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Recent Updates in BIMO Technical Conformance Guidance and Use Case

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ABSTRACT

Since 2017, FDA has recommended that Sponsors submit Bioresearch Monitoring (BIMO) outputs along with a study electronic submission (eSub) package. The BIMO package includes Clinical Study-Level Information, Subject-Level Data Listings by Clinical Site, a Summary-Level Clinical Site Dataset (clinsite.xpt), Data definition file (define.xml) and BIMO Data Reviewer guide (bdrg.pdf). FDA also released detailed requirements per the Bioresearch Monitoring (BIMO) Technical Conformance Guide (TCG) to detail BIMO submission package standards. The BIMO TCG provides detailed specifications, recommendations, and general considerations for preparing and submitting all submission related components. The BIMO eSub package is used by the Center for Drug Evaluation and Research (CDER) for planning of BIMO inspections for new drug applications (NDAs), biologics license applications (BLAs), and Supplemental new drug application (sNDA) or Supplemental biologics application (sBLA) containing clinical data that are regulated by CDER. This paper will include a summary of BIMO preparation requirements recommended by FDA per the BIMO TCG V2.0 (released in 2020) versus V3.0 (released in 2022). In addition, author(s) will also present one of Alnylam's use case/experience preparing and submitting BIMO, including lessons learned and best practices (i.e., where the analysis need triggered updates in developing the Summary-Level Clinical Site Dataset, and where BIMO population flags and related variables were updated by Alnylam's Statistical Programming and Statistics team to accommodate specific analysis needs).

INTRODUCTION

Bioresearch Monitoring Information and Operations (BIMO) Technical Conformance Guide (TCG) outlines the FDA's expectations for the submission of clinical trial data as part of electronic submissions (eSub) for new drug applications (NDAs), supplemental NDAs (sNDAs), biologics license applications (BLAs), and supplemental BLAs (sBLAs). The guide specifies the format and content of the subject-level data listings, summary-level clinical site dataset, data definition file, and BIMO data reviewer guide that must be submitted as part of the eSub package.

While the BIMO TCG provides a standard approach for submitting clinical trial data, sponsors may adopt alternative approaches as long as they comply with applicable regulations and standards. The goal of the BIMO TCG is to ensure the quality, consistency, and accuracy of the clinical trial data submitted to the FDA, which ultimately helps the agency make informed decisions about the safety and effectiveness of new drugs and biologics.

BIMO TCG UPDATES

BIMO TCG has evolved over time to accommodate the various analysis needs and sponsor comments. Keeping the data submission guidance updated is important to ensure that the information being submitted is relevant and accurate. The addition and deletion of variables, as well as the renaming of variables, can provide a better understanding of the study and its results. For instance, the split of the "number of protocol deviation" (PROTVIOL) variable into "Num of Important Protocol Deviation" (IMPDEV) and "Num of Non-Important Protocol Deviation" (NOIMPDEV) can provide more detailed information on the nature of the deviations and can help to better understand their impact on the study. The adoption of FDA recommended updates is also a positive step in ensuring the quality and accuracy of the data being analyzed and submitted. FDA recommended updates are presented in Table 1.

Table 1: BIMO Updates

Recent	Dates	Deleted/Added Variable	Rename	Revision
Version 1.0	12/28/2017	-	-	-
Version 2.0	07/23/2020	➢ Deleted request for SITEFFE and SITEFFS variables in clinsite.xpt ➢ COHORT was added in clinsite.xpt		➢ Revised PROTVIOL variable to IMPDEV and NOIMPDEV variables ➢ Provided additional instructions for placement of files per eCTD format

Version 3.0	08/11/2022	➢ Added EFFPOP, TRTEFFR2, and CENSOR2 Variables ➢ Deleted request for TRTEFFS	➢ TRTEFFR to TRTEFFR1	➢ Rename BIMO Review Guide to BIMO Data Review Guide ➢ Change instructions for use of ISO codes to use of Geopolitical Entities, Names and Codes (GENC) code list.

RECENT EXPERIENCES AND USE CASE

The Alnylam team faced several challenges during recent BIMO packages creation, but team was able to overcome these with innovative solutions. Creating multiple variables instead of the suggested variable can help provide more clarity and detail on the data being submitted, which can be particularly important in a complex study design. The tweaks made to the subject-level listings to provide a clear and concise understanding of the complex study design also demonstrate the team's commitment to ensuring that the information being presented is easy to understand and relevant to the reviewers. These efforts to provide high-quality, accurate, and clear data can help to support successful submission review and ultimately contribute to the advancement of submission standards.

CHALLENGE

The main challenge we encountered during the BIMO package creation for a recent sNDA was patient population update. For the Month *x* analysis, only patients who received Placebo or study drug and had their Month *x* efficacy visit within 3 calendar months of the protocol-planned Month *x* efficacy visit window (mITT) were included. The Randomized Treatment Extension (RTE) analysis, on the other hand, only considered patients who underwent RTE randomization and had received any amount of study drug treatment during the RTE period (RTEPOP). Alnylam team recognized the challenge with the mITT population not being applicable for the RTE period and took steps to address it. The differences in the primary objectives of an NDA and an sNDA impacted the listing structure of the BIMO package. The team needed to tweak the listing structure to ensure that the sNDA package meets the specific need of analysis in RTE period.

Table 2: Key comparisons of Month *x* and RTE analysis periods

	Primary Objective	**Analysis Population**
Month *x* Period	Change from baseline in the Efficacy Parameter Score) compared to the placebo group of the *YYY* study at Month *x*.	mITT population was defined as the patient who had Month *x* efficacy visit date within 3 calendar months of protocol-planned Month *x* efficacy visit window.
RTE Period	To evaluate the safety, Pharmacodynamic, and efficacy of the dosing regimen of A treatment to B treatment	RTE population was define as All patients who underwent RTE randomization and who received any amount of *XXX* treatment during the RTE period. Patients will be analyzed according to the treatment to which they were randomized in the RTE period.

APPROACH

To address potential challenge and increase the transparency of the study results between the NDA and sNDA submissions, the Alnylam team came up with the idea of adding additional population flags (RTEPOP) to the clinsite.xpt file. Furthermore, the team added corresponding variables such as TRTEFFR3, NSAE3, SAE3, and DEATH3 to determine the number of patients who met the criteria for RTEPOP. The addition of this new population flag and corresponding variables will help to minimize confusion and provide further clarity for the reviewer.

Table 3: NDA vs sNDA (clinsite data)

Following table depicts the details of variable included in cliniste data between NDA and sNDA package. Highlighted variables were updated in sNDA based on following reason:

1) Guidance update i.e. TTREFFR, TRTEFFS, SITEEFFE, SITEEFFS, CENSOR, PROTVIOL

2) Analysis needs updates i.e. TTREFFR#, NSAE#, SAE#, DEATH#, IMPDEV#, NOIMPDV#

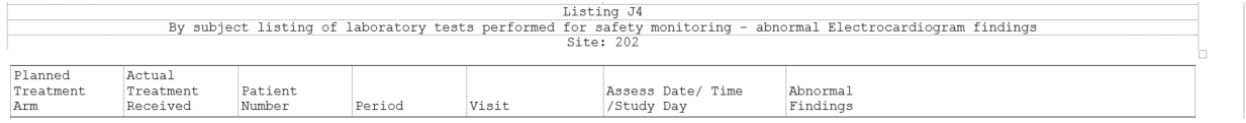
Submission	Population	Analysis related Variables included in clinsite
NDA (Month *x*)	SAFPOP	SCREEN, DISCSTUD, DISCTRT, ENDPOINT, ENDTYPE, TRTEFFR, TRTEFFS, SITEEFFE, SITEEFFS, CENSOR, NSAE, SAE, DEATH, PROTVIOL
sNDA (RTE)	SAFPOP	SCREEN, DISCSTUD1, DISCTRT1, ENDPOINT, ENDTYPE, TRTEFFR1, CENSOR1, NSAE1, SAE1, SAE2, SAE3, DEATH1, IMPDEV1, NOIMPDV1,
sNDA (RTE)	EFFPOP	DISCSTUD2, DISCTRT2, TRTEFFR2, CENSOR2, NSAE2, DEATH2, IMPDEV2, NOIMPDV2
sNDA (RTE)	RTEPOP	DISCSTUD3, DISCTRT3, TRTEFFR3, NSAE3, DEATH3, IMPDEV3, NOIMPDV3

NDA vs sNDA listings:

As discussed earlier that listing's structure was updated to accommodate analysis needs in RTE period. The team presented planned/actual treatment arm for Month *x* safety listings however for RTE listings we presented treatment sequence. In addition, team also realized that adding Day columns respective to analysis period i.e. Treatment, legacy extension and RTE will help reviewer.

Safety Listings:

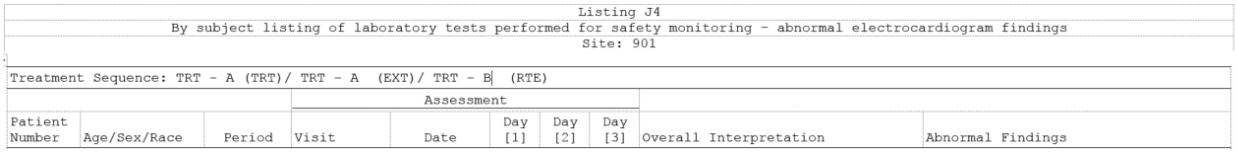
NDA:



Listing J4
By subject listing of laboratory tests performed for safety monitoring - abnormal Electrocardiogram findings
Site: 202

Planned Treatment Arm	Actual Treatment Received	Patient Number	Period	Visit	Assess Date/ Time /Study Day	Abnormal Findings

sNDA:



Listing J4
By subject listing of laboratory tests performed for safety monitoring - abnormal electrocardiogram findings
Site: 901

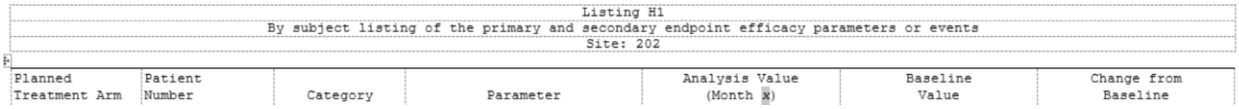
Treatment Sequence: TRT - A (TRT)/ TRT - A (EXT)/ TRT - B (RTE)

			Assessment						
Patient Number	Age/Sex/Race	Period	Visit	Date	Day [1]	Day [2]	Day [3]	Overall Interpretation	Abnormal Findings

Efficacy Listing:

For Month x efficacy listings, team presented results, baseline value and change from baseline however for RTE period listing we presented 2 additional columns i.e., RTE baseline value and change from RTE baseline.

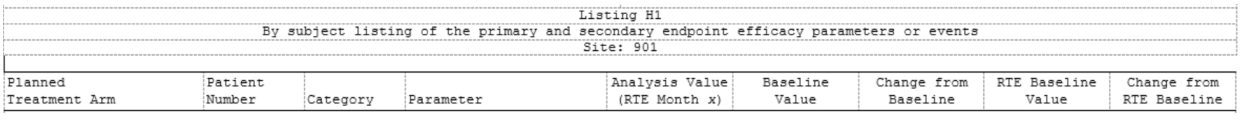
NDA:



Listing H1
By subject listing of the primary and secondary endpoint efficacy parameters or events
Site: 202

Planned Treatment Arm	Patient Number	Category	Parameter	Analysis Value (Month x)	Baseline Value	Change from Baseline

sNDA:



Listing H1
By subject listing of the primary and secondary endpoint efficacy parameters or events
Site: 901

Planned Treatment Arm	Patient Number	Category	Parameter	Analysis Value (RTE Month x)	Baseline Value	Change from Baseline	RTE Baseline Value	Change from RTE Baseline

CONCLUSION

It is obvious that BIMO TCG will continue to evolve and provide more detailed instruction in the future. We as sponsors may encounter more scenarios where BIMO package may need to deviate from guidance to add clarity for reviewers. When such situations arise, it's important for the sponsor team to have open and transparent discussions to ensure that the decision-making process is well-informed and all perspectives are considered. This may involve coordination among different functional groups, such as statistical programming, statistics, finance, and medical monitoring, to ensure that the package provided to the reviewer is robust and of high quality. It's also important to ensure that any deviations or changes made to the guidance are well-documented and explained in the BDRG, with clear justification for the deviation of why the sponsor chose to deviate from guidance. This will help the reviewer to better understand the reasoning behind any changes.

REFERENCES

Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (V2.0): FDA Guidance – July 27, 2020

Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (V3.0): FDA Guidance – August 11, 2022

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