

A Practical Approach to Multiple-Period CLINSITE Preparation

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ABSTRACT

The preparation of the summary-level clinical site dataset (e.g., CLINSITE) for a Bioresearch Monitoring (BIMO) package in an NDA submission requires consistent, traceable, and regulatory-compliant data structuring across study periods. In the study described, two periods were included: a double-blind (DB) treatment period, which contained two primary efficacy endpoints and safety evaluations for two different population sets, and an open-label extension (OLE) period, which focused exclusively on safety assessments at the time of the primary analysis database lock. To maintain consistency in data review and downstream validation without introducing any variable that is not in the FDA BIMO updated technical conformance guide (TCG, Version 3.0, August 11, 2022), the variable STUDYID in CLINSITE was structured to incorporate both DB and OLE data. ENDPOINT and ENDPTYPE were set to the same values in DB period, while TRTEFFR1 and TRTEFFR2 were intentionally set to missing value for the OLE period because no formal efficacy endpoints were evaluated at that time.

This paper outlines the technical and regulatory challenges encountered, and presents practical solutions implemented to prepare a CLINSITE dataset aligned with the TCG version 3.0.

INTRODUCTION

The CLINSITE, a component of an FDA BIMO package, provides key site-level information that helps the FDA assess the quality, reliability, and integrity of clinical trial data submitted in a new drug application (NDA). It supports the agency's risk-based inspection planning, demonstrates sponsor oversight, and helps verify good clinical practice (GCP) and regulatory compliance. It also provides transparency on site performance including enrollment, monitoring, protocol deviations, and data quality, allowing reviewers to identify potential risks or inconsistencies.

While the creation of CLINSITE must strictly align with TCG Version 3.0, the technical execution becomes significantly more complex when study designs deviate from standard single-period models. For studies that include multiple periods, such as a double-blind (DB) treatment period followed by an open-label extension (OLE) period, preparing a consistent and compliant CLINSITE package becomes more complex. In one of PharmaSUG papers (Elizabeth Li et al., 2024), the authors introduced a variable APERIODC which is not one of the variables per BIMO TCG version 3.0. In the study described here, we proposed a new method without adding any non-BIMO variable. Besides, in our study, the DB period included efficacy assessments and safety assessments for two analysis population sets, while the OLE period included only safety assessments for subjects who enrolled into OLE period after completing the DB period. This paper outlines the approach, challenges, and solutions used to prepare the CLINSITE dataset for an FDA submission involving both DB and OLE periods.

CLINSITE PREPARATION FOR A TWO-PERIOD Study

This work describes how CLINSITE was prepared in accordance with the BIMO within the electronic Common Technical Document (eCTD) framework. Dataset development followed the FDA BIMO Technical Conformance Guide (TCG), which defines the structure and content necessary to support inspection planning, compliance assessment, and regulatory decision-making.

Data quality checks and validation procedures were implemented to ensure completeness, consistency, and traceability across contributing sources

STUDY DESIGN

Figure 1 is the study design which featured two sequential periods:

- Double-Blind (DB) period: two primary efficacy endpoints and safety assessments.
- Open-Label Extension (OLE) period: safety assessments only.

Only subjects who completed DB treatment could continue into OLE period. The primary analysis was conducted after the last subject completed DB period. The second primary endpoint was evaluated as a predefined subset of the overall population.

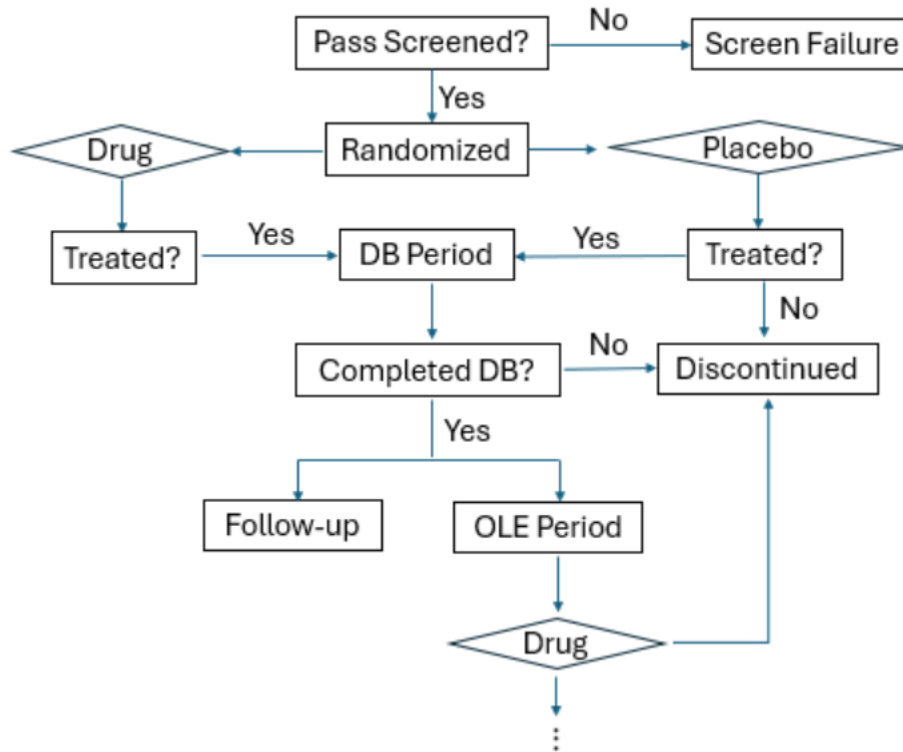


Figure 1. Study Design

CLINSITE STRUCTURE

At the time of the primary analysis, the last participant completed the DB period, and 71% of participants continued into the OLE period.

To accommodate this two-period design:

- STUDYID was structured to differentiate DB and OLE periods.
- Each period contained two primary endpoints (overall and subgroup, respectively), consistent with the DB structure, even though OLE endpoints were not evaluated.
- Variables such as SAFPOP, EFFPOP, DISCSTUD, DISCRT, NSAE, SAE, DEATH, IMPDEV, and NOIMPDEV were generated for each combination of:
 - STUDYID
 - SITEID
 - ARM
 - ENDPOINT

Table 1. A Simplified Representation of Key Endpoint Metadata

STUDYID	ENDPTYPE ENDPOINT	TRTEFFR1/2	CENSOR1/2
XX DB Period	Other Primary endpoint 1	Event rate per patient year for the composite outcome by ARM at a given STUDYID, SITEID for given population (SAFPOP, EFFPOP)	Set to missing since primary endpoint is not time to event
XX DB Period	Other Primary endpoint 2	Event rate per patient year for the composite outcome by ARM at a given STUDYID, SITEID for given population (SAFPOP, EFFPOP)	Set to missing since primary endpoint is not time to event
XX OLE Period	Other Primary endpoint 1	Set to missing	Set to missing since primary endpoint is not time to event
XX OLE Period	Other Primary endpoint 2	Set to missing	Set to missing since primary endpoint is not time to event

Like the other PharmaSUG paper (Elizabeth Li et al., 2024), we modified the variable labels of the variables (Table 2) to compliance with the label length limitation, which were slightly different from that in the paper.

Table 2: Variable Label Modification

Variable	Label in BIMO TCG 3.0	Label in our CLINSITE
EFFPOP	Number of Subjects in Efficacy Population	No. Subjects in Efficacy Population
NOIMPDEV	Number of Non-Important Protocol Deviations	No. Non-Important Protocol Deviations

EXAMPLES OF CLINICAL DATASET ON KEY VARIABLES

Below are the examples of a few sites for the main variables in CLINSITE dataset with dummy data (Table 3):

SITEID 001: There were total 18 subjects were screened, and one of them was screen failure, there were ten subjects treated with active drug and six of them continued to OLE period after completing DB period, while there were seven subjects were treated with placebo and three of them continued to OLE period after completing DB period. Total 17 subjects were included for primary endpoint 1 analysis, and no subject for primary endpoint 2 analysis.

SITEID 002: There were total two subjects screened and were treated with placebo, then continued to OLE period after they completed DB period. Total two subjects were included for primary endpoint 1 analysis, and two subjects for primary endpoint 2 analysis.

SITEID 003: There were total six subjects were screened, and three of them were screen failure, there was one subject treated with active drug and continued to OLE period after completing DB period, while there were two subjects were treated with placebo and continued to OLE period after completing DB period. Total three subjects were included for primary endpoint 1 analysis, and one subject for primary endpoint 2 analysis.

SITEID 004: There were three subjects screened, and only one was screened successfully and received active drug but discontinued study during the DB period. There was no subject continuing to OLE period. Total one subject was included for primary endpoint 1 analysis and primary endpoint 2 analysis, respectively.

SITEID 005: There was three subject screened and failed in the screening, so there was only record in CLINSITE dataset with missing ENDPOINT, TRTEFFR1/2, DISCSTUD, DISCRT, NSAE, SAE, DEATH, IMPDEV, and NOIMPDEV.

Table 3: An Example of CLINSITE Dataset

STUDYID	SITEID	ARM	SAFPOP	EFFPOP	SCREEN	DISCSTUD	DISCRT
XX DB Period	001	DRUG	10	10	18	4	4
XX DB Period	001	DRUG	0	0	18	0	0
XX OLE Period	001	DRUG/OLE DRUG	6	6	18	1	1
XX OLE Period	001	DRUG/OLE DRUG	0	0	18	0	0
XX DB Period	001	PLACEBO	7	7	18	4	4
XX DB Period	001	PLACEBO	0	0	18	0	0
XX OLE Period	001	PLACEBO/OLE DRUG	3	3	18	0	0
XX OLE Period	001	PLACEBO/OLE DRUG	0	0	18	0	0
XX DB Period	002	PLACEBO	2	2	2	0	0
XX DB Period	002	PLACEBO	2	2	2	0	0
XX OLE Period	002	PLACEBO/OLE DRUG	2	2	2	0	0
XX OLE Period	002	PLACEBO/OLE DRUG	2	2	2	0	0
XX DB Period	003	DRUG	1	1	6	0	0
XX DB Period	003	DRUG	0	0	6	0	0
XX OLE Period	003	DRUG/OLE DRUG	1	1	6	0	0
XX OLE Period	003	DRUG/OLE DRUG	0	0	6	0	0
XX DB Period	003	PLACEBO	2	2	6	0	0
XX DB Period	003	PLACEBO	1	1	6	0	0
XX OLE Period	003	PLACEBO/OLE DRUG	2	2	6	0	0
XX OLE Period	003	PLACEBO/OLE DRUG	1	1	6	0	0
XX DB Period	004	DRUG	1	1	3	1	1
XX DB Period	004	DRUG	1	1	3	1	1
XX DB Period	005	SCREEN FAILURE	0	0	3		

Table 3: An Example of CLINSITE Dataset (Cont'd)

ENDPOINT	TRTEFFR1	TRTEFFR2	NSAE	SAE	DEATH	IMPDEV	NOIMPDEV
PRIMARY ENDPOINT 1	0.611	0.611	38	21	2	4	30
PRIMARY ENDPOINT 2	0	0	0	0	0	0	0
PRIMARY ENDPOINT 1			15	3	1	1	2
PRIMARY ENDPOINT 2			0	0	0	0	0
PRIMARY ENDPOINT 1	0.921	0.921	40	29	4	1	15
PRIMARY ENDPOINT 2	0	0	0	0	0	0	0
PRIMARY ENDPOINT 1			0	0	0	0	1
PRIMARY ENDPOINT 2			0	0	0	0	0
PRIMARY ENDPOINT 1	0.28	0.28	26	2	0	0	16
PRIMARY ENDPOINT 2	0.28	0.28	25	2	0	0	16
PRIMARY ENDPOINT 1			2	0	0	0	0
PRIMARY ENDPOINT 2			2	0	0	0	0
PRIMARY ENDPOINT 1	0	0	7	2	0	0	5
PRIMARY ENDPOINT 2	0	0	0	0	0	0	0
PRIMARY ENDPOINT 1			1	0	0	0	0
PRIMARY ENDPOINT 2			0	0	0	0	0
PRIMARY ENDPOINT 1	0.163	0.163	10	1	0	2	7
PRIMARY ENDPOINT 2	0	0	7	1	0	1	3
PRIMARY ENDPOINT 1			6	0	0	0	0
PRIMARY ENDPOINT 2			3	0	0	0	0
PRIMARY ENDPOINT 1	0	0	0	0	0	1	9
PRIMARY ENDPOINT 2	0	0	0	0	0	1	9

CHALLENGES AND SOLUTIONS

Challenge 1: Multiple Periods

Issue

There is no specific variable in the standard CLINSITE TCG 3.0 for different periods, and extra variable added to CLINISTE would trigger validation warnings/errors.

Solution

- STUDYID was expanded to include period-level identifiers, avoiding any non-BIMO TCG 3.0 variable while maintaining traceability.
- This approach preserved the integrity of the CLINSITE structure and minimized downstream review complications.

Challenge 2: Two Analysis Population Sets for Safet Assessments at OLE Period

Issue

The standard CLINSITE TCG 3.0 requires counts on SAFPOP, EFFPOP, ENDPOINT, TRTEFFR1/2, DISCSTUD, DISCRT, NSAE, SAE, DEATH, IMPDEV, and NOIMPDEV within STUDYID, SITEID, ARM, and ENDPOINT. In this study:

- DB Period: Included two primary efficacy endpoints and safety assessments for both the overall population and a subgroup population, and two primary endpoints were used to summarize the purpose.
- OLE Period: Included safety assessments for the two population sets (overall and subgroup) who continued into the OLE period after completing the DB period, and BIMO inspection planning relies heavily on endpoint-based site performance. Because the OLE period did not have efficacy assessments, site-level safety metrics for the OLE period could not be distinguished when two records shared the same ARM value within a site but represented different population sets (overall and subgroup populations).

Solution

- ENDPOINT and ENDPTYPE were set to have the same values in OLE period as that in DB period to enable differentiation and clarify and resolve P21 issues.
- TRTEFFR1 and TRTEFFR2 were populated for DB period only and set to be missing for the OLE period.
- A Reviewer’s Guide explanation was provided although there was no BIMO validation warnings/errors.

CONCLUSION

Preparing a BIMO package for a multi-period clinical study—with efficacy endpoints and safety assessments in the DB period and safety-only assessments in the OLE period—requires careful planning, metadata management, and clear documentation. With such data structure of CLINSITE, although missing endpoint fields for the OLE period are technically compliant, they can trigger automated review checks unless proactively addressed.

By structuring STUDYID to distinguish periods and two ENDPOINT values for enable differentiation of analysis population in OLE period clearly documenting the rationale for missing TRTEFFR1/2 fields, the project team delivered a CLINSITE dataset that was both regulator-ready and reviewer-friendly. Transparent communication and consistent metadata were essential for achieving a clean validation outcome and a smooth regulatory review process.

REFERENCES

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