Population Pharmacokinetic Analysis Data (ADPPK) Programming in {admiral} and the Pharmaverse

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# 1. Abstract

Population Pharmacokinetic modeling is an important tool for drug development. The CDISC ADaM Population PK Implementation Guide was released on October 6, 2023. Population PK models generally make use of nonlinear mixed effects models that require numeric variables. The data used in the models will include both dosing and concentration records, relative time variables, and numeric covariate variables. {admiral} is an open-source R package for creating CDISC ADaM data. It can be used effectively to create Population PK analysis data (ADPPK). Additional tools from other Pharmaverse packages such as {metacore}, {metatools} and {xportr} can be used to simplify the workflow. I will discuss some of the challenges of Population Pharmacokinetic analysis data programming and show some of the solutions developed in {admiral} and the Pharmaverse.

# 2. Introduction

Pharmacokinetics considers the effect of the body on a drug. Typically samples are drawn at set time intervals after dose administration as illustrated in the schematic above. The resulting concentration profiles can be analyzed. With population pharmacokinetic models, variations within and between populations can be assessed. The CDISC ADaM Population PK Analysis Data Implementation Guide was released on October 6, 2023. Population PK models generally make use of nonlinear mixed effects models that require numeric variables. The data used in the models will include both dosing and concentration records, relative time variables, and numeric covariate variables. A DV or dependent variable is often expected, typically the concentration. This is equivalent to the ADaM AVAL variable and will be included in addition to AVAL for ADPPK. The relative time variables are listed in the table below. Also below are the expected variables unique to ADPPK and the numeric covariates.

The Population PK Analysis Data (ADPPK) follows the CDISC Implementation Guide (<https://www.cdisc.org/standards/foundational/adam/basic-data-structure-adam-poppk-implementation-guide-v1-0>). Population PK models generally make use of nonlinear mixed effects models that require numeric variables. The data used in the models will include both dosing and concentration records, relative time variables, and numeric covariate variables. A DV or dependent variable is often expected. This is equivalent to the ADaM AVAL variable and will be included in addition to AVAL for ADPPK.

## 2.1 Time Variables (ADPPK)

| Variable | Variable Label |
| --- | --- |
| NFRLT | Nominal Rel Time from First Dose |
| AFRLT | Actual Rel Time from First Dose |
| NPRLT | Nominal Rel Time from Previous Dose |
| APRLT | Actual Rel Time from Previous Dose |

## 2.2 ADPPK Covariates

* <COV>BL for baseline covariate, (e.g., WTBL, BMIBL)
* <COV>N for numerical version of categorical covariate (e.g., SEXN, RACEN)
* <COV>I for any covariates with imputed values (e.g., WTI, BMII)
* <COV>GRy for grouping covariates (e.g. AGEGR1)

# 3. {admiral}

{admiral} is an open-source R package for creating CDISC analysis datasets. It is modular and consists of a set of functions for many of the operations required for dataset construction. There are template programs available for most CDISC ADaM datasets including for PK (i.e. ADPPK, ADNCA and ADPP). The table to the right shows the functions used in the creation of the ADPPK dataset. Follow the link in the QR code below to see an ADPPK template example and run the code in Posit Cloud.

## 3.1 {admiral} Functions Used

* derive\_vars\_dtm()
* derive\_vars\_dtm\_to\_dt()
* derive\_vars\_dtm\_to\_tm()
* derive\_vars\_dy()
* derive\_vars\_duration()
* create\_single\_dose\_dataset()
* derive\_vars\_merged()
* derive\_vars\_joined()
* derive\_vars\_transposed()
* compute\_bmi()
* compute\_bsa()
* compute\_egfr()

## 3.2 Programming Workflow.

* Load Specs with {metacore}
* Derive PC Dates
* Expand Dosing Records
* Find First Dose
* Find Previous Dose
* Find Previous Nominal Dose
* Derive Covariates Using {metacore}
* {metacore} Checks
* {xportr} Steps

## 3.3 Load Specifications for {metacore}

We have saved our specifications in an Excel file and will load them into {metacore} with the metacore::spec\_to\_metacore() function. The spec file can be found [here](https://github.com/pharmaverse/examples/blob/main/adam/pk_spec.xlsx)

# ---- Load Specs for Metacore ----  
metacore <- spec\_to\_metacore("pk\_spec.xlsx") %>%  
 select\_dataset("ADPPK")

### 3.3.1 Derive PC Dates

At this step, it may be useful to join ADSL to your PC and EX domains as well. Only the ADSL variables used for derivations are selected at this step. The rest of the relevant ADSL variables will be added later. In this case we will keep TRTSDT/TRTSDTM for day derivation and TRT01P/TRT01A for planned and actual treatments.

In this segment we will use admiral::derive\_vars\_merged() to join the ADSL variables and the following {admiral} functions to derive analysis dates, times and days:

* derive\_vars\_dtm()
* derive\_vars\_dtm\_to\_dt()
* derive\_vars\_dtm\_to\_tm()
* derive\_vars\_dy()

We will also create NFRLT for PC data based on PCTPTNUM. We will create an event ID (EVID) of 0 for concentration records and 1 for dosing records.

# ---- Derivations ----  
  
# Get list of ADSL vars required for derivations  
adsl\_vars <- exprs(TRTSDT, TRTSDTM, TRT01P, TRT01A)  
  
pc\_dates <- pc %>%  
 # Join ADSL with PC (need TRTSDT for ADY derivation)  
 derive\_vars\_merged(  
 dataset\_add = adsl,  
 new\_vars = adsl\_vars,  
 by\_vars = exprs(STUDYID, USUBJID)  
 ) %>%  
 # Derive analysis date/time  
 # Impute missing time to 00:00:00  
 derive\_vars\_dtm(  
 new\_vars\_prefix = "A",  
 dtc = PCDTC,  
 time\_imputation = "00:00:00"  
 ) %>%  
 # Derive dates and times from date/times  
 derive\_vars\_dtm\_to\_dt(exprs(ADTM)) %>%  
 derive\_vars\_dtm\_to\_tm(exprs(ADTM)) %>%  
 # Derive event ID and nominal relative time from first dose (NFRLT)  
 mutate(  
 EVID = 0,  
 DRUG = PCTEST,  
 NFRLT = if\_else(PCTPTNUM < 0, 0, PCTPTNUM), .after = USUBJID  
 )

### 3.3.2 Expand Dosing Records

The function admiral::create\_single\_dose\_dataset() will be used to expand dosing records between the start date and end date. The nominal time will also be expanded based on the values of EXDOSFRQ, for example “QD” will result in nominal time being incremented by 24 hours and “BID” will result in nominal time being incremented by 12 hours.

# ---- Expand dosing records between start and end dates ----  
# Updated function includes nominal\_time parameter  
  
ex\_exp <- ex\_dates %>%  
 create\_single\_dose\_dataset(  
 dose\_freq = EXDOSFRQ,  
 start\_date = ASTDT,  
 start\_datetime = ASTDTM,  
 end\_date = AENDT,  
 end\_datetime = AENDTM,  
 nominal\_time = NFRLT,  
 lookup\_table = dose\_freq\_lookup,  
 lookup\_column = CDISC\_VALUE,  
 keep\_source\_vars = exprs(  
 STUDYID, USUBJID, EVID, EXDOSFRQ, EXDOSFRM,  
 NFRLT, EXDOSE, EXDOSU, EXTRT, ASTDT, ASTDTM, AENDT, AENDTM,  
 VISIT, VISITNUM, VISITDY,  
 TRT01A, TRT01P, DOMAIN, EXSEQ, !!!adsl\_vars  
 )  
 ) %>%  
 # Derive AVISIT based on nominal relative time  
 # Derive AVISITN to nominal time in whole days using integer division  
 # Define AVISIT based on nominal day  
 mutate(  
 AVISITN = NFRLT %/% 24 + 1,  
 AVISIT = paste("Day", AVISITN),  
 ADTM = ASTDTM,  
 DRUG = EXTRT  
 ) %>%  
 # Derive dates and times from datetimes  
 derive\_vars\_dtm\_to\_dt(exprs(ADTM)) %>%  
 derive\_vars\_dtm\_to\_tm(exprs(ADTM)) %>%  
 derive\_vars\_dtm\_to\_tm(exprs(ASTDTM)) %>%  
 derive\_vars\_dtm\_to\_tm(exprs(AENDTM))

### 3.3.3 Find First Dose

We find the first dose for the concentration records using the function admiral::derive\_vars\_merged()

# ---- Find first dose per treatment per subject ----  
# ---- Join with ADPPK data and keep only subjects with dosing ----  
  
adppk\_first\_dose <- pc\_dates %>%  
 derive\_vars\_merged(  
 dataset\_add = ex\_exp,  
 filter\_add = (!is.na(ADTM)),  
 new\_vars = exprs(FANLDTM = ADTM, EXDOSE\_first = EXDOSE),  
 order = exprs(ADTM, EXSEQ),  
 mode = "first",  
 by\_vars = exprs(STUDYID, USUBJID, DRUG)  
 ) %>%  
 filter(!is.na(FANLDTM)) %>%  
 # Derive AVISIT based on nominal relative time  
 # Derive AVISITN to nominal time in whole days using integer division  
 # Define AVISIT based on nominal day  
 mutate(  
 AVISITN = NFRLT %/% 24 + 1,  
 AVISIT = paste("Day", AVISITN),  
 )

### 3.3.4 Find Previous Dose

For ADPPK we will find the previous dose with respect to actual time and nominal time. We will use `admiral::derive\_vars\_joined().

# ---- Find previous dose ----  
  
adppk\_prev <- adppk\_first\_dose %>%  
 derive\_vars\_joined(  
 dataset\_add = ex\_exp,  
 by\_vars = exprs(USUBJID),  
 order = exprs(ADTM),  
 new\_vars = exprs(  
 ADTM\_prev = ADTM, EXDOSE\_prev = EXDOSE, AVISIT\_prev = AVISIT,  
 AENDTM\_prev = AENDTM  
 ),  
 join\_vars = exprs(ADTM),  
 join\_type = "all",  
 filter\_add = NULL,  
 filter\_join = ADTM > ADTM.join,  
 mode = "last",  
 check\_type = "none"  
 )

### 3.3.5 Find Previous Nominal Dose

Here we use admiral::derive\_vars\_joined() to also find the previous nominal dose.

# ---- Find previous nominal dose ----  
  
adppk\_nom\_prev <- adppk\_prev %>%  
 derive\_vars\_joined(  
 dataset\_add = ex\_exp,  
 by\_vars = exprs(USUBJID),  
 order = exprs(NFRLT),  
 new\_vars = exprs(NFRLT\_prev = NFRLT),  
 join\_type = "all",  
 join\_vars = exprs(NFRLT),  
 filter\_add = NULL,  
 filter\_join = NFRLT > NFRLT.join,  
 mode = "last",  
 check\_type = "none"  
 )

## 3.4 Derive Covariates Using Metacore

In this step we will create our numeric covariates using the metatools::create\_var\_from\_codelist() function.

#---- Derive Covariates ----  
# Include numeric values for STUDYIDN, USUBJIDN, SEXN, RACEN etc.  
  
covar <- adsl %>%  
 create\_var\_from\_codelist(metacore, input\_var = STUDYID, out\_var = STUDYIDN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = SEX, out\_var = SEXN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = RACE, out\_var = RACEN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = ETHNIC, out\_var = AETHNIC) %>%  
 create\_var\_from\_codelist(metacore, input\_var = AETHNIC, out\_var = AETHNICN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = ARMCD, out\_var = COHORT) %>%  
 create\_var\_from\_codelist(metacore, input\_var = ARMCD, out\_var = COHORTC) %>%  
 create\_var\_from\_codelist(metacore, input\_var = COUNTRY, out\_var = COUNTRYN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = COUNTRY, out\_var = COUNTRYL) %>%  
 mutate(  
 STUDYIDN = as.numeric(word(USUBJID, 1, sep = fixed("-"))),  
 SITEIDN = as.numeric(word(USUBJID, 2, sep = fixed("-"))),  
 USUBJIDN = as.numeric(word(USUBJID, 3, sep = fixed("-"))),  
 SUBJIDN = as.numeric(SUBJID),  
 ROUTE = unique(ex$EXROUTE),  
 FORM = unique(ex$EXDOSFRM),  
 REGION1 = COUNTRY,  
 REGION1N = COUNTRYN,  
 SUBJTYPC = "Volunteer",  
 ) %>%  
 create\_var\_from\_codelist(metacore, input\_var = FORM, out\_var = FORMN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = ROUTE, out\_var = ROUTEN) %>%  
 create\_var\_from\_codelist(metacore, input\_var = SUBJTYPC, out\_var = SUBJTYP)

## 3.5 Check Data With Metacore

We use {metacore} to perform a number of checks on the data. We will drop variables not in the specs and make sure all the variables from the specs are included.

# Final Steps, Select final variables and Add labels  
# This process will be based on your metadata, no example given for this reason  
# ...  
  
  
# Apply metadata and perform associated checks ----  
# uses {metatools}  
  
adppk <- adppk\_prefinal %>%  
 drop\_unspec\_vars(metacore) %>% # Drop unspecified variables from specs  
 check\_variables(metacore) %>% # Check all variables specified are present and no more  
 check\_ct\_data(metacore) %>% # Checks all variables with CT only contain values within the CT  
 order\_cols(metacore) %>% # Orders the columns according to the spec  
 sort\_by\_key(metacore) # Sorts the rows by the sort keys

## 3.6 Apply Labels and Formats with xportr

Using {xportr} we check variable type, assign variable lenght, add variable labels, add variable formats, and save a transport file.

adppk\_xpt <- adppk %>%  
 xportr\_type(metacore) %>% # Coerce variable type to match spec  
 xportr\_length(metacore) %>% # Assigns SAS length from a variable level metadata  
 xportr\_label(metacore) %>% # Assigns variable label from metacore specifications  
 xportr\_format(metacore) %>% # Assigns variable format from metacore specifications  
 xportr\_df\_label(metacore) %>% # Assigns dataset label from metacore specifications  
 xportr\_write(file.path(dir, "adppk.xpt")) # Write xpt v5 transport file

# 4. Conclusions

Analsis data standards for Population PK (ADPPK) have been recently released. Within a few years submissions to regulatory agencies such as the FDA may require submissions of ADPPK analysis data. As we begin to see submissions programmed in R the use of packages such as {admiral} will become more widespread. The code presented here shows that {admiral} and other Pharmaverse packages provide an excellent way to program ADPPK analysis data.

# 5. Contact Information

Your comments and questions are valued and encouraged. Contact the author at: Author Name: Jeffrey Dickinson Company: Navitas Data Sciences Address: 1610 Medical Drive, Suite 300, Pottstown, PA 19464 USA Work Phone: : +1 402 319 9380 Email: jeff.dickinson@navitaslifesciences.com Website: : www.navitaslifesciences.com