits. The visit completing the consecutive requirement is retained as the abnormal visit, and its date is propagated to downstream composite endpoints.

Illustrative Example: SIGSYM Component

SIGSYM illustrates the approach. Because any qualifying symptom recurrence represents relapse, all records within a visit window are assessed together using a worst-case rule.

If any record shows symptom recurrence requiring escape or rescue treatment, the visit is marked as relapse and the earliest qualifying date is retained. Otherwise, the visit is marked as no relapse and the latest assessment date may be retained.

This ensures consistent capture of the clinically relevant loss of remission across derivation layers.

Table 3 Illustrative Example: SIGSYM Component

USUBJID	PARAMCD	PARAM	VISIT	AVISIT	ADT	AVALC	AVAL	ANL01FL

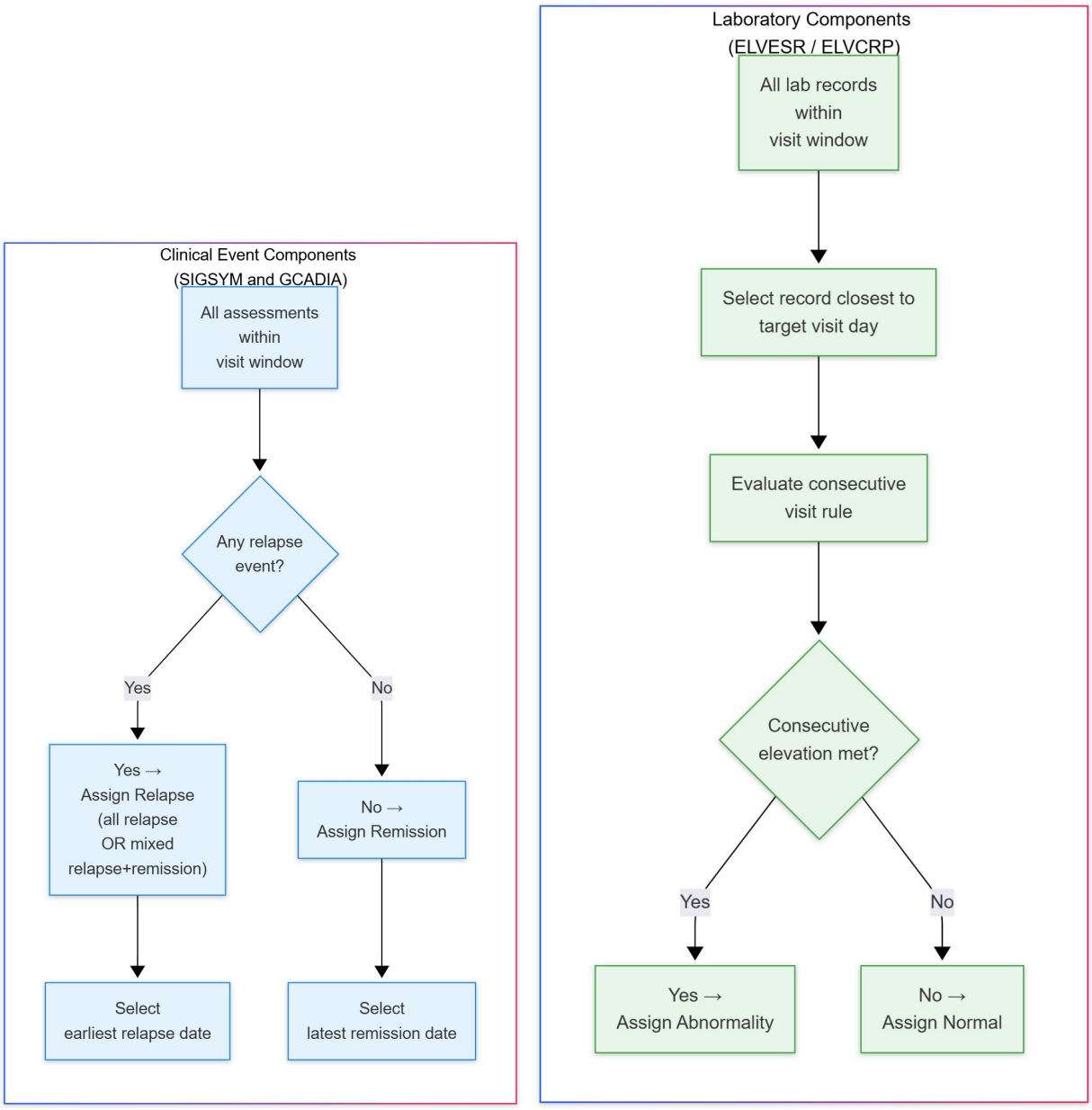
1001	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Week 12	Week 12	2024-03-20	N	0	
1001	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Unscheduled visit – Week 12	Week 12	2024-03-22	N	0	Y
1002	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Week 12	Week 12	2024-03-20	Y	1	Y
1002	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Unscheduled visit – Week 12	Week 12	2024-03-22	Y	1	
1003	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Week 12	Week 12	2024-03-20	N	0	
1003	SIGSYM	PMR signs or symptoms requiring escape/rescue treatment	Unscheduled visit – Week 12	Week 12	2024-03-22	Y	1	Y

In Table 3, ANL01FL = Y identifies the assessment finally selected for analysis within the Week 12 visit window.

- Subject 1001 has two non-relapse assessments within the window. Because no qualifying relapse is present, the latest non-relapse assessment on 2024-03-22 is selected as the final assessment.
- Subject 1002 has two relapse assessments within the window. Because all assessments indicate relapse, the earliest relapse assessment on 2024-03-20 is selected to capture the onset of relapse.
- Subject 1003 has one non-relapse assessment followed by one relapse assessment. Under the worst-case selection rule, the relapse assessment on 2024-03-22 is selected as the final assessment.

The SIGSYM example illustrates how a clinical event component is handled when multiple assessments fall within the same visit window. More generally, visit-window selection is component dependent: clinical event components use a worst-case rule to capture any qualifying relapse, whereas laboratory components use target-aligned selection followed by consecutive-visit evaluation to represent biomarker status consistently. Figure 2 summarizes these complementary strategies.

Figure 2. Component-driven visit window strategies for clinical and laboratory endpoints.



SUSTAINED LOGIC ACROSS TIME

Evaluation of Sustained Absence

A sustained responder must show absence of relapse at all eligible visits within the evaluation window. Because sustained remission represents uninterrupted disease control, any qualifying event during the window invalidates sustained status.

Operationally, all visit-level values in the sustained window are scanned: any abnormity leads to non-response, while sustained success requires all relevant visits to meet the success criterion. If any component is missing and no component shows abnormity, the REFL for the current visit is set to missing.

Example of Layered Derivation: From Components to REW12FL, REFL, and SRE52FL

The examples below illustrate how component events are combined into REFL, how the Week 12 record becomes REW12FL, and how the longitudinal REFL sequence is used to derive SRE52FL.

The examples are simplified to illustrate derivation logic rather than reproduce production outputs. Interpretation of Y and N depends on the derivation layer:

- At the component level, N represents normal or no event, and Y represents that the event is present.
- For REFL and REW12FL, Y means remission is achieved, and N means remission is not achieved.
- For SRE52FL, Y means sustained remission is achieved, and N means sustained remission is not achieved.

Step 1. Deriving REFL from Visit-Level Component Criteria

At each visit, remission is derived by combining the components event criteria:

- For Week 12 and earlier visits, REFL is derived from three component event criteria: use of escape or rescue treatment, PMR signs or symptoms requiring escape or rescue treatment, and new GCA diagnosis requiring escape or rescue treatment.
- For visits after Week 12, REFL is derived using only the latter two components: PMR signs or symptoms requiring escape or rescue treatment and new GCA diagnosis requiring escape or rescue treatment.

A subject is in remission only when none of these events is present:

- if all component values are N (normal), then REFL = Y
- if any component value is Y (abnormal), then REFL = N

Table 4 Example visit-level component results used to derive REFL

SUBJID	AVISIT	Escape or rescue treatment (Y= abnormal)	PMR signs or symptoms requiring escape/rescue treatment (Y= abnormal)	New GCA diagnosis requiring escape/rescue treatment (Y= abnormal)	Derived REFL (Y= remission)
1001	Baseline	N	N	N	Y
1001	Week 4	N	N	N	Y
1001	Week 8	N	N	N	Y
1001	Week 12	-	N	N	Y
1001	Week 24	-	N	N	Y
1001	Week 36	-	N	N	Y
1001	Week 52	-	N	N	Y
1002	Baseline	N	N	N	Y
1002	Week 4	N	N	N	Y
1002	Week 8	N	N	N	Y

1002	Week 12	-	Y	N	N
1002	Week 24	-	Y	N	N
1002	Week 36	-	N	N	Y
1002	Week 52	-	N	N	Y
1003	Baseline	N	N	N	Y
1003	Week 4	N	N	N	Y
1003	Week 8	N	N	N	Y
1003	Week 12	-	N	N	Y
1003	Week 24	-	N	N	Y
1003	Week 36	-	N	N	Y
1003	Week 52	-	Y	N	N
1004	Baseline	N	N	N	Y
1004	Week 4	N	N	N	Y
1004	Week 8	N	N		
1004	Week 12	-	N	N	Y
1004	Week 24	-	N	N	Y
1004	Week 36	-		N	
1004	Week 52	-	N	N	Y

Table 4 shows repeated application of the same rule across visits to derive REFL.

- Subject 1001 has no qualifying event at any illustrated visit, so REFL = Y throughout.
- Subject 1002 has PMR signs or symptoms requiring escape or rescue treatment at Weeks 12 and 24, so REFL = N at those visits.
- Subject 1003 remains event-free through most of follow-up but has a PMR signs or symptoms event at Week 52, so REFL = N at Week 52.
- Subject 1004 has missing component data at Week 8 and Week 36, REFL is set to missing at these visits.

This longitudinal remission profile is the basis for both the Week 12 milestone and the sustained endpoint.

Step 2. Selecting the Week 12 REFL Record to Derive REW12FL

REW12FL is derived directly from the Week 12 value of REFL.

Table 5 Week 12 REFL records selected as REW12FL

SUBJID	Source Parameter	Analysis Visit	Source Value	Derived Parameter	Derived Value	Interpretation
1001	REFL	Week 12	Y	REW12FL	Y	No component event present at Week 12
1002	REFL	Week 12	N	REW12FL	N	At least one component event present at Week 12
1003	REFL	Week 12	Y	REW12FL	Y	No component event

						present at Week 12
1004	REFL	Week 12	Y	REW12FL	Y	No component event present at Week 12

Table 5 shows that subjects 1001, 1003 and 1004 have REW12FL = Y, while subject 1002 has REW12FL = N because the Week 12 REFL is N due to a qualifying component event.

Step 3. Deriving SRE52FL from the Longitudinal REFL Sequence

SRE52FL is derived from the longitudinal REFL pattern. Sustained remission requires remission to be maintained from Week 12 through Week 52:

- if all relevant REFL records from Week 12 through Week 52 are Y, then SRE52FL = Y
- if any relevant REFL record from Week 12 through Week 52 is N, then SRE52FL = N

Table 6 Longitudinal REFL pattern used to derive SRE52FL

SUBJID	REFL at Week 12	REFL at Week 24	REFL at Week 36	REFL at Week 52	Derived SRE52FL	Interpretation
1001	Y	Y	Y	Y	Y	Remission maintained from Week 12 through Week 52
1002	N	N	Y	Y	N	Non-remission observed during follow-up
1003	Y	Y	Y	N	N	Remission lost at Week 52
1004	Y	Y		N		Remission status missing at Week 52

Table 6 demonstrates the sustained logic clearly.

- Subject 1001 remains in remission at all required post-Week 12 visits and therefore meets sustained remission.
- Subject 1002 is not in remission during part of the follow-up period and therefore does not meet sustained remission.
- Subject 1003 achieves remission at Week 12 but loses remission at Week 52, so sustained remission is not met.
- Subject 1004 has missing remission status at Week 36 and non-remission at Week 52, so sustained remission is not met.

These examples show the key principle: one non-remission record during the required interval is enough to invalidate sustained remission. The same framework is used for complete remission (CREFL) and complete sustained remission (CSRE52FL), with added ESR and hsCRP criteria.

The examples above describe observed SRE52FL only. In practice, final primary-analysis endpoints also depend on missing data handling and intercurrent event rules under the estimand framework, as described next.

ESTIMAND, MISSING DATA HANDLING, AND INTERCURRENT EVENTS

The previous section described the derivation logic for the observed endpoint. However, for the primary analysis, observed visit-level records are not always used directly. The final analysis endpoint must also reflect the estimand strategy, including how intercurrent events and missing data are handled.

For the primary estimand, relevant intercurrent events such as treatment discontinuation and prohibited medication use are handled using a composite strategy. Once a qualifying event occurs, affected visits are treated as non-response. Missing data are then handled according to whether they are related to an intercurrent event.

For the primary estimand, the handling rules can be summarized as follows:

Table 7 Primary Estimand Handling of Intercurrent Events and Missing Data

Category	Situation	Primary Estimand Handling
Intercurrent event handling	Treatment discontinuation	Composite strategy
Intercurrent event handling	Prohibited medication use	Composite strategy
Missing data handling	ICE-related missing data	Non-responder imputation
Missing data handling	Non-ICE-related intermittent missing	If the visits before and after the missing visit both show remission, impute remission
Missing data handling	Other non-ICE-related missing	Non-responder imputation

Programming can be summarized in two steps:

- Step 1: create the visit-level REFL data set with observed records, missing visit placeholders, and any added records required for intercurrent event handling.
- Step 2: select the records required for the primary estimand and apply non-ICE-related missing data rules to create the primary-analysis visit-level remission parameter, REFLPRI.

The final sustained remission endpoint is then derived from REFLPRI rather than observed REFL alone. For simplicity, this section focuses only on the primary estimand. Supplementary estimands and sensitivity analyses can be handled using the same general structure, but with different record-selection rules or handling strategies.

In this example:

- PARAMCD = REFL represents the visit-level remission parameter before primary-estimand selection.
- PARAMCD = REFLPRI represents the primary-analysis version of the visit-level remission parameter.
- ICERELFL = Y indicates that the visit is ICE-related. N indicates that the visit is not ICE-related.
- DTYPE = PHANTOM indicates a missing visit placeholder; therefore, AVALC is blank in the working data set.
- DTYPE = NOCB indicates an intermittent missing value imputed as remission because remission was observed before and after the missing visit.
- DTYPE = WC indicates non-responder imputation.
- EST01RFL = Y identifies records selected for the primary estimand.

In this example, the intercurrent event occurs just before the Week 36 assessment date, so Week 36 is the first ICE-related analysis visit.

Step 1. Create Visit-Level REFL Records With Observed, Missing, and Added ICE Records

The first step is to create the full visit-level record structure. Before Week 36, the subject is not affected by the intercurrent event, so the data set contains observed records or missing visit placeholders. From Week 36 onward, the intercurrent event is relevant. Therefore, both the observed record and an added non-responder record may exist for the same visit.

Table 8 Visit-level REFL records before primary estimand selection and missing data imputation

SUBJID	PARAMCD	AVISIT	ICERELFL	AVALC	DTYPE	EST01RFL
1005	REFL	Week 12	N	Y		Y
1005	REFL	Week 16	N		PHANTOM	Y
1005	REFL	Week 20	N	Y		Y
1005	REFL	Week 24	N	Y		Y
1005	REFL	Week 28	N	Y		Y
1005	REFL	Week 32	N		PHANTOM	Y
1005	REFL	Week 36	Y	Y		
1005	REFL	Week 36	Y	N	WC	Y
1005	REFL	Week 40	Y		PHANTOM	
1005	REFL	Week 40	Y	N	WC	Y
1005	REFL	Week 44	Y	Y		
1005	REFL	Week 44	Y	N	WC	Y
1005	REFL	Week 48	Y	Y		
1005	REFL	Week 48	Y	N	WC	Y
1005	REFL	Week 52	Y		PHANTOM	
1005	REFL	Week 52	Y	N	WC	Y

Table 8 shows the working structure before final primary-estimand selection. Up to Week 32, the records are not ICE-related. Week 16 and Week 32 are non-ICE-related missing visit placeholders, so AVALC is blank and DTYPE = PHANTOM.

Because the intercurrent event occurs just before Week 36, all visits from Week 36 onward are ICE-related. At these visits, the observed record is retained for traceability. In addition, a second record is added with AVALC = N and DTYPE = WC. This added record represents non-responder imputation under the composite strategy for the primary estimand and is flagged with EST01RFL = Y.

Step 2. Select Primary Estimand Records and Apply Non-ICE Missing Data Rules

The second step is to select the primary-estimand records (EST01RFL = Y), update PARAMCD from REFL to REFLPRI, and apply non-ICE missing-data rules.

For non-ICE-related missing values:

- If the missing visit is intermittent and the selected records before and after the missing visit both indicate remission, the missing value is imputed as remission;
- Otherwise, the missing value is imputed as non-response.

- In this example:Week 16 is an intermittent non-ICE missing visit because the selected records at Week 12 and Week 20 are both Y. Therefore, Week 16 is imputed as Y with DTYPE = NOCB.
- Week 32 is non-ICE missing, but it is not supported by remission on both sides in the selected primary-estimand sequence because Week 36 is represented by the ICE-related non-responder record. Therefore, Week 32 is imputed as N with DTYPE = WC.

Table 9 Primary estimand REFLPRI records after selection and non-ICE missing data handling

SUBJID	PARAMCD	AVISIT	ICERELFL	AVALC	DTYPE
1005	REFLPRI	Week 12	N	Y	
1005	REFLPRI	Week 16	N	Y	NOCB
1005	REFLPRI	Week 20	N	Y	
1005	REFLPRI	Week 24	N	Y	
1005	REFLPRI	Week 28	N	Y	
1005	REFLPRI	Week 32	N	N	WC
1005	REFLPRI	Week 36	Y	N	WC
1005	REFLPRI	Week 40	Y	N	WC
1005	REFLPRI	Week 44	Y	N	WC
1005	REFLPRI	Week 48	Y	N	WC
1005	REFLPRI	Week 52	Y	N	WC

Table 9 is the primary-estimand data set derived from Table 8. Before Week 36, selected records are observed or non-ICE imputed values; from Week 36 onward, selected records are the added non-responder records created under the composite strategy.

Step 3. Derive SRE52FL Using the Estimand-Adjusted Records

The final sustained endpoint is then derived using the same longitudinal rule as before, but with REFLPRI as input rather than observed REFL.

Sustained remission requires remission to be maintained from Week 12 through Week 52. Therefore:

- if all selected REFLPRI records in the required period are Y, then SRE52FL = Y;
- if any selected REFLPRI record is N, then SRE52FL = N.

Table 10 Deriving SRE52FL from primary-estimand REFLPRI records

SUBJID	Selected REFLPRI Pattern from Week 12 to Week 52	Derived SRE52FL	Interpretation
1005	Y, Y, Y, Y, Y, N, N, N, N, N, N	N	Week 16 is imputed as remission; Week 32 and all ICE-related visits from Week 36 onward are imputed as non-response

In this example, sustained remission is not met under the primary estimand because the selected REFLPRI sequence contains non-response records. This reinforces the main point of this section: the final primary-analysis sustained endpoint should be derived from the estimand-adjusted visit-level records, after both missing data and intercurrent event handling have been applied.

CONCLUSION

The implementation of sustained and complete sustained remission illustrates the value of a layered, component-driven programming framework for complex composite endpoints. By decomposing the endpoint into clearly defined clinical components, visit-level remission flags, and subject-level sustained endpoints, the derivation becomes more transparent, traceable, and easier to validate.

Visit-level parameters such as REFL and CREFL provide an important intermediate layer between component derivations and final endpoints. This structure avoids repeated programming of the same clinical logic and allows downstream endpoints such as REW12FL, SRE52FL, and CSRE52FL to be derived from consistent and reusable building blocks.

In addition, separating observed derivations from estimand-adjusted records, such as REFL versus REFLPRI, supports clear implementation of missing data and intercurrent event handling. This separation preserves traceability while ensuring that the final analysis endpoints reflect the clinical and statistical intent defined in the protocol and SAP.

Overall, this approach provides a scalable and reusable framework for programming longitudinal composite endpoints. It improves reviewability, reduces programming risk, and can be adapted to other complex time-dependent endpoints in clinical trials.

REFERENCES

CDISC. 2021. “Analysis Data Model Implementation Guide, Version 1.3.” *Clinical Data Interchange Standards Consortium*. Published November 29, 2021. Accessed June 15, 2026. Available at https://www.cdisc.org/standards/foundational/adam/adamig-v1-3

International Council for Harmonisation. 2019. “E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.” *ICH Official Guidelines*. Adopted November 20, 2019. Accessed June 15, 2026. Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf