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IMPLEMENTING ULCERATIVE COLITIS DIARY AND ENDOSCOPIC EFFICACY ENDPOINTS (A REPRODUCIBLE ADAM-ORIENTED FRAMEWORK AND SYNTHETIC-DATA SENSITIVITY STUDY)

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ABSTRACT

Background: Ulcerative colitis (UC) trials integrate symptom diaries and endoscopic assessment, often under distinct visit windows and missingness rules. The SELECTION trial of filgotinib provides a published clinical context, but reproducible endpoint programming requires separate, auditable specifications.

Objective: To present a component-first, ADaM-oriented implementation framework and experimentally assess the sensitivity of an illustrative UC remission classification to a change in diary eligibility.

Methods: We specified source-to-analysis lineage, visit anchoring, component aggregation, endpoint construction and validation controls, informed by public clinical and regulatory literature. Using a fixed random seed (20261101), we generated 500 entirely synthetic profiles with seven preassessment diary days and artificial baseline and endoscopic subscores. For each symptom component, we required four valid diary days and applied round-half-up to the mean. Two scenarios retained all seven preceding days or omitted day −1, respectively.

Results: Of 500 profiles, 491 were classifiable under both scenarios. Remission classification differed for 21/491 (4.3%); 92/491 (18.7%) met the illustrative remission condition with all days versus 89/491 (18.1%) after excluding day −1. Unclassifiable profiles numbered 1 and 9, respectively, among all 500.

Conclusions: Altering diary eligibility can change derived classifications and evaluability in a constructed computational example. Results are not clinical estimates, a replication of SELECTION, or validation of a regulatory endpoint. The framework supports transparent rule testing and traceability prior to protocol-specific implementation.

Keywords: Ulcerative Colitis, Mayo Score, Diary Data, Electronic Patient-Reported Outcomes; Endoscopy, Adam, Missing Data; Adam; Synthetic Data; Reproducibility; Sensitivity Analysis.

1 INTRODUCTION

Ulcerative colitis is evaluated using both patient-reported symptom burden and objective mucosal assessments. The historical four-component Mayo Clinic Score (MCS) includes stool frequency (SF), rectal bleeding (RB), endoscopic findings (ES), and physician global assessment (PGA), each scored 0–3, for a total of 0–12. A partial Mayo score omits endoscopy (0–9); a modified Mayo score omits PGA (0–9). These are distinct instruments, and their remission and response thresholds are not interchangeable [1,3]. Research developing interim patient-reported outcomes supports the relevance of SF and RB alongside endoscopy, rather than assuming that symptom scores alone reproduce endoscopic remission [5].

The Gilead-affiliated andecaliximab study by Sandborn and colleagues, including Matt McKevitt, operationalized an endoscopy/bleeding/stool (EBS) remission definition at Week 8: endoscopic subscore 0 or 1, rectal bleeding 0, and a stool-frequency decrease of at least one point to 0 or 1 [2]. The subsequent Gilead-funded SELECTION study provides published context for induction and maintenance of UC efficacy analyses [3]. These publications provide clinical context, not access to patient-level data or proprietary implementation details.

For programmers, the challenge is not merely adding subscores. Daily diary entries and infrequent endoscopy assessments may be misaligned; procedure preparation can alter diary eligibility under some protocols; central and local endoscopic reads may differ; induction and maintenance baselines may not be the same; and missingness can propagate into composite endpoints. Published research on centralized endoscopic reading underscores why reader provenance should remain explicit [6]. Clinical endpoint definitions must be established in the protocol and statistical analysis plan (SAP), with sensitivity analyses addressing assumptions about missingness [7,8]. CDISC ADaM supports traceable analysis structures but does not prescribe a universal UC clinical algorithm [4].

This work makes two narrowly defined contributions: (i) a reusable, audit-oriented derivation specification connecting diary observations to endoscopy-based endpoint records and (ii) an executable synthetic experiment quantifying the sensitivity of one illustrative remission rule to exclusion of the day preceding endoscopy. We do not infer treatment effects or report actual trial outcomes.

1.1 Clinical study context and scope

Filgotinib (GS-6034, formerly GLPG0634; Jyseleca) is an oral preferential Janus kinase 1 inhibitor with a pharmacologically active metabolite. Namour and colleagues investigated filgotinib pharmacokinetics and pharmacokinetic/pharmacodynamic modeling, including the contribution of its active metabolite, in work published in 2015 [9]. This pharmacology provides treatment context but does not determine diary or endoscopic scoring algorithms. In the published SELECTION phase 2b/3 induction–maintenance program, filgotinib was evaluated in adults with moderately to severely active UC [3]. The study is associated with publicly registered protocol GS-US-418-3898. This manuscript addresses the methodological problem of transforming symptoms and endoscopic observations into analysis endpoints; it does not re-analyze SELECTION outcomes or use trial records.

The author contributed directly to efficacy endpoint analyses for GS-US-418-3898. That practical experience motivated the endpoint-programming questions examined here; it does not constitute permission to publish internal code, patient-level datasets, or nonpublic specifications. This independent methodological study uses only artificial observations and publicly available evidence. The historical Gilead–Galapagos relationship is included solely as treatment-development background.

2 METHODS

2.1 Study Design and Data Provenance

This original computational methods study evaluated how alternative diary eligibility conventions affect an illustrative ulcerative colitis (UC) remission classification. The methodological framework was informed by clinical trial publications available through October 31, 2021, including the SELECTION filgotinib induction–maintenance study and earlier UC efficacy endpoint research, as well as Mayo Score methodology and CDISC ADaM principles.

The author's professional experience working on efficacy endpoint analyses for Protocol GS-US-418-3898 motivated the choice of implementation problems examined. The present experiment was independently constructed and used only synthetic observations. No actual trial records, confidential sponsor programs, treatment assignments, or patient outcomes were used. The simulation rules are methodological assumptions, not a reconstruction of the protocol or a regulatory recommendation.

2.2 Component-First Analysis Architecture

The proposed architecture preserves component-level records before calculating composite endpoints. Daily stool frequency (SF) and rectal bleeding (RB) observations are assigned to an analysis visit and summarized into visit-level components. Endoscopic subscores (ES) retain assessment dates and reader provenance. Physician global assessment (PGA) is included for historical full and partial Mayo scores but not for modified Mayo scores.

For auditability, an analysis record should retain subject identifier, assessment date, analysis visit, source value, source or reader, eligibility reason, component identifier, baseline type, derivation type, and analysis-selection indicator. Appropriate ADaM BDS-style variables may include PARAMCD, AVAL, ADT, AVISIT, ABLFL, BASE, CHG, DTYPE, and analysis flags; exact implementation depends on the adopted standard and SAP.

Table 1: Conceptual Analysis-Data Lineage and Required Validation Controls

Analysis layer	Inputs / outputs	Required audit control
Diary component	Daily SF/RB to visit summary	Source date, window status, eligible-day count
Endoscopy component	Endoscopic observations to selected ES	Reader, date, selection flag, source
Mayo component	SF, RB, ES, and PGA as applicable	Endpoint-specific score and baseline
Efficacy endpoint	Remission/response indicator	Endpoint definition, Prespecified threshold, missingness, selection

2.3 Temporal eligibility and aggregation

For each synthetic profile, seven daily SF and RB values were generated for calendar days −7 through −1 relative to an assessment anchor date (day 0). Scenario A considered all seven preceding days eligible. Scenario B excluded day −1 to model a possible bowel-preparation exclusion convention. No observed diary data were substituted for missing values.

Each component was derived independently using its eligible nonmissing days. At least four valid days per component were required; otherwise the visit-level component was missing. The mean of the valid daily values was rounded using round-half-up. These minimum-day and rounding rules were expressly specified for the experiment and are not asserted to be GS-US-418-3898 requirements.

For each symptom component X, the visit-level mean was calculated as $\bar{X} = (\Sigma X_i)/n$, where n is the number of eligible nonmissing observations. Endoscopy-day records were not included because the candidate diary period ended at day −1.

2.4 Composite endpoints and source selection

The historical four-component Mayo Clinic Score (MCS) is SF + RB + ES + PGA (range 0–12). Partial Mayo (pMCS) is SF + RB + PGA (range 0–9), and modified Mayo (mMS) is SF + RB + ES (range 0–9). These measures are conceptually covered by the architecture but were not all separately evaluated in the simulation.

The simulation applied one illustrative EBS-like remission rule: RB = 0; SF = 0 or 1; ES = 0 or 1, with friability absent if ES = 1; and either an SF improvement relative to the simulated baseline or SF = 0. Missing required components produced an unclassifiable outcome. This algorithm is not presented as the precise clinical remission estimand or complete endpoint specification used by SELECTION.

For real clinical trial implementation, reader-source selection, baseline selection, treatment-failure handling, and imputation must be prespecified in the protocol and SAP. These dimensions were not experimentally compared here.

2.5 Computational experiment

Using Python 3 and a fixed pseudorandom seed (20261101), 500 independent synthetic subject profiles were generated. Each profile contained seven preassessment daily stool-frequency (SF) and rectal-bleeding (RB) observations, artificial baseline SF and RB subscores, an endoscopic subscore ranging from 0 to 3, and a synthetic friability indicator.

Daily symptom scores were generated from bounded, rounded Gaussian samples, with a 9% missingness probability for each component on each day. To examine sensitivity to diary-window eligibility, day −1 observations were assigned

an increased probability of symptom elevation (65% for SF and 35% for RB). These distributions were selected for methodological testing rather than estimated from clinical trial data.

Two scenarios were evaluated using identical synthetic profiles. Scenario A included diary observations from days −7 through −1, whereas Scenario B excluded day −1. For each scenario, eligible observations were selected, component averages were calculated and rounded, minimum valid-day requirements were applied, and an illustrative remission classification was derived.

The resulting subject-level records retained component subscores, eligibility status, and remission classifications under both scenarios. The experiment was designed to assess the sensitivity of endpoint derivation to diary eligibility conventions, not to estimate clinical treatment efficacy or reproduce outcomes from GS-US-418-3898.

2.6 Analysis plan and computational validation

The primary descriptive outcome was the percentage of paired-evaluable profiles with discordant remission classifications: 100 × (number of paired-evaluable discordant profiles)/(number of profiles evaluable under both scenarios). Secondary outcomes were the number and percentage classified as remitters in each scenario and the number of unclassifiable profiles under each eligibility convention.

Counts and percentages were reported without clinical hypothesis testing, treatment-effect estimation, or inferential claims about actual UC populations. The computational analysis was checked by re-executing the fixed-seed simulation and comparing the output totals with the manuscript summary. A code-level independent reimplementation would provide stronger external validation and is recommended before journal submission.

3 SOURCE DATA AND ANALYSIS DATASETS

Diary observations, endoscopy reads, and physician assessments arrive with different dates and structures. A useful architecture preserves each source as a component-level analysis record before creating composite scores. Diary domains can feed an analysis dataset with both daily records and visit-level summaries. Endoscopy can feed a dedicated dataset that distinguishes central and local reads. A Mayo analysis dataset can then combine the selected components by subject, visit, and baseline type. A final efficacy dataset can hold endpoint-level values and response flags.

Table 2: Proposed source-to-analysis architecture for UC efficacy endpoints

Analysis layer	Typical content	Key control
Diary component	Daily stool-frequency and rectal-bleeding responses	Valid diary day and visit anchor
Endoscopy component	Endoscopic subscore and reader type	Reader-source selection and assessment date
Mayo component	PGA and derived MCS/pMCS subscores	Common visit window and baseline type
Efficacy endpoint	MCS, pMCS, endoscopic remission or composite response	Endpoint definition and missing-data method

This structure preserves traceability from source to table and avoids hiding component decisions inside a composite. Foundational SDTM and ADaM standards support consistent representation, but they do not define the clinical endpoint itself [4].

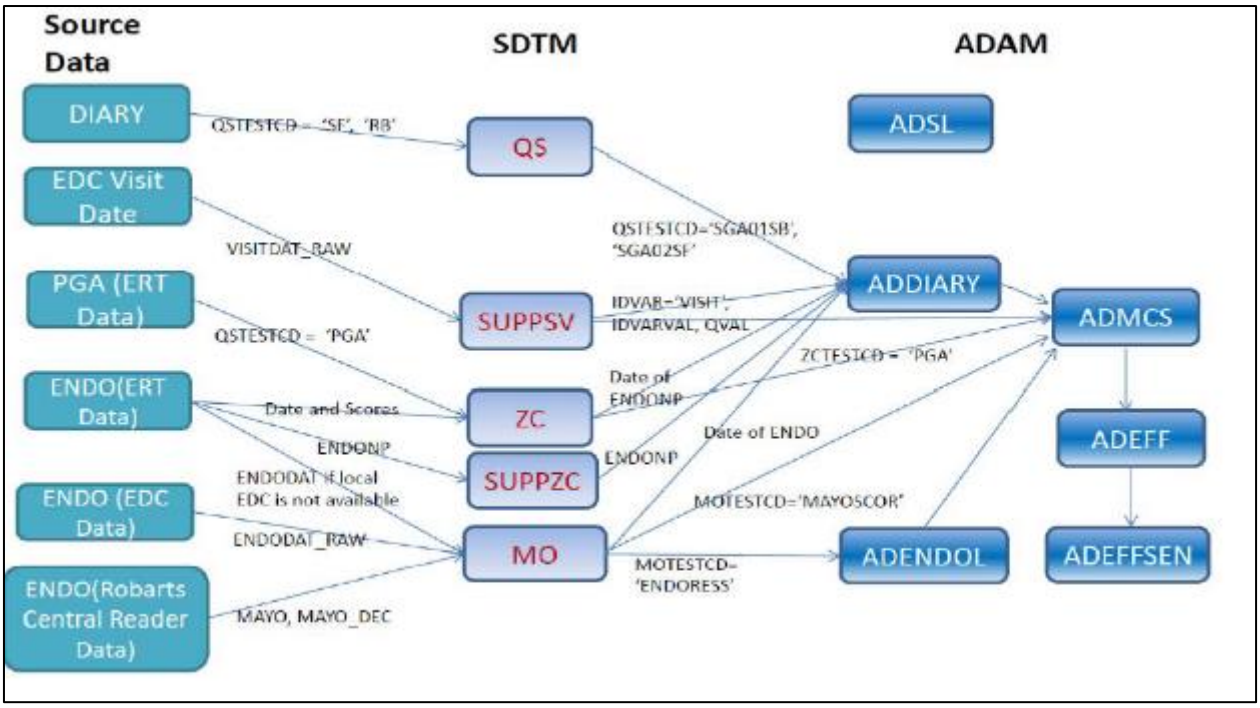


Figure 1: Source-to-analysis data flow for the derivation of ulcerative colitis diary, endoscopic, and Mayo efficacy endpoints.

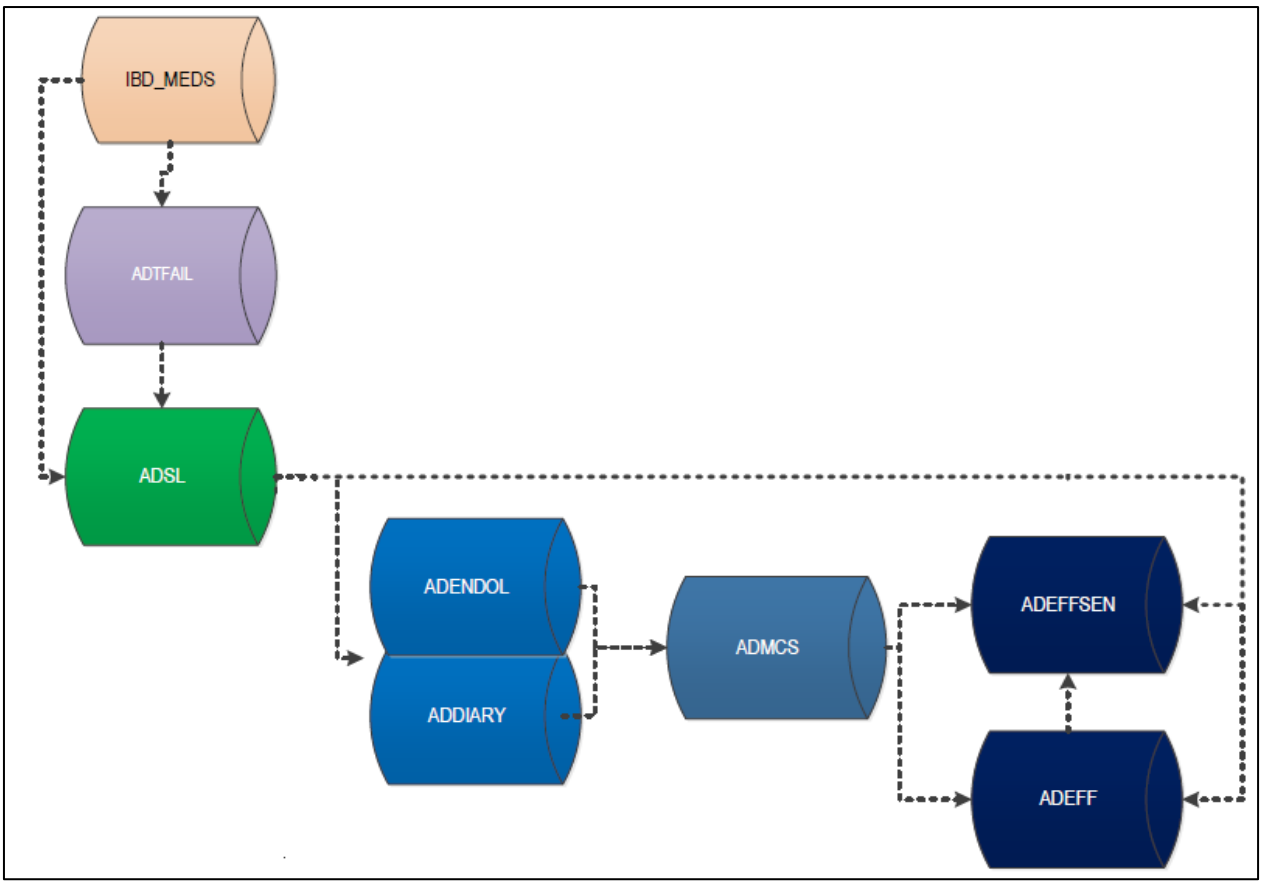


Figure 2: Analysis dataset dependencies supporting the derivation and validation of ulcerative colitis efficacy endpoints using an ADaM-oriented architecture.

4 ANALYSIS DATASETS ADMCS

Table 3: ADMCS component and composite parameter outline

Parameter	Input components	Calculation or traceability
MCS	SF, RB, ES, PGA	SF + RB + ES + PGA; range 0–12
pMCS	SF, RB, PGA	SF + RB + PGA; range 0–9
mMS	SF, RB, ES	SF + RB + ES; range 0–9
EBS remission flag	SF, RB, ES, baseline SF	Protocol-defined Boolean endpoint; not a numeric sum

Table 3.1: Illustrative ADMCS component and composite parameter specifications

Analysis	Composite Score		Component Sub-Score		Data Source
	Type	PARAMCD	Type	PARAMCD	
Treatment Failure	Mayo Clinical Score	MCS	Rectal Bleeding	RBLDSC	ADDIARY (PARAMCD of 'PRBLDSC')
	Mayo Clinical Score	MCS	Stool Frequency	STOOLSC	ADDIARY (PARAMCD of 'PSTOOLSC')
	Mayo Clinical Score	MCS	Physician's Global Assessment	PGA	SDTM.ZC (ZCTESTCD of 'PGA')
	Mayo Clinical Score	MCS	Endoscopic Score	ENDOSCR	SDTM.MO (MOTESTCD of 'MAYOSCOR')
Observed			Rectal Bleeding	RBLDSCO	ADDIARY (PARAMCD of 'PRBLDSCO')
			Stool Frequency	STOOLSCO	ADDIARY (PARAMCD of 'PSTOOLSO')

Analysis	Composite Score		Component Sub-Score		Data Source
	Type	PARAMCD	Type	PARAMCD	
Treatment Failure	Partial Mayo Clinical Score	PMCS	Rectal Bleeding	PRBLDSC	ADDIARY (PARAMCD of 'PRBLDSC')
	Partial Mayo Clinical Score	PMCS	Stool Frequency	PSTOOLSC	ADDIARY (PARAMCD of 'PSTOOLSC')
	Partial Mayo Clinical Score	PMCS	Physician's Global Assessment	PPGA	SDTM.ZC (ZCTESTCD of 'PGA')
Observed			Rectal Bleeding	PRBLDSCO	ADDIARY (PARAMCD of 'PRBLDSCO')
			Stool Frequency	PSTOOLSO	ADDIARY (PARAMCD of 'PSTOOLSO')
Treatment Failure	EBS Score	EBS	Endoscopic Score	ENDOSCR	SDTM.MO (MOTESTCD of 'MAYOSCOR')
	EBS Score	EBS	Rectal Bleeding	RBLDSC	ADDIARY (PARAMCD of 'PRBLDSC')
	EBS Score	EBS	Stool Frequency	STOOLSC	ADDIARY (PARAMCD of 'PSTOOLSC')
Sensitivity Analysis			Endoscopic Score – Locally Read	ENDOSCRL	ADENDOL (PARAMCD of 'ENDOSCRL')

5 DTYPE AND BASETYPE VALUES

Table 4: DTYPE Metadata

Metadata	Illustrative meaning	Safeguard
DTYPE=AVERAGE	Derived average when duplicates cannot be chronologically ordered	Retain original records and derivation rule
DTYPE=LOCF	Carried-forward observed component when SAP permits	Do not label as observed
DTYPE=IMPUTED_LOCF	Derived carried-forward composite when SAP permits	Keep distinct from measured value
BASETYPE=BASELINE	Induction baseline context	Explicit source date and eligibility
BASETYPE=RE-BASELINE	Maintenance baseline context	Document maintenance selection rule

Table 4.1: Illustrative derived-record (DTYPE) metadata for endpoint programming

DTYPE Value	Derivation or Source	Used In
AVERAGE	If multiple numeric assessments on the same date/time exist where chronological order cannot be determined, then an additional record was created to capture the arithmetic mean for the multiple records.	ADDIARY, ADMCS
LVPD	Last non-missing observation from Induction studies that was repeated as Re-baseline for the Maintenance study.	ADDIARY, ADENDOL, ADMCS
LOCF	For non-derived parameters only. Last non-missing observation after analysis windowing that was carried forward as an additional record for missing analysis visits.	ADDIARY, ADMCS
IMPUTED_LOCF	For derived parameters only. Last non-missing observation after analysis windowing that was carried forward as an additional record for missing analysis visits.	ADMCS

Table 4.2: Illustrative derived-record (BASELINE) metadata for endpoint programming

BASETYPE Value	Description
BASELINE	All data collected in the Induction studies, as well as data collected during screening phase that can serve as baseline for the Induction analyses.
RE-BASELINE	All data collected in the Maintenance study, as well as data repeated from the Induction studies that can serve as the baseline for the Maintenance analyses.

6 ANCHOR DATE AND SEVEN-DAY DIARY WINDOW

The source framework assigns a diary anchor date for each analysis visit. For screening, the diary period is tied to the endoscopy assessment. For baseline and post-baseline visits, the visit date serves as the anchor. The seven days preceding the anchor are candidates for the stool-frequency and rectal-bleeding summaries. The example rules exclude the endoscopy day and the day immediately before endoscopy, because preparation and the procedure may affect diary reporting. For post-baseline windows, the anchor day itself is not included in the lookback.

Clarification for this independent paper: the omission of day −1 is an explicit scenario assumption in the synthetic experiment, not a generalized regulatory instruction. Diary eligibility and minimum completion requirements in any clinical study are governed by the applicable protocol and SAP.

A reproducible algorithm computes the relative study day for every diary record, identifies the window, applies the exclusion rule, and counts evaluable days. It then calculates the mean component value and applies the protocol-defined rounding convention to produce the final subscore. When too few values remain, the component is missing. A programming specification should say whether the minimum count is based on valid records per component or on jointly valid days, how duplicates are resolved, and how partial dates or time zone differences are handled.

The same approach should be applied consistently at induction and maintenance visits, while retaining separate baseline types when maintenance uses a re-baseline value. The observed diary records should not be overwritten by a derived score. Instead, the derived record should point to the included source dates and carry the relevant derivation type.

7 ENDPOINT COMPONENTS AND COMPOSITES

The MCS contains stool frequency, rectal bleeding, physician global assessment, and endoscopy. The pMCS contains the three non-endoscopic components. Each component keeps its original clinical scale and source before any derived subscore is assigned. For repeated assessments, the analysis-window rule must choose one record or apply a documented aggregation rule. A central reader and a local read should remain distinguishable, especially when a sensitivity analysis uses the local assessment.

Table 5: Historical remission and response definitions presented as implementation examples

Endpoint example	Component rule	Programming note
MCS remission	Total MCS at or below 2, with no component above 1	Requires all four component values under the specified source-selection rule
EBS remission	Endoscopic score 0 or 1, rectal bleeding 0, and a prespecified stool-frequency improvement to 0 or 1	State the baseline comparison and reader source
Alternative MCS remission	Symptom and physician components at 0, endoscopic score 0 or 1, and total score at or below 1	Keep as a separate endpoint from the primary remission definition
MCS response	Decrease of at least 3 points and at least 30% from baseline, plus a rectal-bleeding decrease of at least 1 point or an absolute score of 0 or 1	Define baseline, denominator handling, and threshold inclusivity

Endpoint definitions can differ across regional or regulatory analyses. Preserve each prespecified definition as its own endpoint and analysis flag rather than forcing a single definition across all outputs. The analysis dataset should retain the continuous component values and binary endpoint classifications separately. The thresholds in the table summarize one historical programming example. Endpoint names should not imply that definitions are interchangeable. In particular, a response definition, an endoscopic remission definition, and an MCS remission definition answer different questions. Each should be coded as a separate parameter or flag with a clear label and analysis population.

Table 6: Illustrative Mayo Clinic Scoring Details

Mayo Clinic Score				
	Score			
Variables	**0**	**1**	**2**	**3**
Endoscopic Findings	Normal or inactive	Mild disease	Moderate disease	Severe disease
Rectal Bleeding	None	Streaks of blood in stool less than half the time	Obvious blood in stool half or more than half of the time	Blood alone passes
Stool Frequency	Normal number of daily stools for patient	1-2 stools per day more than normal	3-4 stools per day more than normal	≥ 5 stools per day more than normal
Physician Global Assessment	None	Mild disease	Moderate disease	Severe disease

8 BASELINE TYPES AND DERIVED RECORDS

Induction and maintenance analyses may use different baselines. A baseline type can identify screening and induction observations as the induction baseline, and maintenance-period observations plus any protocol-authorized repeated values as a maintenance re-baseline. The baseline-selection rule should be implemented at the component level before calculating change from baseline or a response classification. This prevents a maintenance endpoint from silently comparing a Week 58 value with an induction baseline.

Derived-data type values can identify special records. Examples include an average created when multiple same-day assessments cannot be ordered, a last valid induction observation repeated as a maintenance re-baseline, and LOCF or imputed LOCF records for missing visits. The exact codes should be defined in metadata and used consistently. If both the observed and derived records are retained, analysis flags must make the intended record selection unambiguous.

9 MISSING DATA AND VALIDATION

Missing-data treatment must follow the SAP and should be endpoint-specific. An observed component with no visit-level score differs from a missing composite caused by a required component. A derived LOCF value differs from an observed value, and the dataset should preserve that distinction. The analysis plan should specify whether missing diary values make the subscore missing, whether an imputation is permitted for a derived score, how early discontinuation is handled, and whether the primary analysis uses a nonresponder strategy.

Quality checks should cover diary-window boundaries, excluded preparation days, minimum completion thresholds, same-day duplicates, visits without endoscopy, baseline and re-baseline selection, reader-source selection, score bounds, total-score arithmetic, and exact values at endpoint cutoffs. Independently reproduce a sample of derivations from source-level records. For every patient-level endpoint, it should be possible to identify the contributing component records and explain why any component was missing or imputed.

10 SYNTHETIC-DATA RESULTS

Among the 500 artificial profiles, 491 were classifiable in both scenarios. Of these, 21 (4.3%) changed remission classification between inclusion and exclusion of day −1. In the paired-evaluable set, 92/491 (18.7%) met the illustrative remission rule in Scenario A and 89/491 (18.1%) in Scenario B. Among all 500 profiles, one was unclassifiable in Scenario A and nine were unclassifiable in Scenario B. This illustrates a potential joint effect on score aggregation and analysis eligibility, conditioned entirely on the specified simulation inputs.

Table 7: Executed fixed-seed synthetic sensitivity experiment (not patient outcomes)

Measure	Scenario A: all 7 days	Scenario B: omit day −1
Profiles generated	500	500
Paired-evaluable profiles	491	491
Illustrative remission in paired set	92 (18.7%)	89 (18.1%)
Unclassifiable of all generated	1	9
Discordant classification (paired)	21/491 (4.3%)	Same matched comparison

11 DISCUSSION AND LIMITATIONS OF THE EXPERIMENT

The results confirm that a small change in a programmed eligibility rule can affect derived scores, endpoint classifications, and evaluability in a controlled computational test. They do not establish how often this occurs in actual trials. The simulation intentionally increases day −1 symptoms and therefore cannot be generalized to unperturbed diary records. It does not model repeated visits, treatment groups, competing events, dropout, treatment failure, or centrally adjudicated reader discrepancies. Further independent validation and realistic, pre-registered sensitivity scenarios would strengthen external relevance. The underlying clinical endpoint definitions and programming decisions must always be reconciled with the trial protocol, SAP, and applicable standards; sensitivity to missing-data assumptions should be assessed [4,7,8].

12 CONCLUSION

A reliable ulcerative colitis endpoint pipeline starts with explicit source and time rules. Diary anchors and exclusions determine symptom subscores; reader selection determines the endoscopic component; baseline type determines change calculations; and missing-data rules determine the final response classification. Preserving these decisions as traceable component records makes the analysis easier to review and validate. Before use, reconcile every threshold and derivation with the current protocol, SAP, regulatory guidance, and CDISC standards adopted for the submission.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author declares no conflicts of interest regarding this manuscript.

Disclaimer

The views are the author's own; no proprietary or confidential employer information is included.

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