

Analysis Data Reviewer's Guide

R Consortium R Submission Pilot 2

R Consortium

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1 Introduction

1.1 Purpose

The Analysis Data Reviewer's Guide (ADRG) provides specific instructions for executing a Shiny application created with the R-language for viewing analysis results and performing custom subpopulation analysis based on the data sets and analytical methods used in the R Consortium R Submission Pilot 1. This document provides context for the analysis datasets and terminology that benefit from additional explanation beyond the Data Definition document (define.xml), as well as a summary of ADaM conformance findings. Appendix 1 provides detailed procedures for installing and configuring a local R environment to view the included Shiny application.

1.2 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM v1.4/ SDTM IG v3.1.2
ADaM	ADaM v2.1/ ADaM IG v1.0
Controlled Terminology	SDTM CT 2011-12-09 ADaM CT 2011-07-22
Data Definitions	define.xml v2.0
Medications Dictionary	MedDRA v8.0

1.3 Source Data Used for Analysis Dataset Creation

The ADaMs we used to regenerate the outputs were the PHUSE CDISC Pilot replication ADaMs following ADaM IG v1.0. The ADaM dataset and its corresponding SDTM data set are publicly available at the PHUSE Github Repository (https://github.com/phuse-org/phuse-scripts/blob/master/data/adam/TDF_ADaM_v1.0.zip, https://github.com/phuse-org/phuse-scripts/blob/master/data/sdtm/TDF_SDTM_v1.0%20.zip)

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

The reference documents can be found at <https://bitbucket.cdisc.org/projects/CED/repos/sdtm-adam-pilot-project/browse/updated-pilot-submission-package/900172/>

2.2 Protocol Design in Relation to ADaM Concepts

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.

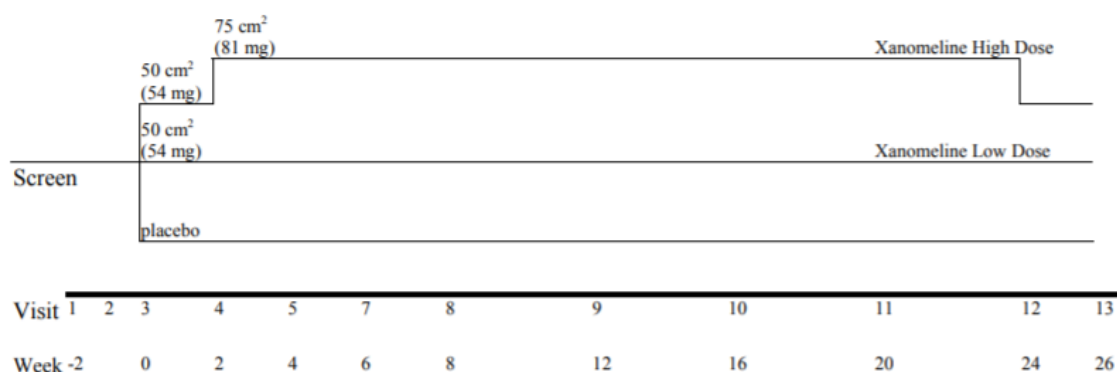
Methodology:

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.

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
USUBJID	Unique subject identifier
STUDYID	Study Identifier
SITEID	Study Site Identifier
TRTSDT	Date of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
AGE	Age
AGEGR1	Pooled Age Group 1
AGEGR1N	Pooled Age Group 1 (N)
SEX	Sex
RACE	Race
RACEN	Race (N)

3.2 Treatment Variables

- Are the values of ARM equivalent in meaning to values of TRTxxP? Yes
- Are the values of TRTxxA equivalent in meaning to values of TRTxxP? Yes
- Are both planned and actual treatment variables used in analyses? Yes

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

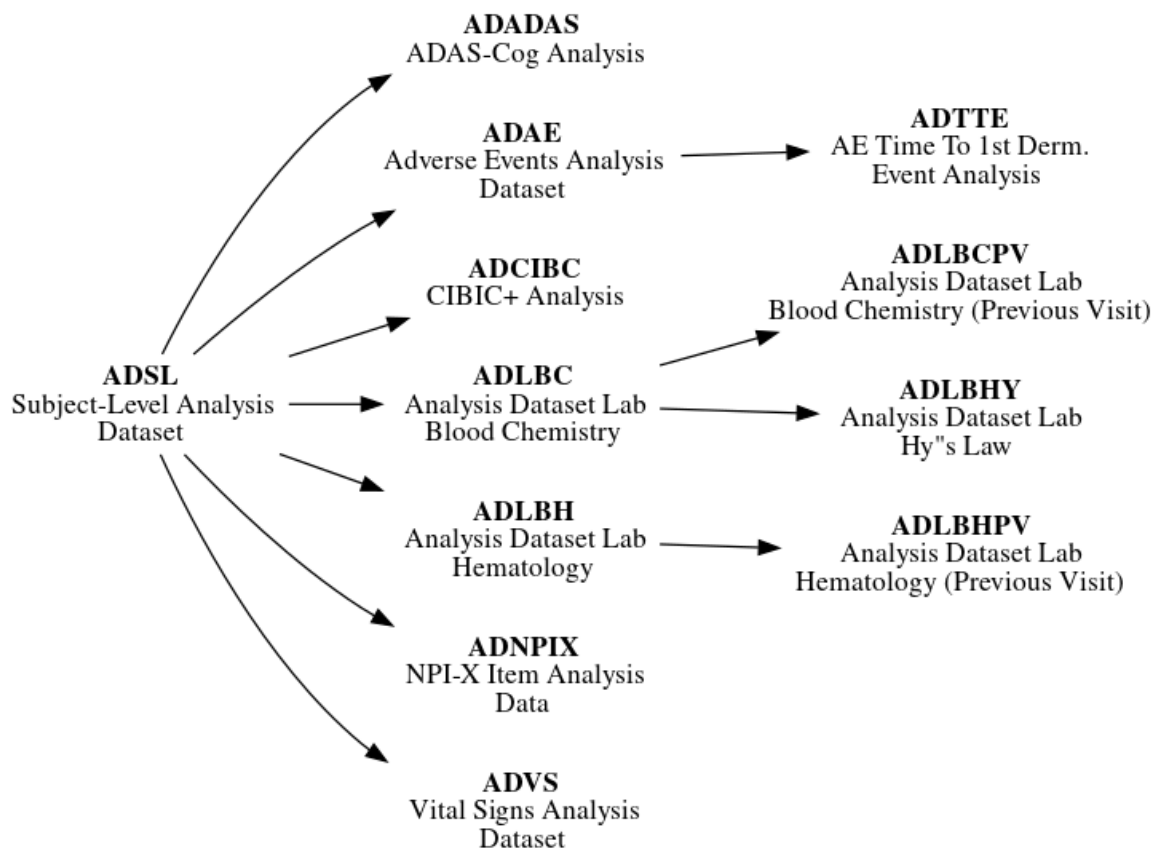
- Was windowing used in one or more analysis datasets? Yes
- Were unscheduled visits used in any analyses? Yes

3.4 Imputation/Derivation Methods

Not applicable

4 Analysis Data Creation and Processing Issues

4.1 Data Dependencies



Dataset	Label	Class	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
ADSL	Subject Level Analysis Dataset	ADSL			x		One observation per subject
ADAE	Adverse Events Analysis Dataset	ADAM OTHER		x			One record per subject per adverse event
ADTTE	Time to Event Analysis Dataset	BASIC DATA SSTRUCTURE		x			One observation per subject per analysis parameter
ADLBC	Analysis Dataset Lab Blood Chemistry	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit
ADLBPCV	Analysis Dataset Lab Blood Chemistry (Previous Visit)	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit
ADLBH	Analysis Dataset Lab Hematology	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit
ADLBHPV	Analysis Dataset Lab Hematology (Previous Visit)	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit
ADLBHY	Analysis Dataset Lab Hy's Law	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit
ADADAS	ADAS-Cog Analysis	BASIC DATA SSTRUCTURE	x			x	One record per subject per parameter per analysis visit per analysis date
ADCIBC	CIBIC+ Analysis	BASIC DATA SSTRUCTURE	x				One record per subject per parameter per analysis visit per analysis date
ADNPIX	NPI-X Item Analysis Data	BASIC DATA SSTRUCTURE	x				One record per subject per parameter per analysis visit
ADVS	Vital Signs Analysis Dataset	BASIC DATA SSTRUCTURE		x			One record per subject per parameter per analysis visit

5 Analysis Dataset Description

5.1 Overview

The analysis codes and outputs submitted in Pilot 1 and the Shiny application modules in Pilot 2 cover part of the efficacy and safety objectives of the initial protocol. More specifically, 4 analysis outputs are included, covering demographics analysis, primary efficacy endpoint analysis, and safety analysis.

5.2 Analysis Datasets

The following table provides detailed information for each analysis dataset included in the Pilot 1 submission. The Shiny application for this pilot utilizes the following analysis datasets: ADSL, ADTTE, ADADAS, ADLBC.

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 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.

5.2.3 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”.

5.2.4 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.

5.2.5 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.

5.2.6 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.

5.2.7 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.

5.2.8 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).

6 Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks? Yes, Version of CDISO ADaM Validation Checks and software used: Pinnacle 21 Enterprise version 4.1.1
- Were the ADaM datasets evaluated in relation to define.xml? Yes
- Was define.xml evaluated? Yes

6.2 Issues Summary

Rule ID	Dataset(s)	Diagnostic Message	Severity	Explanation
AD0258	ADAE	Record key from ADaM ADAE is not traceable to SDTM.AE (extra ADAE recs)	Error	There are derived records in ADAE, this has no impact on the analysis.
AD0018	ADLBC, ADLBPCPV, ADLBH, ADLBHPV, ADVS, ADCIBC, ADLBNPIX	Variable label mismatch between dataset and ADaM standard	Error	The label for ANL01FL in these datasets are 'Analysis Record Flag 01', this is in conformance with ADaM IG 1.0, this is an issue in P21 checks, and has no impact on the analysis.
AD0320	ADSL	Non-standard dataset label	Error	The label for ADSL is 'ADSL', this has no impact on the analysis

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 4.1.2.

7.2 ADaM Programs

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

7.3 Analysis Output Programs

The Shiny application included in this pilot follows a different structure than a traditional collection of analysis programs such as those included in the Pilot 1 eCTD transfer. The application is developed with a modular approach and assembled with the [golem](#) R package for enhanced code organization. A description of the primary scripts used within the application is given in the table below. The recommended steps to execute the Shiny application are described in Appendix 2.

Program Name	Purpose
app.R	Facilitate execution of Shiny application in a local R session or deployed on a server
app_teal.R	Assemble the application modules for use with the Teal package
tm_t_demographic.R	Shiny module for demographic and baseline characteristics analysis
tm_g_kmplot.R	Shiny module for Kaplan-Meier plot of time to first dermatologic event
tm_t_primary.R	Shiny module for primary endpoint analysis ADAS Cog (11)
tm_t_efficacy.R	Shiny module for primary endpoint analysis Glucose (mmol/L)

For reference, below is a description of the analysis programs utilized 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 Analysis Packages

Package	Title	Version
pilot2wrappers	A Shiny application for executing interactive displays and analyses.	0.1.0

7.5 Open-source R Analysis Packages

The following table lists the open-source R packages used to create and execute the Shiny application in this pilot. A listing of the open-source packages used for the Pilot 1 submission can be found in the ADRG for Pilot 1.

Package	Title	Version
config	Manage Environment Specific Configuration Values	0.3.1
cowplot	Streamlined Plot Theme and Plot Annotations for 'ggplot2'	1.1.1
dplyr	A Grammar of Data Manipulation	1.0.9
emmeans	Estimated Marginal Means, aka Least-Squares Means	1.7.2
ggplot2	Create Elegant Data Visualisations Using the Grammar of Graphics	3.3.5
glue	Interpreted String Literals	1.6.2
golem	A Framework for Robust Shiny Applications	0.3.1
haven	Import and Export 'SPSS', 'Stata' and 'SAS' Files	2.4.3
htmltools	Tools for HTML	0.5.2
huxtable	Easily Create and Style Tables for LaTeX, HTML and Other Formats	5.4.0
magrittr	A Forward-Pipe Operator for R	2.0.3
markdown	Render Markdown with the C Library 'Sundown'	1.1
pkgload	Simulate Package Installation and Attach	1.2.4
reactable	Interactive Data Tables Based on 'React Table'	0.2.3
rtables	Reporting Tables	0.5.1.2
shiny	Web Application Framework for R	1.7.1
stringr	Simple, Consistent Wrappers for Common String Operations	1.4.0
teal	Exploratory Web Apps for Analyzing Clinical Trials Data	0.11.1
teal.data	Data model for teal applications	0.1.1
tibble	Simple Data Frames	3.1.6
tidyr	Tidy Messy Data	1.1.4
tippy	Add Tooltips to 'R markdown' Documents or 'Shiny' Apps	0.1.0
Tplyr	A Grammar of Clinical Data Summary	0.4.4
utils	The R Utils Package	4.2.0
visR	Clinical Graphs and Tables Adhering to Graphical Principles	0.2.0

7.6 List of Output Programs

Not Applicable. This pilot project displays analysis output as a Shiny application where the R programs described in the **Analysis Output Programs** as a whole produce the Shiny

application.

8 Directory Structure

Study datasets and the Shiny application supportive files are organized in accordance to Study Data Technical Conformance Guide.

```
|— m1
|   |— us
|       |— cover-letter.pdf
|— m5
    |— datasets
        |— rconsortiumpilot2
            |— analysis
                |— adam
                    |— datasets
                        |— adadas.xpt
                        |— adlbc.xpt
                        |— adsl.xpt
                        |— adtte.xpt
                        |— define2-0-0.xsl
                        |— define.xml
                    |— programs
                        |— r1pkg.txt
```

Directory	Index	Description
module	1	Refers to the eCTD module in which clinical study data is being submitted.
datasets	2	Resides within the module folder as the top-level folder for clinical study data being submitted for m5.
rconsortiumpilot2	3	Study identifier or analysis type performed
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders
adam	5	Contains subfolders for ADaM datasets and corresponding software programs
datasets	6	Contains ADaM datasets, analysis data reviewer's guide, analysis results metadata and define files
programs	7	Contains software programs for analysis datasets and Shiny application

Appendix 1: Pilot 2 Shiny Application Installation and Usage

To install and execute the Shiny application, follow all of the procedures below. Ensure that you note the location of where you downloaded the Pilot 2 eCTD submission files. For demonstration purposes, the procedures below assume the transfer has been saved to this location: C:\pilot2.

In addition, create a new directory to hold the unpacked Pilot 2 Shiny application files. For demonstration purposes, the procedures below assume the new directory is this location: C:\pilot2_files.

8.1 Installation of R and Optional Software

Download and install R 4.1.2 for Windows from <https://cran.r-project.org/bin/windows/base/old/4.1.2/R-4.1.2-win.exe>. While optional, It is also recommended to view the Shiny application within the RStudio IDE. You can download RStudio for Windows by visiting <https://www.rstudio.com/products/rstudio/download/#download>.

8.2 Installation of R Packages

A minimum set of R packages are required to ensure the Pilot 2 Shiny application 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 0.15.2 of the renv package:
remotes::install_version("renv", version = "0.15.2")
```

i 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.

8.3 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:/pilot2/m5/datasets/rconsortiumpilot2/analysis/adam/programs/r1pkg.txt",
  output = "C:/pilot2_files"
)
```

The console will display messages of unpacking and writing files to the destination directory. Note that the procedure creates a sub-directory called `pilot2wrappers` 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:\pilot2_files\pilot2wrappers
```

8.4 Initialize R Package Environment for Shiny Application

The dependencies for the Shiny application are managed by the `renv` R package management system. To bootstrap the customized R package library used for the Shiny application, 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:

8.4.1 RStudio

Create a new RStudio Project within the `pilot2wrappers` 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 `pilot2wrappers` directory. 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.

8.4.2 R Console

Launch a new R session in the `pilot2wrappers` 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.

Note

The procedure below assumes R 4.1.2 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 4.1.2 entry and select **More -> Open file location**.
4. A new folder window will open with the shortcut R x64 4.1.2 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 `pilot2_files` location for your appropriate directory as needed):

```
Set-Location -Path "C:\pilot2_files\pilot2wrappers"
```

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

```
C:\"Program Files"\R\R-4.1.2\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.

8.5 Update Shiny Application Configuration

The Shiny application needs one configuration update in order to import the ADaM data sets contained in the eCTD transfer. The data files are located in the following relative path within the eCTD transfer directory:

```
m5\datasets\rconsortiumpilot2\analysis\adam\datasets
```

Run the following command in the R console (substitute the `pilot2` location for your appropriate directory as needed):

```
pilot2wrappers::set_data_path("C:/pilot2/m5/datasets/rconsortiumpilot2/analysis/adam/datasets")
```

8.6 Launch Shiny Application

To run the Shiny application, enter the following command in the R console:

```
golem:::run_dev()
```

8.7 Application Usage Guide

The Shiny application contains 5 tabs, with the first table **App Information** selected by default. The relationship between the other application tabs and previously submitted analysis from Pilot 1 are described in the table below:

Application Tab	Pilot 1 Output
Demographic Table	Table 14-2.01 Summary of Demographic and Baseline Characteristics
KM plot for TTDE	Figure 14-1 Tiem to Dermatologic Event by Treatment Group
Primary Table	Table 14-3.01 Primary Endpoint Analysis: ADAS Cog(11) - Change from Baseline to Week 24 - LOCF
Efficacy Table	Table 14-3.02 Primary Endpoint Analysis: Glucose (mmol/L) - Summary at Week 20 - LOCF

The default display in the analysis tabs match with the outputs submitted in Pilot 1. The Shiny application enables subpopulation analysis using *Filters*. Within any tab, there are three sections related to Filters on the right-hand side of the page: **Active Filter Summary**, **Active Filter Variables**, and **Add Filter Variables**

Active Filter Summary

	Obs	Subjects
ADSL	254/254	254/254

Active Filter Variables

ADSL

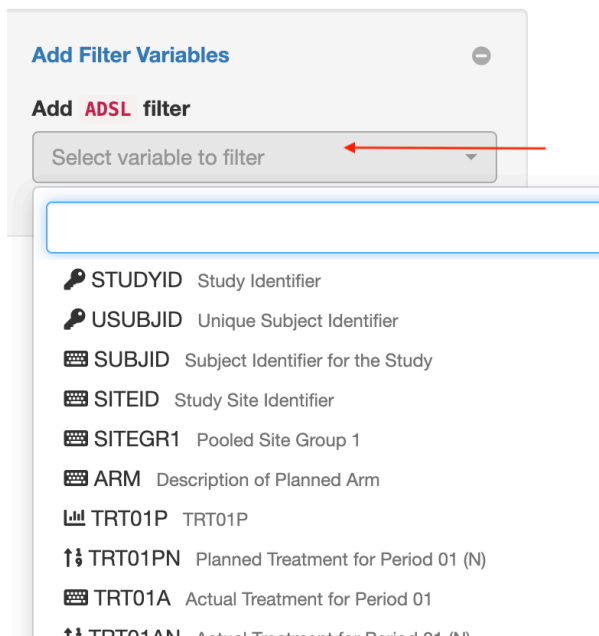
Add Filter Variables

Add ADSL filter

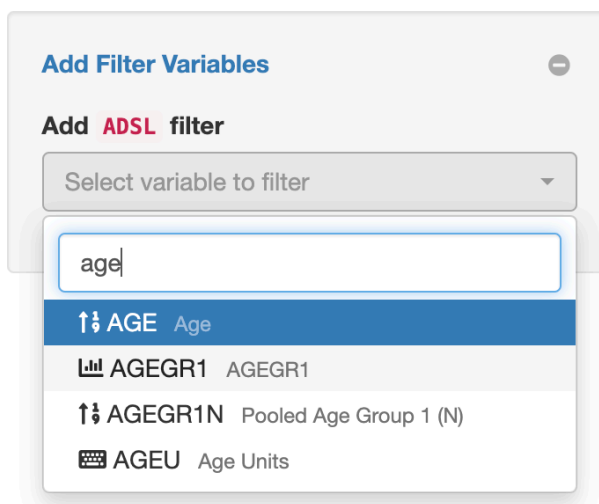
Select variable to filter

Analysis example of performing subpopulation analysis for an age group:

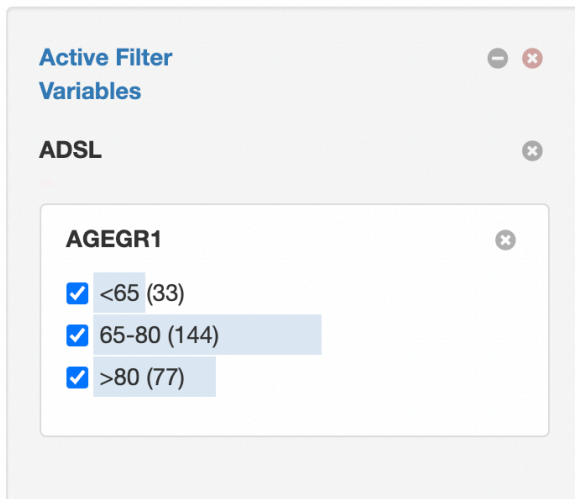
1. Within the **Add Filter Variables** widget, click the box with the placeholder **Select variables to filter**.



2. Scroll up/down or use the search bar to find the variable for subpopulation. Click the desired variable (**AGEYR1** in this example).



3. In the **Active Filter Variables** widget, the selected variable with its available categories or levels will display. In this example, **AGEYR1** in this example) is displayed with three categories. If the selected variable in the previous step is a continuous variable, then a slider will appear for selecting a range of values.



4. Select the target subpopulation (e.g. **>80**) and the analysis output displayed on the left hand side will be updated in real-time according to the selection, which in this example is equivalent to performing a filter on the **ADSL** data by **AGEGR1 == '>80'**.
5. In the Shiny application, the filters are considered as global and shared across the remaining analysis tabs. In this example, **AGEGR1 == '>80'** will be applied in other analysis tabs automatically, hence it is not necessary to manually perform the same filtering operation on the remaining tabs.