# Analysis Data Reviewer's Guide


## Sample Drug Company, Inc.

## Study AB1234

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. Also included are details regarding legacy analysis data conversion to ADaM.

## 1.2 Acronyms

| Acronym | Translation |
|---|---|
| aCRF | Annotated Case Report Form |
| ADaM | Analysis Dataset Model |
| ADRG | Analysis Data Reviewer's Guide |
| AED | Antiepileptic Drug |
| CSSRS | Columbia Suicide Severity Rating Scale |
| CSR | Clinical Study Report |
| DRM | Data Review Meeting |
| eCRF | Electronic Case Report Form |
| eDT | Electronic Data Transfer (e.g. central lab data, ECG vendor data, PK data, etc.) |
| EDV | Early Discontinuation Visit |
| IG | Implementation Guide |
| ILAE | International League Against Epilepsy |
| LTFU | long-term follow-up |
| NA | Not Applicable |
| PBO | Placebo |
| POS | partial onset seizure |
| SDTM | Study Data Tabulation Model |
| TAUG | Therapeutic Area User Guide |

## 1.3 Study Data Standards and Dictionary Inventory

| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | v1.2/IG 3.1.2 Amendment 1 |
| SDTM Controlled Terminology | 2016-09-30 |
| ADaM | v2.1/IG 1.0 |
| ADaM Controlled Terminology | 2016-09-30 |
| Data Definitions | define.xml v2.0 |
| TAUG (if applicable) | NA |
| Medications Dictionary | WHO Drug 2017 Q3 |
| Medical Events Dictionary | Initial: 20.1<br>Final: 20.1 |
| Other standards (optional) | NA |

## 1.4 Source Data Used for Analysis Dataset Creation

The ADaM datasets were derived from legacy analysis datasets. The datasets were derived from the final locked database. Please refer to the Legacy Data Conversion Plan and Report Appendix for additional details.

## 2. Protocol Description

## 2.1 Protocol Number and Title

Protocol Number: AB1234

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study to Evaluate the Efficacy and Safety of TEST DRUG in Subjects with Epilepsy

Protocol Versions:        Amendment 1 and Amendment 2
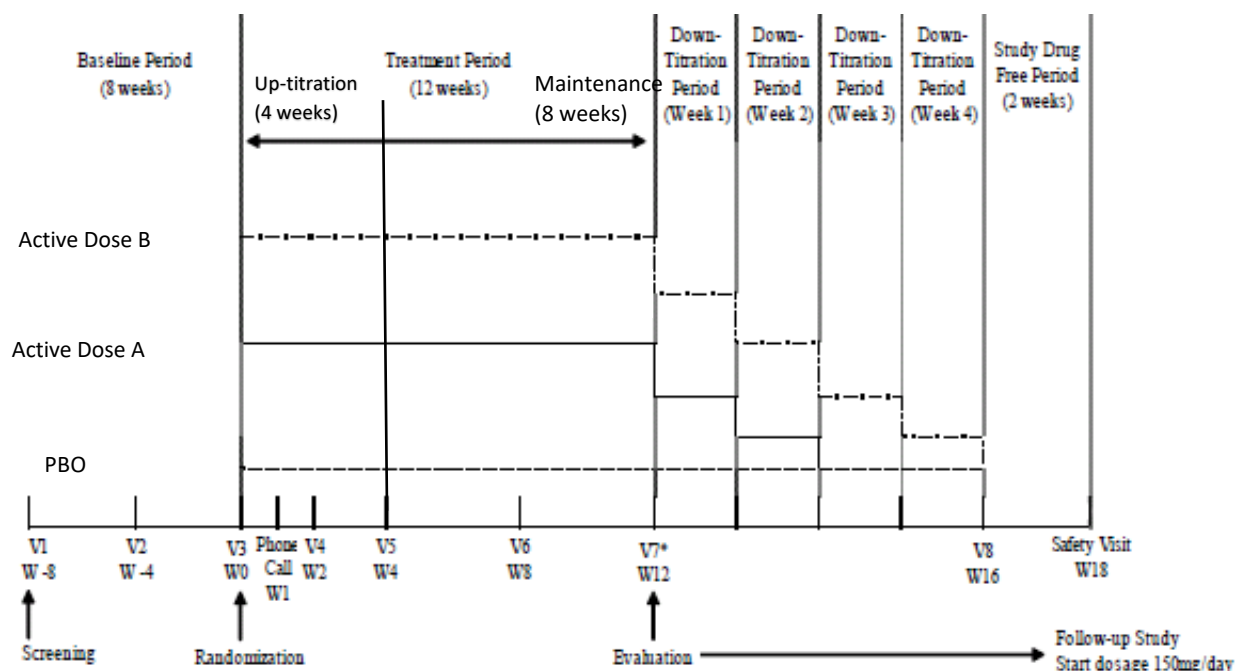
Amendment 1

1.  SAE procedures updated to implement FDA Final Rule requirements

2.  CSSRS added to address FDA requirement that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indicators

Amendment 2

1.  Protocol amended to include an additional secondary efficacy analysis – time to achieving sustained 50% responder status

## 2.2 Protocol Design in Relation to ADaM Concepts

This is a randomized, double-blind, PBO-controlled, multicenter, therapeutic confirmatory study evaluating 2 active doses of TEST DRUG. The subject population will be adults (≥16 years to 80 years) with refractory epilepsy. Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. There is a 4-week Down-Titration Period followed by a 2-week Study Drug Free Period for subjects not entering the LTFU study.



D=dose, V=visit, W=week

* Subjects with an EDV at any time during the Treatment Period should proceed through the 4-week Down-Titration Period and 2-week Study Drug Free Period

## 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 |
| SITEID | Study Site Identifier |

| Variable Name | Variable Description |
|---|---|
| COUNTRY | Country |
| TRT01P | Planned Treatment for Period 01 |
| SEX | Sex |
| AGE | Age |
| AGEU | Age Units |
| RACE | Race |
| SCRNFL | Screened Flag |
| RANDFL | Randomized Population Flag |
| SAFFL | Safety Population Flag |
| ITTFL | Intent-To-Treat Population Flag |
| PPROTFL | Per-Protocol Population Flag |
| DWNTITFL | Entered Down-Titration Period Flag |
| PSTTRTFL | Entered Post-Treatment Period Flag |
| RACEGR1 | Pooled Race Group 1 |
| AGEGR2 | Age Group 2 |
| REGION1 | Geographic Region 1 |
| REGION2 | Geographic Region 2 |
| SITEGR1 | Pooled Site Group 1 |
| WEIGHT | Weight |

## 3.2 Treatment Variables

ARM versus TRTxxP

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

Yes.

ACTARM versus TRTxxA

If TRTxxA is used, then are the values of ACTARM equivalent in meaning to values of TRTxxA?

Yes. TRT01A=TRT01P, the variable ACTARM is not kept in ADSL

Use of ADaM Treatment Variables in Analysis

Are both planned and actual treatment variables used in analyses?

No. Only planned treatment is used since all subjects were treated as planned during the study, with the exception of one dose described below.

Use of ADaM Treatment Grouping Variables in Analysis

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

No. The TR01PG1/TR01PG1N variables were used for all analyses that were broken out by treatment grouping.

## 3.3 Subject Issues that Require Special Analysis Rules

Subjects randomized in error – 001-00007, 013-00015, 024-00105, and 032-00214. These four subjects did not receive any doses of study medication and therefore are not included in the safety population.

Four subjects (004-00003, 019-00078, 045-00103, 048-00457) received an incorrect drug kit for the Treatment Period. The kit was the assigned treatment based on randomization. This was considered to be a conduct deviation.

Subject 025-00135 (randomized to PBO) received an incorrect drug kit (kit number 3021116) for the Treatment Period from 01Oct2013 through 29Oct2013. The kit was not of the assigned treatment; kit was for subjects randomized to ACTIVE DOSE B. This was considered to be an efficacy and conduct deviation. In dataset ADEX the dose for these days was identified as unknown.

## 3.4 Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more analysis datasets?

Yes. Subjects with an EDV that corresponded to a scheduled visit had the assessments from the EDV slotted to the appropriate scheduled visit.

Were unscheduled visits used in any analyses?

Yes. Unscheduled visits were used for last value in ADLB, ADVS and ADEG. See section 3.2.4 of SAP for last value rules.

## 3.5 Imputation/Derivation Methods

If date imputation was performed, were there rules that were used in multiple analysis datasets?

No. Imputation rules were applied to individual domains. See individual datasets in section 5.2 for any date imputation rules.

APHASE values are one of the following: Baseline, Treatment, or Safety Follow-up. There is only one APERIOD/APERIODC of 1/Treatment. Treatment has 2 subperiods: Treatment or Down-Titration.

# 4. Analysis Data Creation and Processing Issues

## 4.1 Split Datasets

No datasets were required to be split.

## 4.2 Data Dependencies

| Analysis Dataset | Dependent on these other Analysis Datasets |
|---|---|
| ADSZP, ADSZFR and ADTTE | ADSZD |
| ADEXD and ADEXS | ADEX |
| ADAE | ADEXD |

## 4.3 Intermediate Datasets

Intermediate datasets were not created.

# 5. Analysis Dataset Descriptions

## 5.1 Overview

Are data for screen failures, including data for run-in screening (for example, SDTM values of ARMCD='SCRNFAIL', or 'NOTASSGN') included in ADaM datasets?

Yes. Screen failure subjects are included in the following domains: ADSL, ADLB, and ADIE

Are data taken from an ongoing study?

No.

Do the analysis datasets support all protocol- and statistical analysis plan-specified objectives?

Yes.

## 5.2 Analysis Datasets

| Dataset<br>Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADSL<br><br>Subject Level Analysis Dataset | ADSL | | | X | | | One observation per subject. |
| ADAE<br><br>Adverse Events | OTHER | | X | | | | One record per subject per event |
| ADCM<br><br>Concomitant Medications | OTHER | | X | | | | One record per medication occurrences or dosing interval per ATC code per subject |
| ADCO<br><br>Comments | OTHER | | | X | | | One record per subject per comment |
| ADCSSRS<br><br>CSSRS | BDS | | X | | | | One record per subject per parameter category per parameter per visit |
| ADDV<br><br>Protocol Deviations | BDS | | X | | | | One record per subject per parameter category per parameter |
| ADEG<br><br>Electrocardiogram | BDS | | X | | | | One record per subject per parameter category per parameter per visit |

| Dataset Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADEPHIS Epilepsy History | BDS | | | X | | | One record per subject per parameter category per parameter per visit |
| ADEX Exposure | BDS | | X | | | | One record per subject per visit |
| ADEXD Daily Exposure | BDS | | X | | | | One record per subject per exposure day |
| ADEXS Exposure Summary | OTHER | | X | | | | One record per subject |
| ADGES Global Evaluation Scale | OTHER | X | | | | | One record per subject per parameter category per parameter per visit |
| ADHADS HADS | OTHER | X | | | | | One record per subject per parameter category per parameter per visit |
| ADIE Inclusion / Exclusion Criteria Not Met | BDS | | | X | | | One record per subject |

| Dataset Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADLB Laboratory Test Results | BDS | | X | | | | One record per subject per parameter category per parameter per visit |
| ADMDRES Medical Resource | BDS | X | | | | | One record per subject per parameter category per parameter per visit |
| ADMH Medical History | OTHER | | | X | | | One record per subject per event |
| ADPC Pharmacokinetic Concentration | BDS | | | | X | | One record per subject per parameter category per parameter per visit |
| ADPE Physical Examination | BDS | | X | | | | One record per subject per parameter category per parameter per visit |
| ADQOLIE QOLIE-31-P | OTHER | X | | | | | One record per subject per parameter category per parameter per visit |
| ADSPS Socio-Professional | OTHER | X | | | | | One record per subject per parameter category per parameter per visit |

| Dataset<br>Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADSV<br>Subject Visits | OTHER | | | X | | | One record per subject per visit |
| ADSZD<br>Daily Seizure Records | BDS | X | | | | | One record per subject per parameter category per parameter per visit |
| ADSZFR<br>Seizure Freedom | BDS | X | | | | X | One record per subject per parameter category per study period |
| ADSZP<br>Period Seizure | BDS | X | | | | X | One record per subject per parameter per visit |
| ADTTE<br>Time to nth Seizure | OTHER | X | X | | | X | One record per subject per parameter category per parameter per visit |
| ADVS<br>Vital Signs | BDS | | X | | | | One record per subject per parameter category per parameter per visit |

### 5.2.1   ADSL – Subject Level Analysis Dataset

Demographics information

In some countries, race is not allowed to be collected. In these instances, race is left missing and RACEGR1is set to the category of MISSING.

In some countries only year can be collected for birth date. In these cases, January 1 is used as the month and year for these subjects. BRTHDTF is populated as 'M' for these cases.

### 5.2.2   ADAE – Adverse Events

Date Imputation Rules

Start Date:

If only the month and year are specified then:

1. Use the 1st of the month if the month and year are not the same as the month and year of the first dose of study medication.

    OR

2. Use the date of first study medication if the month and year are the same as the first dose of study medications.

If only the year is specified then:

1. Use January 1 of that year if the year is not the same as the year of the first dose of study medication.

    OR

2. Use the date of first study medication if the year is the same as the year of the first dose of study medication.


If the start date is completely missing, then set the start date to the subject's first dose date of study medication


Stop Date:

If only the month and year are specified, then use the last day of the month.

If only the year is specified, then use December 31 of that year.

If the stop date is missing (not ongoing), then set the resolution date to the latest of the following dates as long as the AE start date is <= to the dates:

1.  The date of the last dose of study medication.
2.  The date of last contact from the termination CRF.
3.  The date of last scheduled or unscheduled visit.

### 5.2.3   ADCM – Concomitant Medications

Date Imputation Rules:

Start Date:

    If only the month and year are specified, then use the 1st of the month.

    If only the year is specified, then use January 1 of that year.

    If the start date is completely missing, then set the start date to the subject's birth date (after imputation for partial birth dates).

Stop Date:

    If only the month and year are specified, then use the last day of the month.

    If only the year is specified, then use December 31 of that year.

    If the stop date is missing (not ongoing), then set the resolution date to the latest of the following dates, depending on what is available on the CRF: 1) the date of last contact from the termination CRF, 2) the date of last scheduled or unscheduled visit, and 3) the date of last phone contact.

## 6.  Data Conformance Summary

### 6.1 Conformance Inputs

    Specify the software name and version for the analysis datasets

        Pinnacle 21 version 2.2.0

    Specify the version of the validation rules (i.e. CDISC, FDA) for the analysis datasets

        CDISC

    Specify the software name and version for the define.xml

        config-adam-1.0 xml

    Specify the version of the validation rules (i.e. CDISC, FDA) for the define.xml

        CDISC

### 6.2 Issues Summary

| Dataset | Diagnostic Message | Severity | Count | Explanation |
|---|---|---|---|---|
| ADAE | Neither AVAL nor AVALC are present in dataset | Error | 1 | Variables not needed for event analysis |
| ADPC | * TM is not a numeric variable | Error | 1 | LDOSETM is character variable |
| ADSL | TRT01P is present and TR01SDT is not present | Error | 4 | The 4 subjects randomized in error have TRT01P but no start date. |
| ADSL | TRT01P is present and TR01EDT is not present | Error | 4 | The 4 subjects randomized in error have TRT01P but no end date. |

| Dataset | Diagnostic Message | Severity | Count | Explanation |
|---------|-------------------|----------|-------|-------------|
| ADSL | Null value in variable marked as Required | Error | 2 | For variables AGE, AGEU and RACE - 2 subjects randomized in error are missing informed consent date so AGE cannot be calculated, RACE cannot be collected from subjects in France |
| ADSL | Expected variable is not present within dataset | Warning | 4 | TRTSEQP, TR01EDT, TRTSEQA, and TR01SDT variables not needed |

## 7. Submission of Programs

All SAS programs for analysis datasets and primary and secondary efficacy results are submitted.  They were all created on a SAS platform using version 9.3.  The internal reference date used to create dates in ADaM datesets is January 1, 1960.

### 7.1 ADaM Programs

| Program Name | Output | Macro Used |
|--------------|--------|------------|
| adsl.txt | adsl | attrib |
| adae.txt | adae | attrib, partdate |
| adcm.txt | adcm | attrib, partdate |
| adco.txt | adco | attrib |
| adcssrs.txt | adcssrs | attrib |
| addv.txt | addv | attrib |
| adeg.txt | adeg | attrib |
| adephis.txt | adephis | attrib |
| adex.txt | adex | attrib |
| adexd.txt | adexd | attrib |
| adexs.txt | adexs | attrib |
| adges.txt | adges | attrib |
| adhads.txt | adhads | attrib |

| Program Name | Output | Macro Used |
|---|---|---|
| adie.txt. | adie. | attrib |
| adlb.txt | adlb | attrib |
| admdres.txt | admdres | attrib |
| admh.txt | admh | attrib, partdate |
| adpc.txt | adpc | attrib |
| adpe.txt | adpe | attrib |
| adqolie.txt | adqolie | attrib |
| adsps.txt | adsps | attrib |
| adsv.txt | adsv | attrib |
| adszd.txt | adszd | attrib |
| adszfr.txt | adszfr | attrib |
| adszp.txt | adszp | attrib |
| adtte.txt | adtte | attrib |
| advs.txt | advs | attrib |

## 7.2 Analysis Output Programs

| Program Name | Output Number | Title | Input |
|---|---|---|---|
| t_predopbo.txt | 7.1.1 | Percent Reduction Over Placebo for – 28-Day Adjusted POS Frequencycacy - ITT | ADSZP |
| t_predopbo.txt | 7.1.2 | Percent Reduction Over Placebo for 28-Day Adjusted POS Frequencycacy - PP | ADSZP |
| t_resp.txt | 7.2.1 | Fifty Percent Responder Outcome for POS Frequency – ITT | ADSZP |
| t_resp.txt | 7.2.2 | Fifty Percent Responder Outcome for POS Frequency – PP | ADSZP |
| t_szfr.txt | 7.3.1 | Seizure Freedom for All Seizure Types - ITT | ADSZFR |
| t_nthseiz.txt | 7.4 | Time to nth Partial Onset Seizure – ITT | ADTTE |
| t_50resp.txt | 7.6 | Fifty Percent Responder Outcome for POS Frequency By Monthly Periods – ITT | ADTTE |

### 7.3 Macro Programs

| Program Name | Purpose |
|---|---|
| attrib.txt | Automatically set variable attributes based on specifications |
| partdate.txt | Creates full analysis dates from partial start or stop dates based on imputation rules. |

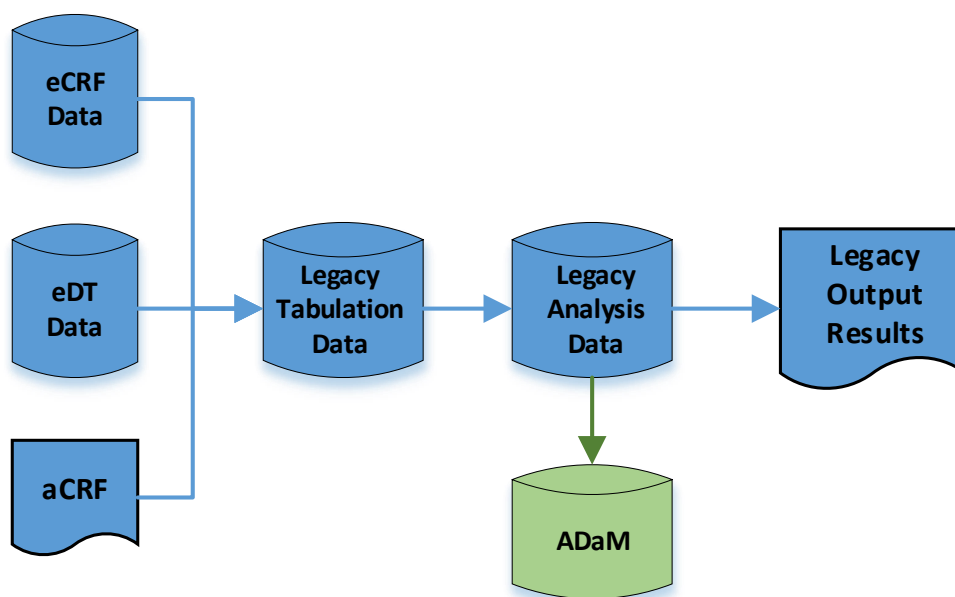# Legacy Data Conversion Plan and Report Appendix

## 1. Purpose

The purpose of this appendix is to document the traceability of key output analysis results with ADaM when the analysis results were generated using a legacy process.

Because of transformations required during ADaM conversion, some of the terms, categories and data formats used in the tabulation data have been translated into CDISC standard formats in the ADaM data. This appendix identifies differences between the legacy analysis and ADaM data, and explains how ADaM represents the equivalent data.

## 2. Conversion Data Flow

The legacy data was converted to ADaM as described in the following data flow diagram.



**Rationale:**

The study started before December 17, 2016. Therefore, standard data is not required. The legacy tabulation data was used to create legacy analysis data, which was used for creating analysis results for the appendix of the CSR.

For this submission,

- Legacy tabulation data was converted to SDTM to assist FDA reviewers
- Legacy analysis data was converted to ADaM to facilitate ISS/ISE ADaM data pools.

## 3. Converted Data Summary

During authoring of the mapping specification from legacy data to ADaM, CDISC Controlled Terminology was applied where applicable. After authoring of a mapping specification and programming of the ADaM SAS datasets, the Pinnacle21 validator was run to check compliance to ADaM IG 1.0 as Pinnacle 21 did not have compliance checks available for ADaM IG 1.1. Checks that signified a programming issue were addressed and the relevant ADaM datasets were updated when possible.

### 3.1 Issues Encountered and Resolved

A comparison between newly created key ADaM datasets and their corresponding legacy analysis data and CSR analysis results was completed to ensure traceability. See below for a description of issues encountered and their resolutions:

- Creation of ADSL was based on the legacy analysis dataset DISPOSIT. This legacy file contained all demographics, disposition and population flags. We have followed ADaM model v2.1 and ADaMIG v1.1 to create ADSL based on the legacy analysis data. Here is a summary of the variable changes:

  - The original population flags were numeric. The numeric values were converted from 1 to Y and 0 to N.

  - The define show how variables were renamed from the legacy data to the correct ADaMIG v1.1 variables.

  - Originally phases were referred to as periods in the legacy analysis data but in order to be ADaM compliant the following changes were made:

    - Baseline Phase is PH1SDT and PH1EDT

    - Treatment Phase is PH2SDT and PH2EDT. This phase contains Up-titration (APERIOD = 1, AP01SDT, AP01EDT), Maintenance (APERIOD=2, AP02SDT, AP02EDT), and Down-titration (APERIOD= 3, AP03SDT, AP03EDT) periods.

    - Safety Follow-up Phase is PH3SDT and PH3EDT.

  - DCSREAS is mapped from the original values to CDISC controlled terminology as follows:
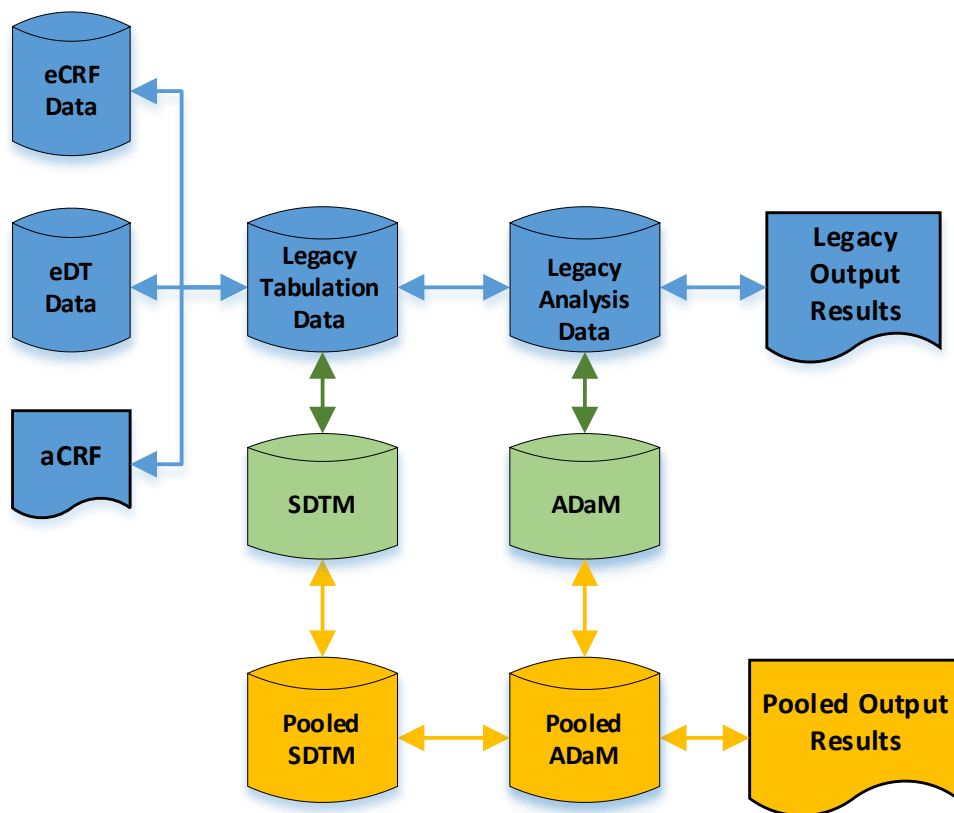
| Legacy Analysis Data Value | Legacy Analysis Count | CSR Reported Value | CSR Count | ADSL.DCSREAS | Count |
|---|---|---|---|---|---|
| termination due to other reasons | 6 | Other | 6 | OTHER | 9 |
| termination due to unsatisfactory compliance of subject | 3 | Non-Compliance | 3 | NON-COMPLIANCE WITH STUDY DRUG | 3 |

| Legacy Analysis Data Value | Legacy Analysis Count | CSR Reported Value | CSR Count | ADSL.DCSREAS | Count |
|---|---|---|---|---|---|
| termination because subject withdrew consent | 15 | Subject Withdrew Consent | 15 | WITHDRAWAL BY SUBJECT | 15 |
| termination with major protocol violation per investigator | 8 | Physician Discontinued Subject Due to Protocol Violation | 7 | PROTOCOL DEVIATION | 7 |
| termination with lack of efficacy | 22 | Lack of Efficacy | 22 | LACK OF EFFICACY | 22 |
| termination due to adverse event | 61 | Adverse Event | 61 | ADVERSE EVENT | 61 |
| lost to follow up, reason for termination unknow | 6 | Lost to Follow-Up | 6 | LOST TO FOLLOW-UP | 6 |

- The original file SEIZP was not in the BDS structure.  This was changed with the creation of ADSZP and the variable names SEIZT, SEIZA, SEIZB, SEIZC, DAYFA, DAYFB, DAYFC, DAYSFREE became PARAMCD and then unique one-to-one matches were created for PARAM.  Please see the define for the full list.  Then BASE, CHG, and PCHG were created along with ANLxxFL and CRITyFLs were created.

- The legacy datasets LAB, VITALS, and ECG were already in a similar structure to BDS but the variables were changed to be ADaMIG v1.1 compliant where necessary.  The define has the code lists for PARAM and PARAMCD.

- Within ADAE and ADMH the coding from the original legacy datasets has been placed in the original MedDRA coding variables from the OCCDS v1.0.  These events were recoded from MedDRA v18.0 v20.1.

- Within ADCM the coding from the legacy dataset have been remapped to the original WHO Drug coding variables from the OCCDS v1.0.  These events were then recoded from WHO Drug 2013 Q2 to 2017 Q3.

## 4.  Traceability Data Flow

The legacy data traceability from collection to submission is described in the following data flow diagram.

## 5.  Outstanding Issues

**ADSL**

The PK population flag did not exist in the legacy analysis data.  The flag was derived and assigned in the output programs.  There is on more subject counted in the PK population represented in the CSR output than the number flagged in the ADSL.  This subject, 007-00201, is not included in the ADSL PK population because their first PK draw was after first dose.

**Adverse Events**

Not all legacy analysis adverse event variable values are traceable to the CSR tables as only subjects with treatment emergent AEs were counted.  The treatment emergent flag was programmed directly into the adverse event table programs.  The ADaM ADAE domain includes the programming for treatment emergent flag.

There were two data issues with relation to start and end dates being switched in the legacy tabulation and analysis data.  This was originally corrected exclusively in the table and listing programs.  This has been corrected in the ADaM ADAE domain.  See the table below for detail concerning the discrepancy:

| SUBJECT AETERM | Legacy Analysis Data Value | CSR Reported Value | ADAE |
|---|---|---|---|
| SUBJECT=007-00103 AETERM=DIARRHEA | AESTDT=03OCT2013 AEENDT=02OCT2013 | AESTDT=02OCT2013 AEENDT=03OCT2013 | AESTDT=02OCT2013 AEENDT=03OCT2013 |
| SUBJECT=007-04102 AETERM=EARACHE | AESTDT=15OCT2013 AEENDT=10OCT2013 | AESTDT=10OCT2013 AEENDT=15OCT2013 | AESTDT=10OCT2013 AEENDT=15OCT2013 |