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Deriving Crohn Disease Efficacy Endpoints from Diary and Endoscopic Data

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Abstract: ***Clinical efficacy analyses in Crohn disease combine patient-reported symptoms, endoscopic assessments, laboratory values, concomitant medication use, and other clinical measures. Turning these sources into reproducible endpoints requires explicit rules for assessment windows, source selection, scoring, missing data, and treatment failure. This paper presents an anonymized programming framework for deriving the Crohn Disease Activity Index (CDAI), the two-item patient-reported outcome (PRO2), and the Simple Endoscopic Score for Crohn Disease (SES-CD), then assembling those measures into an analysis-ready efficacy dataset. The framework uses a visit-centered diary window, preserves segment-level endoscopic scores, and applies endpoint-specific missing-data rules with derivation flags. It also describes a traceability structure from collected data to component analysis datasets and composite endpoints. Illustrative values and thresholds are examples of protocol-defined conventions, not universal recommendations. No patient-level results are presented. The main implementation lesson is to keep observed components, derived scores, and response classifications distinct, with every transformation traceable to the protocol, statistical analysis plan, and source records.***

Keywords: Crohn disease, clinical endpoints, PRO2, CDAI, SES-CD, ADaM, missing data

1. Introduction

Crohn disease efficacy endpoints often pair symptom-based measures with endoscopic evidence of intestinal inflammation. The combined view matters because patient symptoms and visible mucosal disease may not move together. Trial programming therefore has to retain the component observations and the exact rules used to derive each score or response status. The CDAI is a weighted clinical activity index, while the SES-CD summarizes ulcer size, ulcerated surface, affected surface, and narrowing across bowel segments. A two-item patient-reported outcome, commonly called PRO2, focuses on abdominal pain and liquid or very soft stool frequency. [1, 2, 3]

This paper describes a reusable analysis-data pattern for those measures. The source examples came from historical presentation materials and have been anonymized. Sponsor, product, protocol identifiers, treatment assignments, study-specific counts, and other identifying details have been removed. The paper reports no clinical trial results. Any threshold, assessment window, treatment-failure rule, or imputation convention must be confirmed against the governing protocol and statistical analysis plan (SAP) before implementation.

2. Analysis Data Architecture

A practical design separates source observations, component-level analysis records, and endpoint-level records. Diary responses feed a subject-diary analysis data set. Laboratory and vital-sign values feed their respective analysis data sets. Medication and complication information feed component records. Endoscopy feeds a segment-level SES-CD data set. A patient-level efficacy data set then combines these components by subject, analysis visit, parameter, and baseline type.

Layer	Examples of content	Programming purpose
Collected or standardized source	Diary items, laboratory values, medications, endoscopy observations	Retain source date, original value, unit, and provenance
Component analysis data	Daily symptom summaries, CDAI components, five segment scores	Apply component-specific windowing and quality rules
Endpoint analysis data	PRO2, CDAI, SES-CD total, remission or response flags	Derive patient-level outcomes with traceable rules

Each derived record should retain the analysis visit, analysis date when meaningful, baseline type, source identifiers, analysis flags, and derivation type. This supports reconstruction of the endpoint and helps distinguish observed values from imputed or calculated values. ADaM provides standard structures for analysis-ready data, while therapeutic-area guidance supplies disease-specific examples; neither replaces protocol-specific definitions. [4, 5]

ADDIARY

	SUBJID	ADT	PARAM	PARCAT2	AVAL	ANL01FL	ANL02FL	ANL03FL	CNSDFL	CNSRDT	CNSRDESC
1	[redacted]	2017-11-27	Abdominal Pain Score (PRO2)	TREATMENT FAILED	1	Y			Y	2017-11-22	Calculation excluded censored values
2	[redacted]	2017-11-27	Abdominal Pain Score (PRO2) Obser..	OBSERVED	1.57142857	Y					
3	[redacted]	2017-11-17	SGA-Abdominal Pain Evaluable		1		Y		N	2017-11-22	
4	[redacted]	2017-11-18	SGA-Abdominal Pain Evaluable		1		Y		N	2017-11-22	
5	[redacted]	2017-11-19	SGA-Abdominal Pain Evaluable		1		Y	Y	N	2017-11-22	
6	[redacted]	2017-11-20	SGA-Abdominal Pain Evaluable		1		Y	Y	N	2017-11-22	
7	[redacted]	2017-11-21	SGA-Abdominal Pain Evaluable		1		Y	Y	N	2017-11-22	
8	[redacted]	2017-11-22	SGA-Abdominal Pain Evaluable		1			Y	Y	2017-11-22	Censored due to Treatment Failure
9	[redacted]	2017-11-23	SGA-Abdominal Pain Evaluable		2			Y	Y	2017-11-22	Censored due to Treatment Failure
10	[redacted]	2017-11-25	SGA-Abdominal Pain Evaluable		2			Y	Y	2017-11-22	Censored due to Treatment Failure
11	[redacted]	2017-11-26	SGA-Abdominal Pain Evaluable		3			Y	Y	2017-11-22	Censored due to Treatment Failure

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ADPRO2

	SUBJID	ADT	PARAM	PARAMCD	PARCAT2	AVAL	ANL01FL	CNSDFL	CNSRDT	CNSRDESC
1	[redacted]	2017-11-27	Abdominal Pain Score (PRO2)	ABDPAIN2	TREATMENT...	1	Y	Y	2017-11-22	Calculation excluded censored values
2	[redacted]	2017-11-27	Abdominal Pain Score (PRO2) Observed	ABDPAN2O	OBSERVED	2	Y			

ADCOMP

	SUBJID	ADT	VISIT	PARAM	PARAMCD	AVAL	AWTDIFF	ANL01FL	CNSDFL	CNSRDT	CNSRDESC
1	[redacted]	2017-11-27	Week 6	Abdominal Mas...	ABDOMASS	0	0	Y	Y	2017-11-22	Censored due to Treatment Failure
2	[redacted]	2017-12-07	Early Termination	Abdominal Mas...	ABDOMASS	0	10		Y	2017-11-22	Censored due to Treatment Failure
3	[redacted]	2017-11-27	Week 6	Anti-diarrheal...	ANTIDIAR	0	0	Y	Y	2017-11-22	Censored due to Treatment Failure
4	[redacted]	2017-12-07	Early Termination	Anti-diarrheal...	ANTIDIAR	0	10		Y	2017-11-22	Censored due to Treatment Failure
[redacted]		2017-11-27	Week 6	Complications...	COMPLICA	0	0	Y	Y	2017-11-22	Censored due to Treatment Failure
[redacted]		2017-12-07	Early Termination	Complications...	COMPLICA	0	10		Y	2017-11-22	Censored due to Treatment Failure

Diary Windowing and Pro2

Diary scores depend on both the value recorded and the date assigned to that value. In the example framework, screening diary data are selected within a defined pre-baseline window, while post-screening scores are anchored to the analysis visit. The Crohn disease example used a 10-day window and required at least four evaluable records to calculate a diary score. These are implementation choices from a particular SAP, not general clinical standards.

For a typical PRO2 implementation, the abdominal pain component is the mean of daily ratings over the prespecified diary period, and the stool-frequency component is the mean daily count of liquid or very soft stools. A remission classification may require an abdominal pain score at or below 1 and a stool-frequency score at or below 3, with the stool definition specified in the SAP. The derivation should state whether the window includes the anchor day, how non-evaluable days are handled, the minimum number of valid diary entries, and how values are rounded.

A robust algorithm first converts each diary observation to a normalized date and analysis-day offset. It then excludes days that the SAP identifies as invalid, such as diary days affected by endoscopy preparation, checks the minimum evaluable-day count, and calculates each component separately. The composite PRO2 score should only be produced when the required components are available. Keeping daily records and visit-level summaries separate makes it possible to inspect borderline windows and missingness patterns.

	Variable	Variable Description	Multiplier	Source Dataset
1	Liquid or very soft stool	Daily stool count is summed for 7 days	2	ADDIARY
2	Abdominal pain	Sum of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe	5	ADDIARY
3	General wellbeing	Sum of 7 days of daily ratings as 0 = generally well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	7	ADDIARY
4	Complications	Number of listed complications: - Arthritis or arthralgia Erythema nodosum, pyoderma gangrenosum or apthous stomatitis - Iritis or uveitis - Anal fissures or fistulae or abscess - Other fistula - Fever over 37.8 C [100 F] during past week	20	ADCOMP
5	Use of anti-diarrheal medications	Use of diphenoxylate or loperamide or other opiate for diarrhea 0 = No, 1 = Yes	30	ADCOMP
6	Abdominal mass	0 = none, 2 = questionable, 5 = definite	10	ADCOMP
7	Hematocrit	Males: 47 – Hct [%] Females: 42 – Hct [%] *Result must be greater than or equal to 0. If negative result enter 0	6*difference	ADLBHEMA
8	Weight	Percentage deviation from standard weight (1 – weight / standard weight) × 100 *Limit of -10 (Result must be greater than or equal to -10)	1	ADVS
		The CDAI total score is based on a weighted sum (rounded to the nearest integer) of all 8 components		ADCDAI

CDAI Sub scores

	Variable	Variable Description	Source Dataset
1	Liquid or very soft stool	Mean of the daily (liquid or very soft) stool count for 7 days	ADDIARY
2	Abdominal Pain	Mean of 7 days of daily ratings as 0= none, 1= mild, 2= moderate, 3 severe	ADDIARY

PRO2 Sub scores

CDAI Components and Derivation

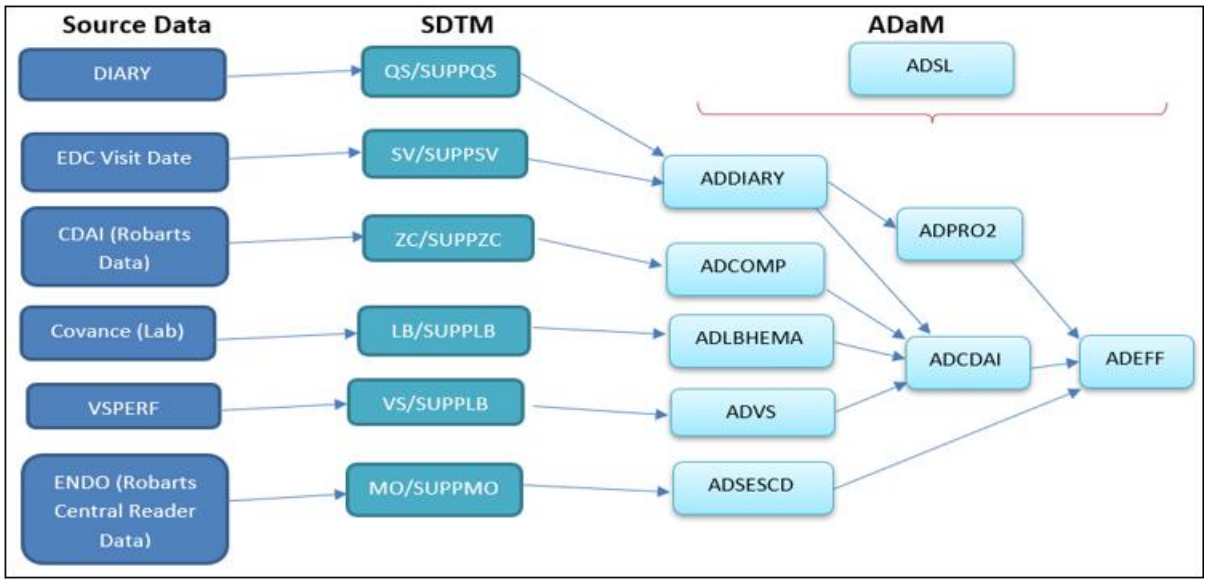
The CDAI combines eight components using prespecified multipliers. Components include seven-day stool counts, abdominal pain and general-wellbeing ratings, complications, antidiarrheal use, abdominal mass, hematocrit, and body-weight deviation. The original index was developed as a weighted measure of disease activity. [1] For programming, the source unit and transformation for each component must be explicit. For example, a hematocrit-derived contribution depends on sex-specific reference values and lower bounds, while weight deviation depends on the specified standard-weight formula and a protocol-defined floor.

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A derivation should calculate each component independently, retain both the raw and weighted values, and sum the weighted contributions only after applying the completeness rule. One example convention treats a score as insufficient when three or more components are missing. If one or two components are missing, the SAP may allow the most recent valid component to be carried forward, with baseline carried forward when no earlier post-baseline value exists. A missing-data code should identify which rule generated the value. This convention must not be generalized beyond a protocol that explicitly specifies it.

The endpoint flag is derived after the total score is available. A commonly used clinical remission threshold is CDAI below 150, and response definitions may include a prespecified decrease from baseline or attainment of remission. The analysis dataset should store the continuous score and each binary classification separately so that later tables can use the correct estimand and missing-data strategy.

Data Flow



SES-CD and Segment-Level Data

The SES-CD scores four endoscopic variables in each of five bowel segments. The variables are ulcer size, ulcerated surface, affected surface, and narrowing. Each variable is scored from 0 to 3; a segment total ranges from 0 to 12, and the overall score is the sum across the evaluated segments. The score was developed and validated as a simplified endoscopic activity measure. [2]

Store the four component scores and the segment total before deriving the overall score. This preserves the information needed to verify the sum and supports segment-level missing-data rules. An example protocol convention assigns a segment score of 12 at a post-baseline visit when that segment was observed at baseline but is missing post-baseline. If the same segment is missing at baseline and post-baseline, the segment may be excluded from both visit totals for the endpoint comparison. Such rules have a direct effect on response classification and must be disclosed in the SAP and programming specification.

For an endoscopic response endpoint, the analysis compares the post-baseline total with the appropriate baseline total and applies the protocol threshold. A 50% reduction is one example used in Crohn disease trials, but the endpoint must specify whether all segments are required, how baseline-zero scores are handled, and how imputed segment values affect the denominator. A central reader and a local read are separate sources and should not be combined without an explicit source-selection rule.

Variables	Score			
	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-.05)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter > 2)
Ulcerated Surface (%)	None	< 10	10-30	> 30
Affected surface (%)	Unaffected segment	< 50	50-75	> 75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Simple Endoscopic Score for Crohn's Disease (SES-CD)

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Treatment Failure and Missing Data

Treatment failure can include medication escalation or initiation, but the relevant medication classes, duration requirements, route changes, and event dates are protocol-defined. The programming plan should identify baseline medications, classify post-baseline changes, apply any consecutive-day requirement, and produce a patient-level failure date or indicator. Medication terminology should be mapped using a controlled and versioned dictionary. A rule that treats one day of a selected rescue therapy as failure should be distinct from a rule that requires several consecutive days for another therapy class.

Missing-data rules should be endpoint-specific. The example SES-CD convention uses a worst-segment value for a segment observed at baseline but missing later. The example CDAI convention uses LOCF or baseline LOCF for one or two missing components and sets the total score to missing when at least three components are absent. These methods represent one prespecified analysis strategy; sensitivity analyses should evaluate whether conclusions depend on the assumptions. Binary endpoints may require a nonresponder imputation (NRI) rule, while continuous component values may use a different strategy. Do not apply an imputation code to an observed record.

Programming Quality Control

Quality control should test the calculations at the component level and at the patient level. Useful checks include boundary values for every scoring item, minimum diary-completion thresholds, missingness at baseline and follow-up, repeated assessments on the same date, unit conversions, segment omissions, medication exposure around the treatment-failure window, and a patient whose score lies exactly on a response threshold. Independent validation should compare source values, derived components, totals, analysis flags, and final classifications. The output should preserve enough information to reproduce each endpoint without relying on undocumented manual review.

A traceability matrix can map each endpoint to its source, analysis visit, baseline, formula, missing-data rule, and output table. This is useful when definitions vary across analyses.

3. Conclusion

Reliable Crohn disease efficacy analyses depend on transparent rules for diary anchoring, component scoring, endoscopic segment handling, and treatment failure. Separating observed data from calculated scores and response flags makes those rules auditable and easier to validate. The methods described here are an anonymized implementation framework. Before use, each definition must be reconciled with the current protocol, SAP, applicable regulatory guidance, and the standards versions adopted for the submission.

References

[1] Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. Gastroenterology. 1976;70(3):439–444

[2] Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal Endoscopy. 2004;60(4):505–512

[3] Clinical Data Interchange Standards Consortium. Crohn's Disease Therapeutic Area User Guide, Version 1.0. https://www.cdisc.org/standards/therapeutic-areas/crohns-disease

[4] Clinical Data Interchange Standards Consortium. Analysis Data Model Implementation Guide, Version 1.3. 2021. https://www.cdisc.org/standards/foundational/adam/adamig-v1-3

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