

Automating BIMO Subject-level data line listings with R

Biographies

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Outlines

- Background and Motivation
- Introduce an R tool to automate and standardize the BIMO listings generation per regulatory authorization requirements and standards
 - Workflow Overview
 - Outcome Examples
 - Key Functions Demo
- Highlight challenges and future directions

Introduction: What is BIMO Package

- ❖ **BIMO (bioresearch monitoring) data package from all major (i.e., pivotal) studies is required by FDA to support NDA, BLA, sNDA, sBLA, and certain INDs in advance of a planned NDA, BLA, or supplemental submission.**
- ❖ BIMO package contains **4 components**:
 - **Subject-level data line listings by site: support safety and efficacy in the application**
 - summary-level clinical site dataset
 - Define file for the clinical site dataset
 - BIMO Data Reviewer's Guide (optional)
- ❖ BIMO listings are provided to FDA field investigators as part of their inspection package. These listings are used in source data verification during site inspections.

References:

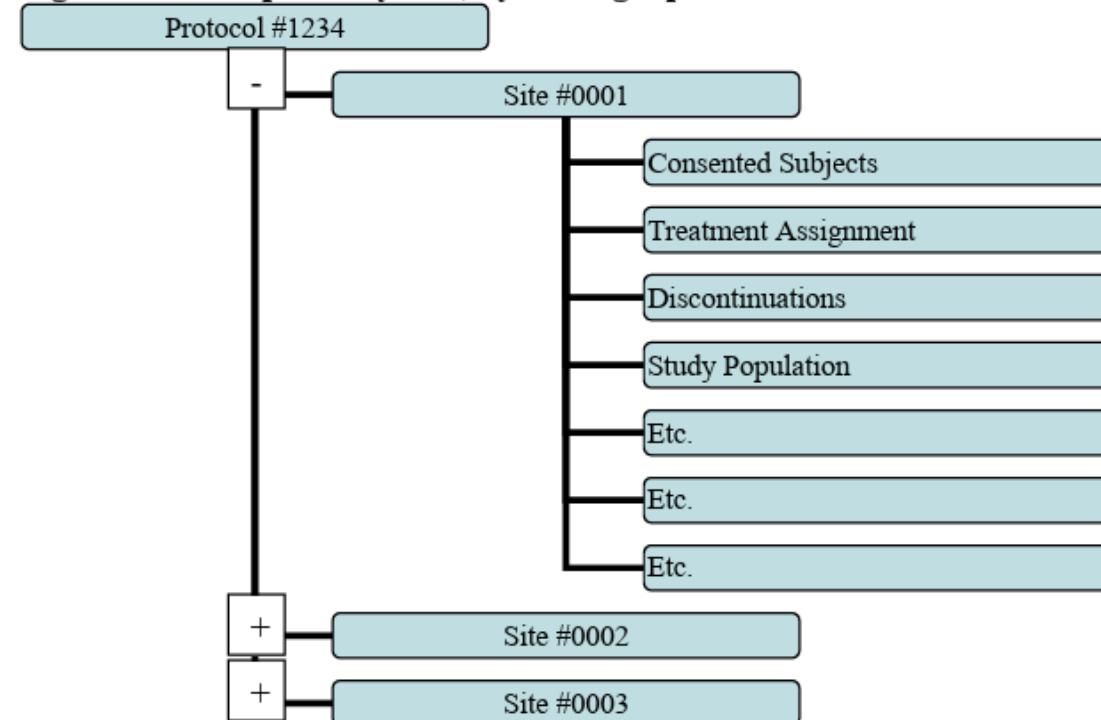
- *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, final version, Dec 2024*
- *Bioresearch Monitoring Technical Conformance Guide Technical Specifications Document, Sep 2024*

Introduction: What is Subject-level Data Line Listings

Subject-level data line listings, by clinical site, should include:

- Listing 1. Consented subjects
- Listing 2. Treatment assignment
- Listing 3. Discontinuations
- Listing 4. Study population
- Listing 5. Inclusion and exclusion criteria
- Listing 6. Adverse events
- Listing 7. Protocol deviations
- Listing 8. Efficacy endpoints
- Listing 9. Concomitant medications
- Listing 10. Safety monitoring

Figure C: Example of By Site, by Listing Option A

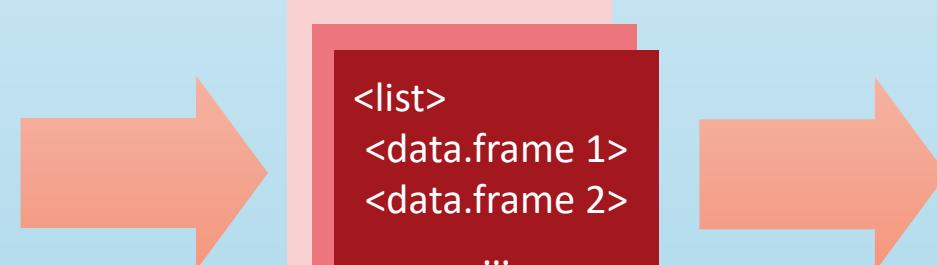


References:

- *Bioresearch Monitoring Technical Conformance Guide Technical Specifications Document, Sep 2024*

Workflow Overview

Clinical Study Report Listings (.rtf)



Automated R tools
From listings to listings

BIMO Site Level Listings (.rtf)



Outcome Examples

- ❖ From **outputs to outputs** without reprogramming listing specifications.
- ❖ Customized page layout and table/listing formatting
- ❖ Generate a batch of outcomes for separate sites

 VX[REDACTED]-site-005-bimo	 VX[REDACTED]-site-016-bimo
 VX[REDACTED]-site-018-bimo	 VX[REDACTED]-site-058-bimo
 VX[REDACTED]-site-059-bimo	 VX[REDACTED]-site-060-bimo
 VX[REDACTED]-site-062-bimo	 VX[REDACTED]-site-063-bimo
 VX[REDACTED]-site-065-bimo	 VX[REDACTED]-site-085-bimo
 VX[REDACTED]-site-145-bimo	 VX[REDACTED]-site-153-bimo
 VX[REDACTED]-site-155-bimo	 VX[REDACTED]-site-169-bimo
 VX[REDACTED]-site-170-bimo	 VX[REDACTED]-site-176-bimo
 VX[REDACTED]-site-177-bimo	 VX[REDACTED]-site-257-bimo
 VX[REDACTED]-site-279-bimo	 VX[REDACTED]-site-280-bimo
 VX[REDACTED]-site-392-bimo	 VX[REDACTED]-site-860-bimo
 VX[REDACTED]-site-867-bimo	

Outcome Examples

Navigation

Search document

Headings Pages Results

Vertex Pharmaceuticals Incorporated
Vertex Program: BIMO

Listing 6
Adverse Events
All Subjects Set

Site: (005) Clinical Trials

Subject	Actual Treatment	SOC/PT/ Verbatim Term	Start Date: Time (1)/ End Date	Severity	Serious	Action Taken	Treatment Required	Outcome
		Gastrointestinal disorders/ Dry mouth/ DRY MOUTH	2023-03-06: 04:50 (T)/2023-03-06	MILD	No			RECOVERED/RE SOLVED
		Nervous system disorders/ Syncope/ SYNCOPE	2023-03-25: 06:50 (T)/2023-03-25	SEVERE	No			RECOVERED/RE SOLVED
		Nervous system disorders/ Headache/ HEADACHE	2023-03-25: 17:30 (T)/2023-03-25	MILD	No			RECOVERED/RE SOLVED
		Gastrointestinal disorders/ Constipation/ CONSTIPATION	2023-03-26: 12:00 (T)/2023-04-04	MILD	No			RECOVERED/RE SOLVED
		Infections and infestations/ Viral pharyngitis/ VIRAL PHARYNGITIS	2023-03-17 (P)/2023-03-22	MODERATE	No			RECOVERED/RE SOLVED
		Injury, poisoning and procedural complications/ Suture related complication/ LOOSE STITCHES SECONDARY TO BUNIONECTOMY, LEFT FOOT	2023-04-01 (T)/2023-04-14	MODERATE	No			RECOVERED/RE SOLVED
		Respiratory, thoracic and mediastinal disorders/ Throat irritation/ ITCHY THROAT	2023-04-14 (T)/2023-04-14	MODERATE	No			RECOVERED/RE SOLVED

- MedDRA version 26.1.
- 1: T - Treatment-emergent, P - Pre-treatment.

Key Function: `r_tfl_rtfread` (SCR listing to R data frame)

- **Description:**
 - Read in rtf file of tables or listings into r data frame
 - Could be used in a wide range of settings, e.g., QC, export to other formats, etc
- **Demo:**

```
ptm <- proc.time()
tlist <- r_tfl_rtfread(rtffile = "./listings/l-ae-aesi-lft.rtf",
                      DisplayColWidths = TRUE)
proc.time() - ptm

##    user  system elapsed
##    0.05    0.06    1.34
```

Key Function: `r_tfl_rtfread`

Listing 16.2.7.2 Elevated Transaminase Events All Subjects Set						
Subject/ Sex ¹ /Age/Race ²	Actual Treatment	SOC/PT/Verbatim Term	Start Date(T)/ Study Day/ Duration (Days)	Ser- ious	Action Taken	Treatment Relationship Required to Study Drug Outcome
	ELX/TEZ/IVA	Investigations/ Alanine aminotransferase increased/ RAISED ALT 105 U/L (> 3 X UPPER LIMIT OF NORMAL)	2020-01-03 (TT) / MILD D1/7	No		RECOVERED/ RESOLVED
		Investigations/ Alanine aminotransferase increased/ RAISED ALT > 3 TIMES UPPER LIMIT	2020-01-17 (TT) / MILD D15/43	No		RECOVERED/ RESOLVED
	ELX/TEZ/IVA	Investigations/ Alanine aminotransferase increased/ RAISED ALT - 72 U/L(>3 X UPPER LIMIT OF NORMAL)	2019-12-16 (TR) / MILD D-25/15	No		RECOVERED/ RESOLVED
	ELX/TEZ/IVA	Investigations/ Alanine aminotransferase increased/ ALT ROSE TO 105	2020-01-14 (TT) / MILD D16/14	No		RECOVERED/ RESOLVED

- MedDRA version 23.0.
 - ¹: F- Female, M- Male.
 - ²: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other.
 - T is the Treatment-emergent flag: TR - Treatment-emergent during the Run-in Period, TT - Treatment-emergent during the Treatment Period, P - Pre-treatment, A - Post-treatment.
 - Study day = AE start date - first dose date in the Treatment Period (+ 1 if AE started on or after first dose date of study drug in the Treatment Period).
 - Duration = AE end date - AE start date + 1.

Data Frame: TFL

h1	h2	h3	tf_id	page	siteid	subjectid	c1	c2	c3
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	1	407			ELX/TEZ/IVA	Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	1	407				Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	1	407			ELX/TEZ/IVA	Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	1	411			ELX/TEZ/IVA	Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	2	411			ELX/TEZ/IVA	Investigations/ Aspart
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	2	416			TEZ/IVA	Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	2	416				Investigations/ Aspart
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	2	705			TEZ/IVA	Investigations/ Alanin
Subject/ Sex1/Age/Race2	Actual Treatment	SOC/PT/Verbatim Term	1	2	705				Investigations/ Aspart

Data Frame: TF

value	type	tf_id
Listing 16.2.7.2 Elevated Transaminase Events All Subjects Set	title	1
- MedDRA version 23.0.	footnote	1
- 1: F- Female, M- Male.	footnote	1
- 2: W- White, B- Black or African American, A- Asian, AA- Amer...	footnote	1
- T is the Treatment-emergent flag: TR - Treatment-emergen...	footnote	1
- Study day = AE start date - first dose date in the Treatmen...	footnote	1
- Duration = AE end date - AE start date + 1.	footnote	1

Key Function: r_tfl_rtfwrite (R data frame to BIMO listings)

- **Description:**

- Write tables/listings from R data frame to formatted RTF file
- For BIMO listings, loop over each site and each listing; the list of Site IDs is obtained by r_tfl_rtfread

- **Demo:**

```
ptm <- proc.time()
r_tfl_rtfwrite(tfl= tlist$tfl, tf = tlist$tf,
                heading = "Vertex Pharmaceuticals Incorporated\nVertex Program: ██████████ BIMO",
                titlenote = "",
                rtfout = 'rtfwrite_example.rtf')
proc.time() - ptm

##      user  system elapsed
##      0.22    0.01   1.58
```

Challenges

- Extract column widths information from CSR rtf content to ensure consistent rtf layouts
- Assemble multiple rtf listings by sections, and create page numbering by sections
- Format titles for each listing and create TOC based on formats
- Generate an empty listing shell page if a site has no data that meets the criteria for a specific listing

Summary

- ❖ By automating and formalizing listing generation, our R tool reduces manual effort, simplifies quality control, and improves traceability from CSR listings to BIMO deliverables.
- ❖ This tool has been tested with two Vertex compounds and has been verified to meet regulatory requirements and standards.
- ❖ The key functions, `r_tfl_rtfread` and `r_tfl_rtfwrite`, have a wide range of applications, such as QC, exporting outputs to other format documents, e.g., PowerPoint, Excel, SAS datasets, etc.

Future Directions

- R markdown generating BIMO Data Reviewer's Guide
 - Automate the Subject-level Listing, Site Summary, and External Datasets and Sources sections of the Reviewer's Guide

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