



DEC 02, 2022

Food and Drug Administration
Center for Drug Evaluation and Research 5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: R Consortium R submission Pilot 3 ADaM extension

Dear Sir/Madam:

This letter serves as a proposal to the R Consortium R submission Pilot 3 (an ADaM extension to Pilot 1) focusing on a working example of R submission in eCTD format to the pharmaceutical industry in compliance with the FDA Electronic Submissions Gateway requirements. Based on the Pilot 1 submission package, Pilot 3 only focuses on the generation of ADaM datasets that were used in the Pilot 1 outputs. The Pilot 3 ADaM datasets will be generated using R. Upon submission to the FDA, the FDA Staff can review and reproduce the submitted R codes. More specifically, with this proposal, we expect the FDA Staff to

- Receive an electronic submission package in eCTD format
- Reconstruct and load the submitted proprietary R package (i.e. “pilot3adamextensionwrappers”))
- Install and load open source packages used in this submission (i.e. including, but not limited to admiral, metacore, metatools, tidyverse, xportr)
- Reproduce the ADaM datasets and analysis results using the submitted R code and packages
- Share potential improvements to the submission deliverables and processes via written communication

All data, code, material and communications from this pilot will be shared publicly.

On behalf of the R Consortium R Submission Working Group, we hope the R submission Pilot 3 (an ADaM extension to Pilot 1) can establish a working example to guide the industry for future submissions using the R language.

Analysis Dataset Description

The following provides detailed information for each analysis dataset included in the Pilot 3 submission, which were used to generate the outputs in Pilot 1. These ADaM datasets are ADSL, ADTTE, ADADAS, ADLBC.

ADSL - Subject Level Analysis Dataset

The subject level analysis dataset (ADSL) contains required variables for demographics, treatment groups, and population flags. In addition, it contains other baseline characteristics that were used in both safety and efficacy analyses. All patients in DM were included in ADSL.

The following are the key population flags are used in analyses for patients:

- SAFFL – Safety Population Flag (all patients having received any study treatment)
- ITTFL – Intent-to-Treat Population Flag (all randomized patients)

ADAE - Adverse Events Analysis Data

ADAE contains one record per reported event per subject. Subjects who did not report any Adverse Events are not represented in this dataset. The data reference for ADAE is the SDTM

- AE (Adverse Events) domain and there is a 1-1 correspondence between records in the source and this analysis dataset. These records can be linked uniquely by STUDYID, USUBJID, and AESEQ.
- Events of particular interest (dermatologic) are captured in the customized query variable (CQ01NAM) in this dataset. Since ADAE is a source for ADTTE, the first chronological occurrence based on the start dates (and sequence numbers) of the treatment emergent dermatological events are flagged (AOCC01FL) to facilitate traceability between these two analysis datasets.

ADTTE - Time to Event Analysis Dataset

ADTTE contains one observation per parameter per subject. ADTTE is specifically for safety analyses of the time to the first dermatologic adverse event. Dermatologic AEs are considered an adverse event of special interest. The key parameter used for the analysis of time to the first dermatological event is with PARAMCD of "TTDE".

ADLBHPV - Laboratory Results Hematology Analysis Data (Previous Visit)

ADLBC and ADLBH contain one record per lab analysis parameter, per time point, per subject. ADLBC contains lab chemistry parameters and ADLBH contains hematology parameters and these data are derived from the SDTM LB (Laboratory Tests) domain. Two sets of lab parameters exist in ADLBC/ADLBH. One set contains the standardized lab value from the LB domain and the second set contains change from previous visit relative to normal range values.

In some of the summaries the derived end-of-treatment visit (AVISITN=99) is also presented. The ADLBC and ADLBH datasets were split based on the values of the indicated variable. Note that this splitting was done to reduce the size of the resulting datasets and to demonstrate split datasets and not because of any guidance or other requirement to split these domains.

ADLBHY - Laboratory Results Hy's Law Analysis Data

ADLBHY contains one record per lab test code per sample, per subject for the Hy's Law based analysis parameters. ADLBHY is derived from the ADLBC (Laboratory Results Chemistry Analysis Data) analysis dataset. It contains derived parameters based on Hy's law.

ADADAS - ADAS-COG Data

ADADAS contains analysis data from the ADAS-Cog questionnaire, one of the primary efficacy endpoints. It contains one record per subject per parameter (ADAS-Cog questionnaire item) per VISIT. Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows.

ADCIBC - CIBC Data

ADCIBC contains analysis data from the from CIBIC+ questionnaire, one of the primary efficacy endpoints. It contains one record per subject per VISIT. Note that for all records, PARAM='CIBIC Score'. Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows.

ADNPIX - NPI-X Item Analysis Data

ADNPIX contains one record per subject per parameter (NPI-X questionnaire item, total score, and mean total score from Week 4 through Week 24) per analysis visit (AVISIT). The analysis visits (represented by AVISIT and AVISITN) are derived from days between assessment date and randomization date and based on the visit windows that were specified in the statistical analysis plan (SAP).

Submission of Programs

Description

The sponsor has provided all programs for analysis results. They are all created on a Linux platform using R version 4.2.1.

List of Analysis Dataset Programs

The following table contains the list of programs that were used to generate the analysis datasets in Pilot 3. It shows the program file name, the analysis dataset name and the label of the analysis dataset.

Program Name	Analysis Dataset Name	Analysis Dataset Label
ad_adsl.R	adsl.xpt	Subject Level Analysis Dataset
ad_adas.R	adas.xpt	ADAS-Cog Analysis Dataset
ad_adlb.R ad_adlbc.R ad_adlbh.R ad_adlbhy.R	adlb.xpt	Lab Blood Chemistry Analysis Dataset Lab Hematology Analysis Dataset Lab Hy's Law Analysis Dataset
ad_adae.R	adae.xpt	Adverse Events Analysis Dataset
ad_adtte.R	adtte.xpt	AE Time to 1 st Derm. Event Analysis

Analysis Output Programs

Not Applicable. This pilot project only submits programs for analysis datasets.

Pilot 3 Installation and Usage

To install and execute the analysis dataset R programs, follow all of the procedures below. Ensure that you note the location of where you downloaded the Pilot 3 eCTD submission files. For demonstration purposes, the procedures below assume the transfer has been saved to this location:

C:\pilot3.

In addition, create a new directory to hold the unpacked Pilot 3 ADaM programs and files. For demonstration purposes, the procedures below assume the new directory is this location:

C:\pilot3-files.

Installation of R and Optional Software

Download and install R 4.2.1 for Windows from <https://cran.r-project.org/bin/windows/base/old/4.2.1/R-4.2.1-win.exe>. While optional, it is also recommended to view this Pilot 3 within the RStudio IDE.

You can download RStudio for Windows by visiting <https://www.rstudio.com/products/rstudio/download/#download>.

Installation of R Packages

A minimum set of R packages are required to ensure the Pilot 3 analysis dataset files are successfully unpacked and the custom package environment used for the application is replicated correctly. The first packages to install are the `remotes` and `pkglite` packages:

```
install.packages(c("remotes", "pkglite"))

# install version 0.16.0 of the renv
package:
remotes::install_version("renv",
version = "0.16.0")
```

ℳ Note

The console may display a warning message about Rtools being required to build R packages. However the packages required by the Shiny application will not require custom compilation involving other languages like C++, hence the Rtools utility is not required for the application.

Extract Application Bundle

Use the `pkglite` package to unpack the Shiny application bundle `r1pkg.txt` within the Pilot 2 eCTD submission transfer. This file is located in the following relative path within the eCTD transfer directory:

```
m5\datasets\rconsortiumpilot2\analysis\adam\programs\r1pkg.txt
```

Enter the following command in the R console to extract the Shiny application files to the destination directory.

```
pkglite::unpack(
input =
"C:/pilot3/m5/datasets/rconsortiumpilot3/analysis/adam/programs
/r1pkg.txt",
output = "C:/pilot3-files"
)
```

The console will display messages of unpacking and writing files to the destination directory. Note that the procedure creates a sub-directory called `pilot3wrappers` in the destination directory. Take note of that particular directory path on your system, as you will use this in the remaining procedures. In this example, the directory is located in the following path:

```
C:\pilot3-files\pilot3wrappers
```

Initialize R Package Environment for ADaM generation

The dependencies for the ADaM generation are managed by the `renv` R package management

system. To bootstrap the customized R package library used to generate the analysis datasets, launch a new R session in the directory where you unpacked the application source files in the previous step. Use either of the following procedures depending on your R computing environment:

RStudio

Create a new RStudio Project within the `pilot3wrappers` directory:

1. Select `File -> New Project`
2. In the Create Project dialog box, choose **Existing Directory**
3. In the Create Project from Existing Directory dialog box, click the **Browse** button and navigate to the `pilot3wrappers` directory.
4. Once the location has been confirmed, click the **Create Project** button.

RStudio will refresh the window and automatically install the `renv` package into the project directory. To complete the process of restoring the pilot R packages, run the following command in the R console:

```
renv::restore(prompt = FALSE)
```

The package installation procedure may take a few minutes or longer depending on internet bandwidth.

Console

Launch a new R session in the `pilot3wrappers` directory of the unpacked application directory. By default, the R Gui interface on Windows will launch a new R session in your default Windows home directory (typically the **Documents** folder). Perform the following steps to ensure R is launched in the proper directory.

ℹ Note

The procedure below assumes R 4.2.1 has been installed in a default location. If you are unsure of the full path to the R GUI executable on your system, you can find the location on your system by performing the following steps:

1. Open the Windows Start Menu and expand to show all applications.
2. Navigate to the R entry and expand the section such that all R program entries are visible.
3. Right-click the R x64 4.2.1 entry and select `More -> Open file location`.
4. A new folder window will open with the shortcut R x64 4.2.1 highlighted. Right-click this entry and select **Properties**
5. In the Properties window, copy the path specified in the **Target** text field. The portion of the text in quotations gives the full path to the `Rgui.exe` location on your system.

1. Open the Windows Powershell program by searching for Windows Powershell in the Windows Start menu.
2. Change the current directory to the `pilot2wrappers` directory by running the following command (substitute the `pilot3-files` location for your appropriate directory as needed):

```
Set-Location -Path "C:\pilot3-files\pilot3wrappers"
```

3. Launch the Windows R GUI in this session by running the following command:

```
C:\"Program Files"\R\R-4.2.1\bin\x64\Rgui.exe
```

The R GUI will launch and automatically install the `renv` package into the project directory. To complete the process of restoring the pilot R packages, run the following command in the R console:

```
renv::restore(prompt = FALSE)
```

The package installation procedure may take a few minutes or longer depending on internet bandwidth.

Analysis Datasets generated from Pilot 3

Upon completion of package installation, you may import the ADaM data sets contained in the eCTD transfer, which were generated using R in this Pilot. The data files are located in the following relative path within the eCTD transfer directory:

```
m5\datasets\rconsortiumpilot3\analysis\adam\datasets
```

Run the following command in the R console (substitute the `pilot3` location for your appropriate directory as needed):

```
Pilot3wrappers::set_data_path("C:/pilot3/m5/datasets/rconsortiumpilot3/analysis/adam/datasets")
```

Executing the R code to reproduce the Analysis Datasets

After importing the analysis datasets generated from Pilot 3, you may now run the R code, which were developed to reproduce the Analysis Datasets for further review. The R programs are located in the following relative path within the eCTD transfer directory:

```
m5\datasets\rconsortiumpilot3\analysis\adam\programs
```

To reproduce the analysis datasets used to generate the outputs in Pilot 1, rerun the following programs :

Program Name	Analysis Dataset Name	Analysis Dataset Label
ad_adsl.R	adsl.xpt	Subject Level Analysis Dataset
ad_adas.R	adas.xpt	ADAS-Cog Analysis Dataset
ad_adlb.R ad_adlbc.R ad_adlbh.R ad_adlbhy.R	adlb.xpt	Lab Blood Chemistry Analysis Dataset Lab Hematology Analysis Dataset Lab Hy's Law Analysis Dataset
ad_adae.R	adae.xpt	Adverse Events Analysis Dataset
ad_adtte.R	adtte.xpt	AE Time to 1 st Derm. Event Analysis

