Analysis Data Reviewer's Guide

R Consortium

R Submission Pilot 3

ADRG Template Version 2019-07-18

Analysis Data Reviewer's Guide

Contents

1. Introduction

1.1 Purpose

This document provides context for the analysis datasets and terminology that benefit from additional explanation beyond the Data Definition document (define.xml). In addition, this document provides a summary of ADaM conformance findings.

1.2 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM Implementation Guide Version 3.1.2 SDTM Version 1.2
SDTM Controlled Terminology	CDISC SDTM Controlled Terminology, 2022-12-16
ADaM	ADaM-IG v1.1 ADaM v2.1
ADaM Controlled Terminology	CDISC ADaM Controlled Terminology, 2022-06-24
Data Definitions	Define-XML v2.0
Medical Events Dictionary	MedDRA version 8.0

1.3 Source Data Used for Analysis Dataset Creation

The ADaM datasets were derived from SDTM version 1.2. For traceability, the SDTM is publicly available at the PHUSE Github Repository :

https://github.com/cdisc-org/sdtm-adam-pilot-project/tree/master/updated-pilot-submission-package/900172/m5/datasets/cdiscpilot01/tabulations/sdtm

Which can be traced back to the original CDISC SDTM & ADaM Pilot Project.

https://github.com/cdisc-org/sdtm-adam-pilot-project

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: CDISCPilot1

Protocol Title: Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease.dummy

The reference documents can be found at

https://github.com/cdisc-org/sdtm-adam-pilot-project/blob/master/updated-pilot-submission-package/900172/m5/53-clin-stud-rep/535-rep-effic-safety-stud/5351-stud-rep-contr/cdiscpilot01/cdiscpilot01.pdf

2.2 Protocol Design in Relation to ADaM Concepts

2.3 Objectives:

The objectives of the study were to evaluate the efficacy and safety of transdermal xanomeline, 50cm and 75cm, and placebo in subjects with mild to moderate Alzheimer's disease.

2.4 Methodology:

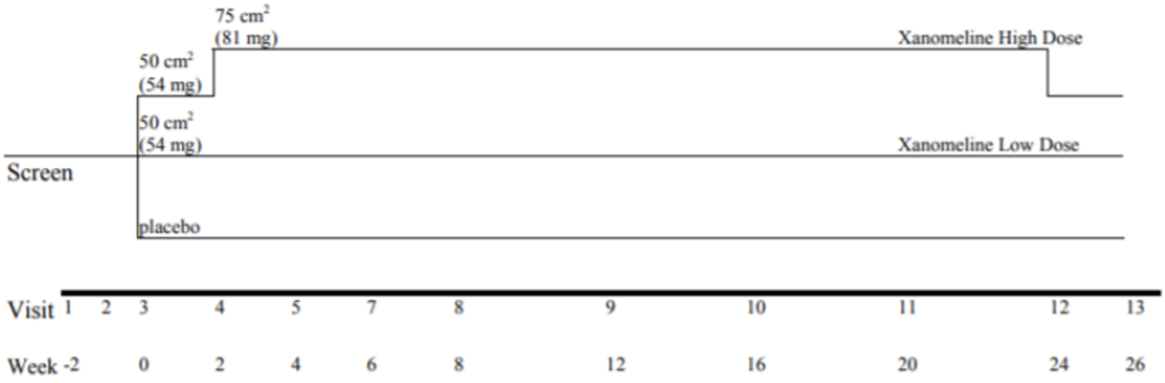
This was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study.

Subjects were randomized equally to placebo, xanomeline low dose, or xanomeline high dose. Subjects applied 2 patches daily and were followed for a total of 26 weeks.

2.5 Number of Subjects Planned:

300 subjects total (100 subjects in each of 3 groups)

Study schema:



3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Core Variables

Core variables are those that are represented across all/most analysis datasets.

Variable Name	Variable Description
STUDYID	Study Identifier
USUBJID	Unique Subject Identifier
SUBJID	Subject Identifier for the Study
SITEID	Study Site Identifier
SITEGR1	Pooled Site Group 1
TRTSDT	Date of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
AGE	Age

Variable Name	Variable Description
AGEGR1	Pooled Age Group 1
AGEGR1N	Pooled Age Group 1 (N)
RACE	Race
RACEN	Race (N)
SEX	Sex
SAFFL	Safety Population Flag
ITTFL	Intent-To-Treat Population Flag
EFFFL	Efficacy Population Flag
COMP24FL	Completers of Week 24 Population Flag
DSRAEFL	Discontinued due to AE?

3.2 Treatment Variables

ARM versus TRT01P

Are the values of ARM equivalent in meaning to values of TRT01P?

Yes.

ACTARM versus TRT01A

If TRT01A is used, then are the values of ACTARM equivalent to values of TRT01A?

Not applicable - ACTARM is not used.

Use of ADaM Treatment Variables in Analysis

Are both planned and actual treatment variables used in analysis?

Yes. Planned treatment variables are used for study population and efficacy analyses, whilst actual treatment variables are used for the safety analysis. All

subjects received the treatment arm to which they were randomised and so the planned treatment is equivalent to the actual treatment for all subjects.

Use of ADaM Treatment Grouping Variables in Analysis

Are both planned and actual treatment grouping variables used in analysis?

Not applicable - treatment grouping variables are not used.

3.3 Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more analysis datasets?

Yes

Were unscheduled visits used in any analyses?

Yes

3.4 Imputation/Derivation Methods

For ASTDT in ADAE, this date was converted to numeric SAS date from AE.AESTDTC. If the day component is missing, a value of '01' is used. If both the month and day are missing no imputation is performed. See define.xml.

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

There were no datasets that required splitting due to size constraints.

4.2 Data Dependencies

Analysis Dataset	Dependent on Following Analysis Datasets
ADAE	ADSL
ADTTE	ADSL, ADAE
ADLBC	ADSL
ADADAS	ADSL

4.3 Intermediate Datasets

No intermediate datasets were created for this trial.

5. Analysis Dataset Descriptions

5.1 Overview

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, ADAE, ADTTE, ADADAS, ADLBC.

5.2 Analysis Datasets

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
ADSL - Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			x		One record per subject
ADADAS - ADAS-COG Analysis Dataset	BASIC DATA STRUCTURE	x			x	One or more records per subject per analysis parameter per analysis timepoint
ADAE - Adverse Events Analysis Dataset	OCCURRENCE DATA STRUCTURE		x			One record per subject per adverse event

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
ADLBC - Analysis Dataset Lab Blood Chemistry	BASIC DATA STRUCTURE		x			One or more records per subject per analysis parameter per analysis timepoint
ADTTE - AE Time To 1st Derm. Event Analysis	BASIC DATA STRUCTURE	x	x			One or more records per subject per analysis parameter per analysis timepoint

5.2.1 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)

5.2.2 ADADAS - ADAS-COG Analysis Dataset

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.

5.2.3 ADAE - Adverse Events Analysis Dataset

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.

5.2.4 ADLBC - Analysis Dataset Lab Blood Chemistry

ADLBC contains one record per lab analysis parameter, per time point, per subject. ADLBC contains lab chemistry parameters and these data are derived from the SDTM LB (Laboratory Tests) domain. Two sets of lab parameters exist in ADLBC. One set contains the standardised 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.

5.2.5 ADTTE - AE Time To 1st Derm. Event Analysis

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".

6. Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks?
  - Yes, Version of CDISC ADaM Validation Checks and software used: Pinnacle 21® Community 4.0.2
- Were the ADaM datasets evaluated in relation to define.xml?
  - Yes
- Was define.xml evaluated?
  - Yes

6.2 Issues Summary

Check ID	Diagnostic Message	Dataset	Count (Issue Rate)	Explanation
AD1012	Secondary custom variable is present but its primary variable is not present	ADSL	1 (50.00%)	This is a Sponsor Extension to the ADaM Model. The VISNUMEN [End of Trt Visit (Vis 12 or Early Term.)] variable is a integer variable which is not related to any character variable.

6.3 QC Findings and Common Issues

In this Pilot 3 study, our focus was to create ADaMs based on Pilot 1 where after ADaM generation we compared them against the analysis datasets used in Pilot 1 as a QC step. With these comparisons we listed the QC Findings with explanations as to why these findings exist. We also came across common issues throughout the ADaM generation process, which could be helpful for improvements utilising the CDISC Pilot data in the future. More details can be found in the appendix (Appendix 2 and Appendix 3).

https://github.com/RConsortium/submissions-pilot3-adam/wiki/QC-Findings

https://github.com/RConsortium/submissions-pilot3-adam/wiki/Common-Issues

7. Submission of Programs

7.1. Description

The sponsor has provided all programs for analysis results. They are all created on a Linux platform using R version 4.2.3.

7.2. ADaM Programs

The following table contains the list of programs that generate the analysis datasets in the R Consortium R submission Pilot 3. It shows the program file name, the analysis

dataset name and the label of the analysis dataset. The recommended steps to execute the analysis results using R are described in the Appendix.

Program Name	Analysis Dataset Name	Analysis Dataset Label
adsl.r	adsl.xpt	Subject-Level Analysis Dataset
adadas.r	adas.xpt	ADAS-Cog Analysis
adlbc.r	adlb.xpt	Analysis Dataset Lab Blood Chemistry
adae.r	adae.xpt	Adverse Events Analysis Dataset
adtte.r	adtte.xpt	AE Time to 1st Derm. Event Analysis

7.3. Analysis Output Programs

The following table contains a list of programs that generate outputs used in the R consortium R submission Pilot 1. These outputs were rerun in Pilot 3 using the analysis datasets generated by the ADaM programs. It shows the program file names, the related outputs, the input datasets and variables used, and any data selection criteria that need to be applied per Pilot 1.

Program Name	**Output Name**	**Analysis Datasets & Variables**	**Selection Criteria**
tlf-demographic.r	tlf-demographic-pilot3.out	ADSL.STUDYID ADSL.TRT01P ADSL.ITTFL ADSL.AGE ADSL.AGEGR1 ADSL.RACE ADSL.HEIGHTBL ADSL.WEIGHTBL ADSL.BMIBL ADSL.MMSETOT	STUDYID== "CDISCPILOT01" Population: ADSL.ITTFL == "Y" Treatment Groups: ADSL.TRT01P Placebo Xanomeline Low Dose Xanomeline High Dose
tlf-primary.r	tlf-primary-pilot3.rtf	ADSL.TRT01P ADSL.USUBJID ADSL.EFFFL ADSL.ITTFL ADADAS.TRTP ADADAS.TRTPCD ADADAS.EFFFL ADADAS.ITTFL ADADAS.PARAMCD ADADAS.ANL01FL ADADAS.AVISIT ADADAS.AVISITN ADADAS.AVAL ADADAS.CHG	STUDYID== "CDISCPILOT01" Population: ADADAS.EFFFL == "Y" ADADAS.ITTFL == "Y" ADADAS.ANL01FL == "Y" Treatment Groups: ADSL.TRTP Placebo Xanomeline Low Dose Xanomeline High Dose Parameters: ADADAS.PARAMCD == "ACTOT

Program Name	**Output Name**	**Analysis Datasets & Variables**	**Selection Criteria**
tlf-efficacy.r	tlf-efficacy-pilot3.rtf	ADSL.STUDYID ADSL.USUBJID ADSL.ITTFL ADLBC.TRTP ADLBC.TRTPN ADLBC.PARAMCD ADLBC.AVISITN ADLBC.BASE ADLBC.AVAL ADLBC.CHG	STUDYID== "CDISCPILOT01" Population: ADSL.ITTFL == "Y" & ADLBC.TRTPN in (0, 81) & ADLBC.PARAMCD == "GLUC" & ADLBC.AVISITN is not missing Treatment Groups: ADLBC.TRTPN Placebo Xanomeline High Dose
tlf-kmplot.r	tlf.kmplot-pilot3.pdf	ADSL.STUDYID ADSL.USUBJID ADSL.SAFFL ADSL.TRT01A ADTTE.STUDYID ADTTE.USUBJID ADTTE.PARAMCD ADTTE.AVAL ADTTE.CNSR	STUDYID== "CDISCPILOT01" Population: ADSL.SAFFL == "Y" Treatment Groups: ADSL.TRT01A Placebo Xanomeline Low Dose Xanomeline High Dose Parameters: ADTTE.PARAMCD == "TTDE"

For reference, below is a description of the analysis programs utilized and outputs generated in Pilot 1.

Program Name	Output Table Number	Title
tlf-demographic.r	Table 14-2.01	Summary of Demographic and Baseline Characteristics
tlf-primary.r	Table 14-3.01	Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
tlf-efficacy.r	Table 14-3.02	ANCOVA of Change from Baseline at Week 20
tlf-kmplot.r	Figure 14-1	KM plot for Time to First Dermatologic Event: Safety population

7.4. Proprietary R Packages

Proprietary R Package	Package version	Analysis Package Description
Pilot3	0.0.1	The objective of this utility package is to support the R Consortium R submission Pilot 3 Project. It contains all utility functions that were used in the generation of the deliverables: formatting of ADaM variables and analysis results summarize mixed model analysis formatting of layouts

7.5. Open-source R Analysis Packages

Open-source R Analysis Package	Package version	Analysis Package Description
admiral	0.10.1	A toolbox for programming Clinical Data Interchange Standards Consortium (CDISC) compliant Analysis Data Model (ADaM) datasets in R. ADaM datasets are a mandatory part of any New Drug or Biologics License Application submitted to the United States Food and Drug Administration (FDA). Analysis derivations are implemented in accordance with the "Analysis Data Model Implementation Guide" (CDISC Analysis Data Model Team, 2021, <https://www.cdisc.org/standards/foundational/adam/adamig-v1-3-release-package>).
cowplot	1.1.1	Provides various features that help with creating publication-quality figures with 'ggplot2', such as a set of themes, functions to align plots and arrange them into complex compound figures, and functions that make it easy to annotate plots and or mix plots with images. The package was originally written for internal use in the Wilke lab, hence the name (Claus O. Wilke's plot package). It has also been used extensively in the book Fundamentals of Data Visualization.

diffdf	1.0.4	Functions for comparing two data.frames against each other. The core functionality is to provide a detailed breakdown of any differences between two data.frames as well as providing utility functions to help narrow down the source of problems and differences.
dplyr	1.1.0	A fast, consistent tool for working with data frame like objects, both in memory and out of memory.
emmeans	1.8.5	Obtain estimated marginal means (EMMs) for many linear, generalized linear, and mixed models. Compute contrasts or linear functions of EMMs, trends, and comparisons of slopes. Plots and other displays. Least-squares means are discussed, and the term "estimated marginal means" is suggested, in Searle, Speed, and Milliken (1980) Population marginal means in the linear model: An alternative to least squares means, The American Statistician 34(4), 216-221 <doi:10.1080/00031305.1980.10483031>.
ggplot2	3.4.1	A system for 'declaratively' creating graphics, based on "The Grammar of Graphics". You provide the data, tell 'ggplot2' how to map variables to aesthetics, what graphical primitives to use, and it takes care of the details.
haven	2.5.2	Import foreign statistical formats into R via the embedded 'ReadStat' C library, <https://github.com/WizardMac/ReadStat>.
lubridate	1.9.2	Functions to work with date-times and time-spans: fast and user friendly parsing of date-time data, extraction and updating of components of a date-time (years, months, days, hours, minutes, and seconds), algebraic manipulation on date-time and time-span objects. The 'lubridate' package has a consistent and memorable syntax that makes working with dates easy and fun.
metacore	0.1.2	Create an immutable container holding metadata for the purpose of better enabling programming activities and functionality of other packages within the clinical programming workflow.

metatools	0.1.5	Uses the metadata information stored in 'metacore' objects to check and build metadata associated columns.
pharmaRTF	0.1.4	Enhanced RTF wrapper written in R for use with existing R tables packages such as 'Huxtable' or 'GT'. This package fills a gap where tables in certain packages can be written out to RTF, but cannot add certain metadata or features to the document that are required/expected in a report for a regulatory submission, such as multiple levels of titles and footnotes, making the document landscape, and controlling properties such as margins.
pilot3	0.1.1	Utilities for the Pilot 3 Submission to the FDA. See section 7.4.
r2rtf	1.0.1	Create production-ready Rich Text Format (RTF) table and figure with flexible format.
rtables	0.6.0	Reporting tables often have structure that goes beyond simple rectangular data. The 'rtables' package provides a framework for declaring complex multi-level tabulations and then applying them to data. This framework models both tabulation and the resulting tables as hierarchical, tree-like objects which support sibling sub-tables, arbitrary splitting or grouping of data in row and column dimensions, cells containing multiple values, and the concept of contextual summary computations. A convenient pipe-able interface is provided for declaring table layouts and the corresponding computations, and then applying them to data.
stringr	1.5.0	A consistent, simple and easy to use set of wrappers around the fantastic 'stringi' package. All function and argument names (and positions) are consistent, all functions deal with "NA"'s and zero length vectors in the same way, and the output from one function is easy to feed into the input of another.

tidyr	1.3.0	Tools to help to create tidy data, where each column is a variable, each row is an observation, and each cell contains a single value. 'tidyr' contains tools for changing the shape (pivoting) and hierarchy (nesting and 'unnesting') of a dataset, turning deeply nested lists into rectangular data frames ('rectangling'), and extracting values out of string columns. It also includes tools for working with missing values (both implicit and explicit).
Tplyr	1.1.0	A traceability focused tool created to simplify the data manipulation necessary to create clinical summaries.
visR	0.3.1	To enable fit-for-purpose, reusable clinical and medical research focused visualizations and tables with sensible defaults and based on graphical principles as described in: "Vandemeulebroecke et al. (2018)" <doi:10.1002/pst.1912>, "Vandemeulebroecke et al. (2019)" <doi:10.1002/psp4.12455>, and "Morris et al. (2019)" <doi:10.1136/bmjopen-2019-030215>.
xportr	0.2.0	Tools to build CDISC compliant data sets and check for CDISC compliance.

8. Directory Structure

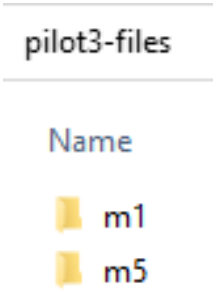
```
m5
└── datasets
    └── rconsortiumpilot3
        ├── tabulations
        │   ├── sdtm
        │   │   ├── blankcrf.pdf
        │   │   ├── define-v1-updated-html.xsl
        │   │   ├── define.pdf
        │   │   ├── define.xml
        │   │   ├── ae.xpt                        # SDTM datasets in XPT format
        │   │   ├── cm.xpt
        │   │   ├── dm.xpt
        │   │   ├── ds.xpt
        │   │   ├── ex.xpt
        │   │   ├── lb.xpt
        │   │   ├── mh.xpt
        │   │   ├── qs.xpt
        │   │   ├── relrec.xpt
        │   │   ├── sc.xpt
        │   │   ├── se.xpt
        │   │   ├── suppae.xpt
        │   │   ├── suppdm.xpt
        │   │   ├── suppds.xpt
        │   │   ├── supplb.xpt
        │   │   ├── sv.xpt
        │   │   ├── ta.xpt
        │   │   ├── te.xpt
        │   │   ├── ti.xpt
        │   │   ├── ts.xpt
        │   │   ├── tv.xpt
        │   │   └── vs.xpt
        └── analysis
            ├── adam
            │   ├── programs
            │   │   ├── adadas.r
            │   │   ├── adae.r
            │   │   ├── adlbc.r
            │   │   ├── adsl.r
            │   │   ├── adtte.r
            │   │   ├── tlf-demographic.r
            │   │   ├── tlf-efficacy.r
            │   │   ├── tlf-kmplot.r
            │   │   ├── tlf-primary.r
            │   │   └── renv.lock
            │   ├── datasets
            │   │   ├── adrg.pdf
            │   │   ├── ADaM - Pilot 3.xlsx
            │   │   ├── define.xml
            │   │   ├── adadas.xpt
            │   │   ├── adae.xpt
            │   │   ├── adlbc.xpt
            │   │   ├── adsl.xpt
            │   │   ├── adtte.xpt
            │   │   └── define2-0-0.xsl
```

Appendix

Appendix 1: Pilot 3 Installation and Usage

To install and execute the 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 and tlf programs and files. For demonstration purposes, the procedures below assume the new directory is this location: `C:\pilot3-files`, where the unpacked files are shown as the m1 and m5 directories.



1. Installation of R and R Studio

Download and install R 4.2.3 for Windows from https://cran.r-project.org/bin/windows/base/old/4.2.3/ . Then download and run the R-4.2.3-win.exe file. Also download RStudio for Windows by visiting https://dailies.rstudio.com/version/2023.03.1+446.pro1/

2. Create a new R Studio project within the pilot3-files directory

- Open R Studio
- Select File -> New Project
- In the Create Project dialog box, choose Existing Directory
- In the Create Project from Existing Directory dialog box, click the Browse button and navigate to the `C:\pilot3-files` directory.
- Once the location has been confirmed, click the Create Project button.

3. Installation of R Packages

A minimum set of R packages are required to ensure the Pilot 3 analysis programs are successfully run and the custom package environment used for the application is replicated correctly.

1. The first package to install is the {remotes} package:

```
Unset
install.packages("remotes")
```

Notes :

1) *The console may display a warning message about Rtools being required to build R packages. However the Rtools utility is not required to run the programs in this pilot 3 study.*
2) *If you receive a warning showing "*`cannot open URL 'https://cran.rstudio.com/src/contrib/PACKAGES'`*", this is due to the default R Studio option 'Use secure download method for HTTP'. In R Studio, go to Tools → Global Options → Packages, then uncheck the 'Use secure download method for HTTP' option, then retry installation.*

2. Then, install the {renv} package, version 0.17.0:

```
Unset
remotes::install_version("renv", version = "0.17.0")
```

Note :

1) *If not already set, please verify that the working directory is already set to the project folder.*
   - *i.* `getwd()`
   - *ii.* *If not pointing to root project directory then do :* `setwd("~/pilot3-files")`

3. Move the 'renv-lock.txt' to the root project directory and rename to 'renv.lock' :

```
Unset
./pilot3-files/m5/datasets/rconsortiumpilot3/analysis/adam/programs/renv-lock.t
xt --> ./pilot3-files/renv.lock
```

4. Run the code below, then select option 1 :

```
Unset
renv::init()


# This project already has a lockfile. What would you like to do?
#
# 1: Restore the project from the lockfile.
# 2: Discard the lockfile and re-initialize the project.
# 3: Activate the project without snapshotting or installing any packages.
# 4: Abort project initialization.
#
# Selection: 1
```

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

Note :

1) *If running {renv} for the first time, you may get a Welcome message describing the renv folder structure and its components. It will also list the packages that will be installed from the renv.lock file. At the end it will ask you if you want to proceed. Select 'y'.*

```
Unset
Do you want to proceed? [y/N]: y
```

2) *If after selecting option 1, you receive a warning such as "`Warning: error downloading 'https://packagemanager.posit.co/cran/2023-03-15/bin/windows/contrib/4.2/PACKAGES.rds' ['CreateProcess' failed to run`*

'C:\WINDOWS\SYSTEM32\curl.exe --config "C:\Users\laxamanj\AppData\Local\Temp\RtmpQrN0y7\renv-download-config-2e24149c3b5f"']", then do

a) run the code below and select option 3 :

```
Unset
renv::init()


# This project already has a lockfile. What would you like to do?
#
# 1: Restore the project from the lockfile.
# 2: Discard the lockfile and re-initialize the project.
# 3: Activate the project without snapshotting or installing any packages.
# 4: Abort project initialization.
#
# Selection: 3
```

Upon this selection you may get this message below, which can be ignored during this set-up. Continue on as you will install the packages needed to run the project analyses in the subsequent steps :

```
Unset
Restarting R session...

* Project '~/pilot3_renv' loaded. [renv 0.17.0]
* One or more packages recorded in the lockfile are not installed.
* Use `renv::status()` for more details.
```

b) Open the .Rprofile : `C:/pilot3-files/.Rprofile` and ensure these 2 lines are there :

```
Unset
Sys.setenv(RENV_DOWNLOAD_FILE_METHOD = "libcurl")
source("renv/activate.R")
```

c) Restart the R Session (again you may ignore the message as mentioned in step a).

d) Then run code below, then select 'y':

```
Unset
renv::restore()

# Do you want to proceed? [y/N]: y
```

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

5. Upon completion of installing packages using {renv}, please restart your R session.
6. Install the {pilot3} package running the code below.

```
Unset
# Option 1
renv::install("RConsortium/submissions-pilot3-utilities")
```

Note :

1) A second option to install the {pilot3} package is using this code.

```
Unset
# Option 2
# install Pilot 3 package
remotes::install_github(
  repo = "RConsortium/submissions-pilot3-utilities",
  host = "api.github.com",
  upgrade = "never",
  force = TRUE,
  dependencies = TRUE
)
```

You may get a warning such as below,

```
Unset
Warning messages:
1: In untar2(tarfile, files, list, exdir, restore_times) :
  skipping pax global extended headers
2: In untar2(tarfile, files, list, exdir, restore_times) :
  skipping pax global extended headers
```

where the solution is to install Rtools. As aforementioned, the Rtools utility is not required to run the programs in this pilot 3 study. You may ignore this warning.

4. **Set the paths to run the analysis programs**

INPUT path: to rerun the analysis programs, define the path variable

- Path for SDTM data: path$sdtm
- Path to ADaM specifications : path$adam

OUTPUT path: to save the analysis datasets and results, define the path variable

- Path for ADaM data: path$adam
- Path for output TLFs: path$output.

All these paths must be defined before executing the analysis programs. For example:

```
Unset
# Modify path to the sdtm, adam and output location
# Output saved in current folder
path <- list(
  sdtm = "~/pilot3-files/m5/datasets/rconsortiumpilot3/tabulations/sdtm",
  adam = "~/pilot3-files/m5/datasets/rconsortiumpilot3/analysis/adam/datasets",
  output = "."
)
```

5. **Execute analysis program**

To reproduce analysis results, rerun the following programs:

- "adsl.r"
- "adae.r"
- "adadas.r"
- "adlbc.r"
- "adtte.r"
- "tlf-demographic.r"
- "tlf-efficacy.r"
- "tlf-kmplot.r"
- "tlf-primary.r"

Appendix 2 : Common Issues

Common Issues

1. Package issue tracking

1.1 Package issues

- `haven::read_xpt()` Some attributes are dropped after using `haven::write_xpt()` `haven::read_xpt()`, e.g., type, length. to do: further check
- `xportr::xportr_length()` `NA_character_` is considered as length 2 - issue resolved on Dec 14, 2022 to do: to be incorporated in pilot3

1.2 Potential improvement

- `metatools::build_from_derived()` https://github.com/pharmaverse/metatools/issues/46 Not urgent feature but nice to have - especially when `define.xml` is not in good quality

2. Knowledge sharing

Summary of similarities and differences between packages, to help user identify the best tool that suits the need. Maybe this could go to Bayer SAS2R catalog in the future,

`metatools` vs `xportr`

- `metatools::set_variable_labels()` vs `xportr::xportr_label()`

`xportr` vs `haven`

- `xportr::xportr_write()` vs `haven::write_xpt()`

`diffdf` vs `arsenal`

- `diffdf::diffdf()` vs `arsenal::comparedf()`

Appendix 3 : QC Findings

QC Findings

Please add any discrepencies you found between the original ADaM datasets from the CDISC Pilot and the ones we've programmed in R below.

ADSL

The R-generated ADSL matches the original ADSL from CDISC pilot data, besides the following mismatches: * Subject 01-702-1082 has a missing value for BMIBLGR1 in the R-generated ADSL, whilst BMIBLGR1 = "<25" in the original ADSL. This is an issue with the original ADSL, as this subject's BMI at baseline (BMIBL) is missing and therefore the subject shouldn't be assigned a BMI at baseline group.

ADAE

The R-generated ADAE matches the original ADAE from CDISC pilot data, besides the following mismatches: There is an issue with the original CDISC pilot dataset. ADURN is blank, where AESEQ is (5, 6, 7, 8) for the original CDISC dataset for Subject below:

```
> adae_orig %>%
    filter(USUBJID=='01-716-1418') %>%
    select(USUBJID,TRTSDT,ASTDT,AENDT,ADURN,ADURU,AESEQ)

# A tibble: 10 × 7
   USUBJID     TRTSDT     ASTDT      AENDT      ADURN ADURU AESEQ
   <chr>       <date>     <date>     <date>     <dbl> <chr> <dbl>
 1 01-716-1418 2013-05-05 2013-05-05 2013-05-07     3 DAY       1
 2 01-716-1418 2013-05-05 2013-05-05 NA            NA NA        2
 3 01-716-1418 2013-05-05 2013-05-05 2013-05-07     3 DAY       3
 4 01-716-1418 2013-05-05 2013-05-07 NA            NA NA        4
 5 01-716-1418 2013-05-05 2013-07-01 2013-09-26    NA NA        5
 6 01-716-1418 2013-05-05 2013-07-01 2013-10-04    NA NA        6
 7 01-716-1418 2013-05-05 2013-07-01 2013-09-26    NA NA        7
 8 01-716-1418 2013-05-05 2013-07-01 2013-10-04    NA NA        8
 9 01-716-1418 2013-05-05 2013-09-26 2013-11-11    47 DAY       9
10 01-716-1418 2013-05-05 2013-09-26 2013-11-11    47 DAY      10
```

Because it seems the original SDTM.AE.AESTDTC was missing Day, where it seems the original ADAE derivation for ADURN was probably using this date instead of the imputed date. Because day is missing in AESTDTC, ADURN can't derive days.

```
> ae %>% filter(USUBJID=='01-716-1418') %>% select(USUBJID,AESTDTC,AESEQ) %>% arrange(AESEQ)
# A tibble: 10 × 3
   USUBJID     AESTDTC    AESEQ
   <chr>       <chr>      <dbl>
 1 01-716-1418 2013-05-05     1
 2 01-716-1418 2013-05-05     2
 3 01-716-1418 2013-05-05     3
 4 01-716-1418 2013-05-07     4
 5 01-716-1418 2013-07        5
 6 01-716-1418 2013-07        6
 7 01-716-1418 2013-07        7
 8 01-716-1418 2013-07        8
 9 01-716-1418 2013-09-26     9
10 01-716-1418 2013-09-26    10
```

but the same records, derived in the Pilot 3 dataset do show a calculation since we are using the imputed

ASTDT, per the define (ADURN=AENDT-ASTDT+1).

```
# AE.AESTDTC, converted to a numeric SAS date. Some events with partial dates are
# imputed in a conservative manner. If the day component is missing, a value of '01'
# is used. If both the month and day are missing no imputation is performed as these
# dates clearly indicate a start prior to the beginning of treatment. There are no
# events with completely missing start dates.

> adae0 %>%
  filter(USUBJID=='01-716-1418') %>%
  select(USUBJID,TRTSDT,ASTDT,AESTDTC,AENDT,AEENDY,ADURN,ADURU,AESEQ)

# A tibble: 10 × 9
   USUBJID     TRTSDT     ASTDT      AESTDTC    AENDT      AEENDY ADURN ADURU AESEQ
   <chr>       <date>     <date>     <chr>      <date>      <dbl> <dbl> <chr> <dbl>
 1 01-716-1418 2013-05-05 2013-05-05 2013-05-05 2013-05-07      3     3 DAY       1
 2 01-716-1418 2013-05-05 2013-05-05 2013-05-05 NA             NA    NA NA        2
 3 01-716-1418 2013-05-05 2013-05-05 2013-05-05 2013-05-07      3     3 DAY       3
 4 01-716-1418 2013-05-05 2013-05-07 2013-05-07 NA             NA    NA NA        4
 5 01-716-1418 2013-05-05 2013-07-01 2013-07    2013-10-04    153    96 DAY       6
 6 01-716-1418 2013-05-05 2013-07-01 2013-07    2013-10-04    153    96 DAY       8
 7 01-716-1418 2013-05-05 2013-07-01 2013-07    2013-09-26    145    88 DAY       5
 8 01-716-1418 2013-05-05 2013-07-01 2013-07    2013-09-26    145    88 DAY       7
 9 01-716-1418 2013-05-05 2013-09-26 2013-09-26 2013-11-11    191    47 DAY       9
10 01-716-1418 2013-05-05 2013-09-26 2013-09-26 2013-11-11    191    47 DAY      10
```

This latter approach should be the correct approach.

Due to this, we have outlined the expected differences here :

```
> diffdf(adae, adae_orig, keys = c("STUDYID", "USUBJID", "AESEQ"))
Differences found between the objects!

A summary is given below.

There are columns in BASE and COMPARE with differing attributes !!
All rows are shown in table below
```

1. ADURN values will be populated in Pilot 3 (i.e. under `BASE`), following the latter derivation approach (i.e. ADURN=AENDT-ASTDT+1) for Subject 01-716-1418 where AESEQ is (5, 6, 7, 8) specified in define.

```
All rows are shown in table below

  ============================================================
   VARIABLE    STUDYID       USUBJID    AESEQ  BASE  COMPARE
  ------------------------------------------------------------
    ADURN    CDISCPILOT01  01-716-1418    5     88    <NA>
    ADURN    CDISCPILOT01  01-716-1418    6     96    <NA>
    ADURN    CDISCPILOT01  01-716-1418    7     88    <NA>
    ADURN    CDISCPILOT01  01-716-1418    8     96    <NA>
  ------------------------------------------------------------
```

2. ADURU should be set to 'DAYS' (i.e. under `BASE`) instead of 'DAY' when ADURN is not missing. Updated in Pilot 3 define.

```
First 10 of 718 rows are shown in table below
```

```
=============================================================
 VARIABLE    STUDYID       USUBJID     AESEQ  BASE  COMPARE
-------------------------------------------------------------
  ADURU    CDISCPILOT01  01-701-1015     3    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1023     1    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1023     4    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1047     1    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1047     2    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1097     2    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1097     3    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1097     5    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1097     6    DAYS    DAY
  ADURU    CDISCPILOT01  01-701-1097     7    DAYS    DAY
-------------------------------------------------------------
```

ADLBC

The R-generated ADLBC matches the original ADLBC from CDISC pilot data, besides the following mismatches:

Three variables from R-generated ADLBC have class date while the same variables are numeric in the CDISC ADLBC. We opted to keep the date class in our R-generated ADLB.

```
> diffdf(adlbc, qc_adlbc, keys = c("STUDYID", "USUBJID", "AVISIT", "LBSEQ"))
Differences found between the objects!

A summary is given below.

There are columns in BASE and COMPARE with different classes !!
All rows are shown in table below

==================================
 VARIABLE  CLASS.BASE  CLASS.COMP
----------------------------------
    ADT        Date      numeric
  TRTEDT       Date      numeric
  TRTSDT       Date      numeric
----------------------------------
```

ADADAS

The R-generated ADADAS matches original adadas from CDISC pilot data, except for the records where `PARAMCD=ACTOT, DTYPE=LOCF`. This is an issue from the CDISC ADADAS.

- CDISC SDTM/qs: 818 records for `QSTESTCD=ACTOT`
- CDISC ADaM/adadas: 1040 records for `PARAMCD=ACTOT`, 799 (directly from qs, **should be 818**) + 241 imputed records (`DTYPE=LOCF`)
- adadas generated by R: 1040 records for `PARAMCD=ACTOT`, 818 (directly from qs) + 222 imputed records (`DTYPE=LOCF`)

Take a detailed example USUBJID="01-701-1294"

CDISC qs:

```
> qs %>% filter(QSTESTCD=="ACTOT") %>%
+   select(USUBJID, QSSEQ, VISIT, QSTESTCD, QSTEST,QSSTRESN) %>%
+   filter(USUBJID=="01-701-1294")
```

```
# A tibble: 4 × 6
  USUBJID     QSSEQ VISIT     QSTESTCD QSTEST                QSSTRESN
  <chr>       <dbl> <chr>     <chr>    <chr>                    <dbl>
1 01-701-1294  5015 BASELINE  ACTOT    ADAS-COG(11) Subscore        9
2 01-701-1294  5030 WEEK 8    ACTOT    ADAS-COG(11) Subscore       14
3 01-701-1294  5045 WEEK 12   ACTOT    ADAS-COG(11) Subscore        6
4 01-701-1294  5060 RETRIEVAL ACTOT    ADAS-COG(11) Subscore        9
```

CDISC adadas:

For the record with QSSEQ=5045 and AVISIT=Week 8, DTYPE is populated as LOCF , but this record is directly from qs dataset, not imputed.

```
> qc_adadas %>% filter(PARAMCD=="ACTOT") %>%
+   select(USUBJID, QSSEQ, PARAMCD, AVISITN, AVISIT, VISIT, AVAL, DTYPE, ANL01FL, ADT, ADY) %>%
+   arrange(USUBJID, AVISITN) %>% filter(USUBJID=="01-701-1294")
# A tibble: 5 × 11
  USUBJID     QSSEQ PARAMCD AVISITN AVISIT   VISIT      AVAL DTYPE  ANL01FL ADT          ADY
  <chr>       <dbl> <chr>     <dbl> <chr>    <chr>     <dbl> <chr>  <chr>   <date>     <dbl>
1 01-701-1294  5015 ACTOT         0 Baseline BASELINE      9 ""     "Y"     2013-03-24     1
2 01-701-1294  5030 ACTOT         8 Week 8   WEEK 8       14 ""     "Y"     2013-05-22    60
3 01-701-1294  5045 ACTOT         8 Week 8   WEEK 12      14 "LOCF" ""      2013-06-14    83
4 01-701-1294  5045 ACTOT        16 Week 16  WEEK 12      14 "LOCF" "Y"     2013-06-14    83
5 01-701-1294  5060 ACTOT        24 Week 24  RETRIEVAL     9 ""     "Y"     2013-10-08   199
```

adadas generated by R:

DTYPE is not LOCF for the record with QSSEQ=5045 and AVISIT=Week 8, as this record is directly from qs.

```
> adadas %>% filter(PARAMCD=="ACTOT") %>%
+   select(USUBJID, QSSEQ, PARAMCD, AVISITN, AVISIT, VISIT, AVAL, DTYPE, ANL01FL, ADT, ADY) %>%
+   arrange(USUBJID, AVISITN) %>% filter(USUBJID=="01-701-1294")
# A tibble: 5 × 11
  USUBJID     QSSEQ PARAMCD AVISITN AVISIT   VISIT      AVAL DTYPE  ANL01FL ADT          ADY
  <chr>       <dbl> <chr>     <dbl> <chr>    <chr>     <dbl> <chr>  <chr>   <date>     <dbl>
1 01-701-1294  5015 ACTOT         0 Baseline BASELINE      9 ""     "Y"     2013-03-24     1
2 01-701-1294  5030 ACTOT         8 Week 8   WEEK 8       14 ""     "Y"     2013-05-22    60
3 01-701-1294  5045 ACTOT         8 Week 8   WEEK 12       6 ""     ""      2013-06-14    83
4 01-701-1294  5045 ACTOT        16 Week 16  WEEK 12       6 "LOCF" "Y"     2013-06-14    83
5 01-701-1294  5060 ACTOT        24 Week 24  RETRIEVAL     9 ""     "Y"     2013-10-08   199
```

The same issue occurred for other subjects and resulted in the following discrepancies:

```
Not all Values Compared Equal
All rows are shown in table below

  ============================
   Variable  No of Differences
  ----------------------------
     AVAL            47
     CHG             47
     PCHG            47
    DTYPE            19
  ----------------------------
```

In the CDISC ADADAS, there are 19 subjects whose records have the incorrect DTYPE=LOCF value instead of the expected missing DTYPE, resulting in 47 records having incorrect AVAL/CHG/PCHG values for these subjects.

```
> diff <- diffdf(adadas, qc_adadas, keys = c("USUBJID", "PARAMCD", "AVISIT", "ADT"))
> count(diff$VarDiff_AVAL, USUBJID)
# A tibble: 19 × 2
   USUBJID         n
   <chr>       <int>
 1 01-701-1294     2
 2 01-701-1302     2
 3 01-703-1076     3
 4 01-704-1065     3
 5 01-704-1120     3
 6 01-705-1292     1
 7 01-705-1310     3
 8 01-708-1347     3
 9 01-709-1102     3
10 01-709-1259     2
11 01-710-1045     3
12 01-710-1278     3
13 01-710-1300     3
14 01-710-1315     2
15 01-714-1068     3
16 01-715-1107     2
17 01-716-1373     3
18 01-718-1172     2
19 01-718-1250     1
```

ADTTE

The R-generated ADTTE matches original ADTTE from CDISC pilot data except for minor SAS format discrepancies. Since this adtte was generated in R compared to SAS formats, the columns Type & Length in the define should be sufficient enough to describe the attributes of these variables.

```
> diffdf(adtte, qc_adtte, keys = c("STUDYID", "USUBJID", "PARAMCD", "SRCDOM", "STARTDT"))
Differences found between the objects!

A summary is given below.

There are columns in BASE and COMPARE with differing attributes !!
First 10 of 20 rows are shown in table below

  ================================================
   VARIABLE  ATTR_NAME   VALUES.BASE  VALUES.COMP
  ------------------------------------------------
     AGE     format.sas     NULL          3
    AGEGR1   format.sas     NULL         $5
   AGEGR1N   format.sas     NULL          3
   EVNTDESC  format.sas     NULL         $25
    PARAM    format.sas     NULL         $32
   PARAMCD   format.sas     NULL         $4
     RACE    format.sas     NULL         $32
    RACEN    format.sas     NULL          3
    SAFFL    format.sas     NULL         $1
     SEX     format.sas     NULL         $1
  ------------------------------------------------
```

Label discrepancies

In pilot3, variable labels were updated per ADaM IG 1.1, which caused some discrepancies with original CDISC pilot data label.

Dataset	Variable	CDISC pilot data label	Pilot3 label
ADAE	ADURN	Analysis Duration (N)	AE Duration (N)
	ADURU	Analysis Duration Units	AE Duration Units
	AOCCFL	1st Occurrence of Any AE Flag	1st Occurrence within Subject Flag
ADADAS	ANL01FL	Analysis Record Flag 01	Analysis Flag 01
	ITTFL	Intent-to-Treat Population Flag	Intent-To-Treat Population Flag
ADTTE	SRCDOM	Source Data	Source Domain