Unveiling the Potential of ADNCA by CDISC ADaM IG: Revolutionizing Pharmacokinetic Non-Compartmental Analysis Input Data Standardization

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Agenda

- Background of PK NCA
- Conventional Approach
- Standard Approach with ADNCA
- Automation of Standard Variables in ADNCA
- Summary and Conclusion
- Q & A

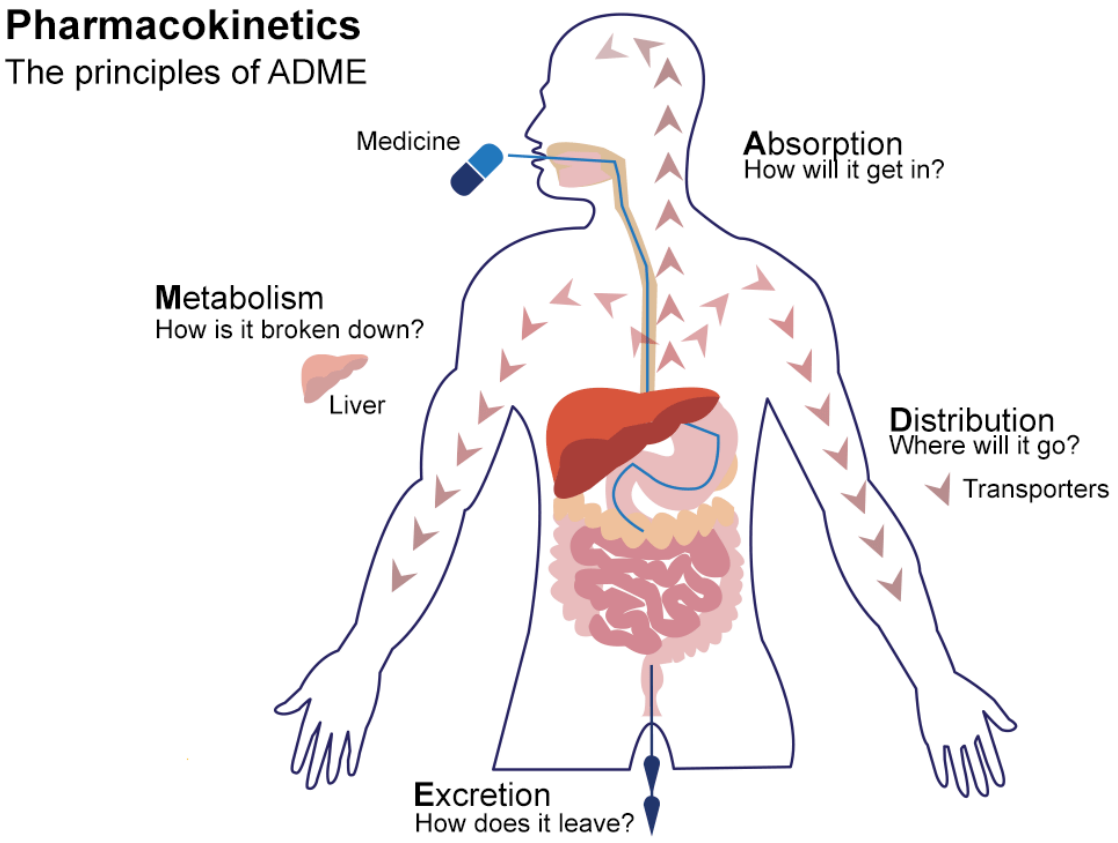
Background of PK NCA

- The pharmacokinetic (PK) of a drug describes what happens to the drug in the body after the administration of the drug.

  PK = What Body Does to the Drug

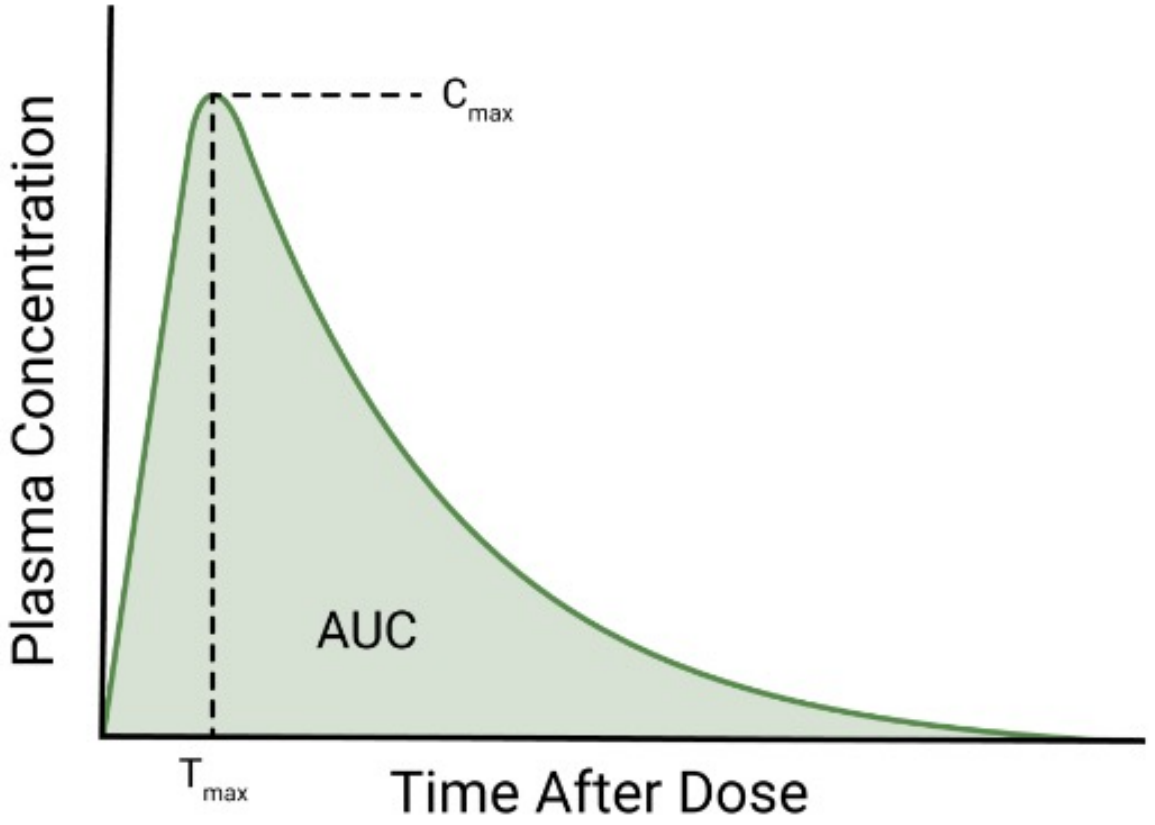
- It is the study of how the body absorbs, distributes, metabolizes, and eliminates drugs or substances. ADME

- PK analysis is usually performed by following various methods based on requirement.
  - ➢ Non-Compartmental Analysis (NCA)
  - ➢ Compartmental Analysis (Model based)
  - ➢ Physiological based PK Analysis (PBPK)
  - ➢ Population PK Analysis (NONMEM)

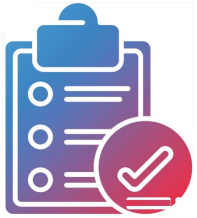


Background of PK NCA

- Non-compartmental Analysis (NCA) is a standard, efficient, and effective method for estimating PK parameters within a single study and for making time-critical dosing decisions (ex. within dose escalation trials).
- It is a simple and quick method for evaluating the exposure of a drug.
- In this analysis method, blood samples from subjects are collected at regular intervals following drug administration and measuring the concentration of the drug in the sample.
- Widely used in Phase 1 clinical studies.
- Common parameters calculated in NCA are
  - Maximum Concentration (Cmax)
  - Time of Maximum Concentration (Tmax)
  - Area Under Curve (AUC)
  - Half Life (t1/2)
  - Volume of Distribution (Vd)
  - Clearance (CL)



Conventional Approach



SOURCE DATA → PROGRAMMING SPECIFICATION → OUTPUT FILE → SUBMISSION

Different Sources

- Raw Datasets
- External Data (Vendor Files)
- SDTM Datasets
- ADaM Datasets

Specification

- PK Scientist + Statistical Programmer
- Excel File Format
- Metadata Information + Variable Derivations

Final input file for NCA

- Named as PreWNL File or PKmerge File
- Provided to PK Scientist in .CSV or .XPT file format to perform NCA

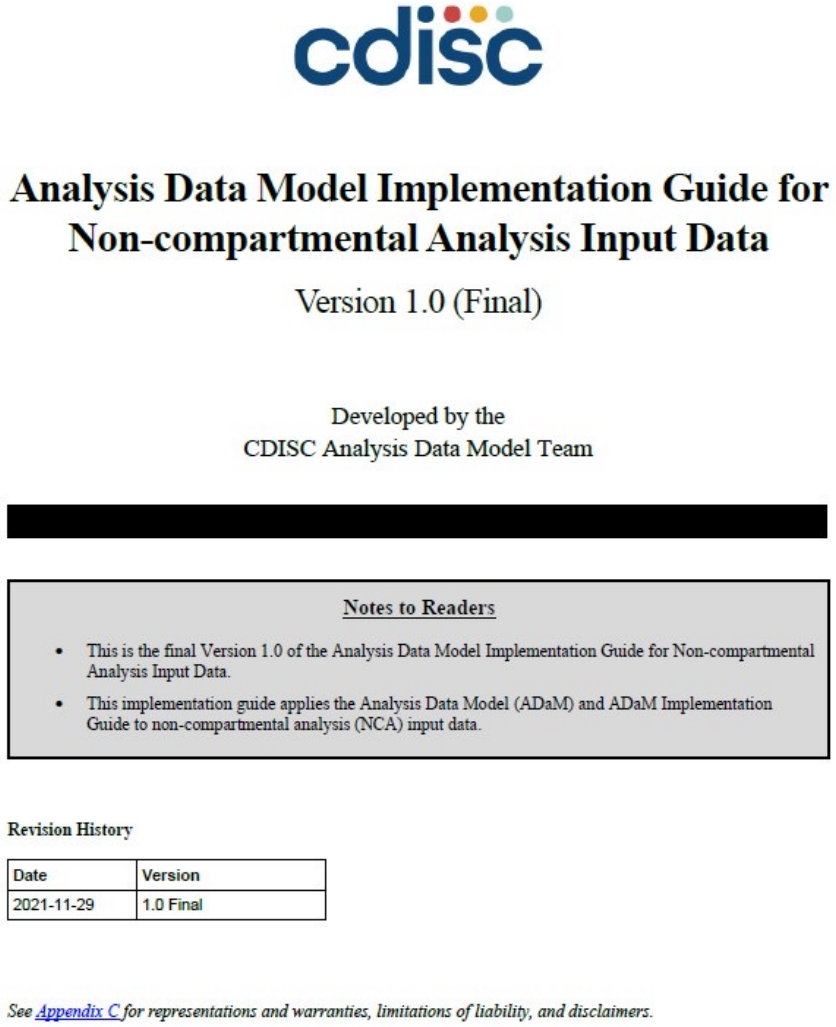
Define.xml + ADRG

- Details for PK NCA input file mentioned in ADPC/ADPP description
- Relationship and Traceability Explained

Conventional Approach

Standard Approach with ADNCA

- The standard approach to create input dataset for PK NCA includes creating ADNCA dataset using CDISC Analysis Data Model Implementation guide leveraging Basic Data Structure (BDS).
- This guideline specifies many of the variables needed for calculation of parameters using NCA and provides general naming conventions that can be leveraged for additional variables. This document also provides specific guidance for all commonly needed variables and should be viewed as the ADaM BDS class plus additional NCA variables.
- Since this dataset is subject to submission to regulatory bodies; utilization of this standard format also promotes compliance with ADaM standards. It is important to build this dataset based on SDTM domains and, if applicable, on the other ADaM datasets (e.g., ADSL) that will be submitted.



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Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data

Version 1.0 (Final)

Developed by the
CDISC Analysis Data Model Team

Notes to Readers

- This is the final Version 1.0 of the Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data.
- This implementation guide applies the Analysis Data Model (ADaM) and ADaM Implementation Guide to non-compartmental analysis (NCA) input data.

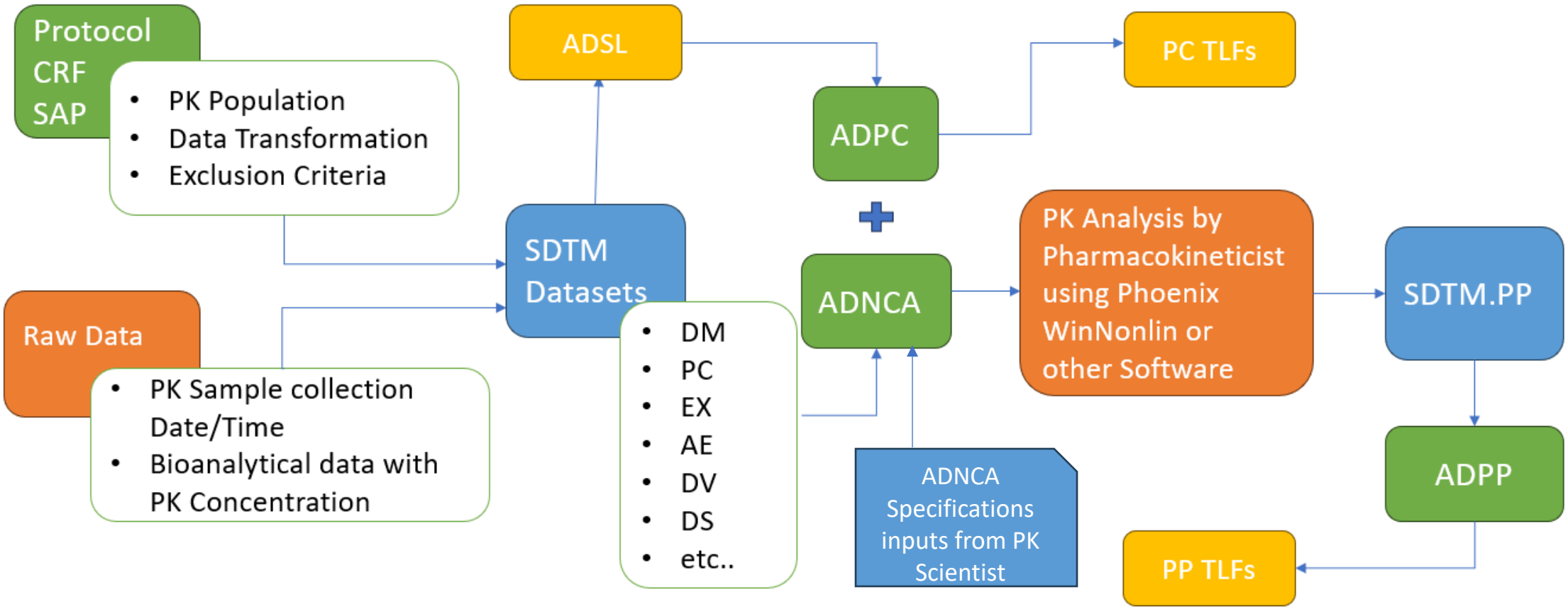
Revision History

Date	Version
2021-11-29	1.0 Final

See Appendix C for representations and warranties, limitations of liability, and disclaimers.

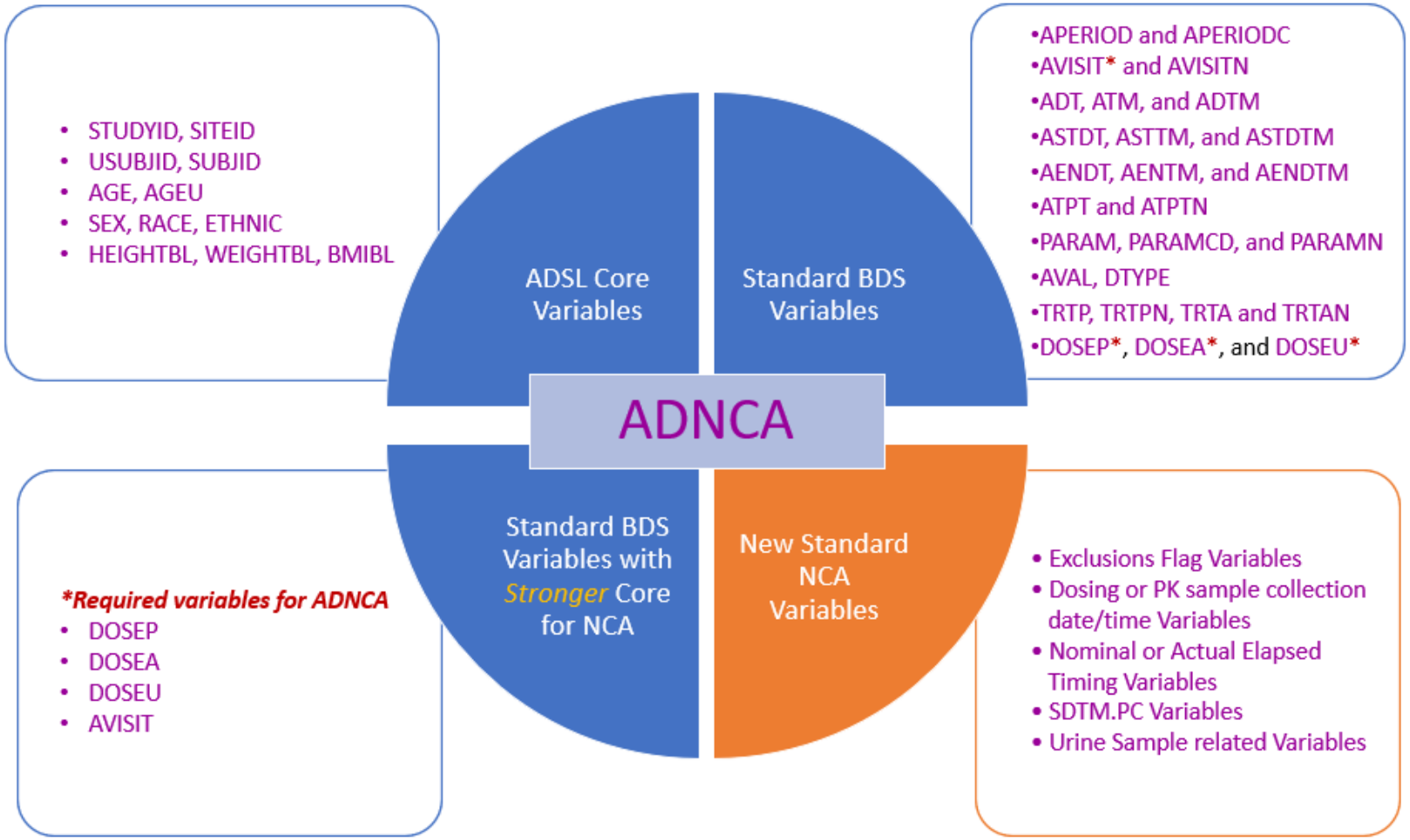
Standard Approach with ADNCA

Workflow of PK Data



Standard Approach with ADNCA

Composition of ADNCA



Standard Approach with ADNCA

Exclusions Flag Variables :

- These variables are typically used to flag the records to be excluded from the NCA or from the calculation of PK summary statistics in TLFs.
- METABFL can be used to distinguish Parent and Metabolite records, respectively.

Variable Name	Variable Label
NCAXFL	PK NCA Exclusion Flag
NCAXFN	PK NCA Exclusion Flag (N)
NCAwXRS	Reason w for PK NCA Exclusion
NCAwXRSN	Reason for PK NCA Exclusion of w (N)
PKSUMXF	PK Summary Exclusion Flag
PKSUMXFN	PK Summary Exclusion Flag (N)
METABFL	Metabolite Flag

STUDYID	USUBJID	ARRLT	NRRLT	RRLTU	AVAL	PCSTRESU	VOMITFL	VRLT	NCAXFL	NCAXFN	NCA1XRS	NCA2XRS	NCA3XRS
CPW	CPW-s001	0	0	h	0	ug/L	Y	0.75					
CPW	CPW-s001	0.33333	0.25	h	19.4	ug/L	Y	0.75					
CPW	CPW-s001	0.5	0.5	h	118.8	ug/L	Y	0.75					
CPW	CPW-s001	1	1	h	115	ug/L	Y	0.75					
CPW	CPW-s001	2	2	h		ug/L	Y	0.75	Y	1	Missing AVAL Value		
CPW	CPW-s001	4	4	h	91.2	ug/L	Y	0.75					
CPW	CPW-s001	8	8	h	67.6	ug/L	Y	0.75					
CPW	CPW-s002	0	0	h	0	ug/L							
CPW	CPW-s002	0.25	0.25	h	18.4	ug/L							
CPW	CPW-s002	0.5	0.5	h	114	ug/L							
CPW	CPW-s002	1	1	h	115	ug/L							
CPW	CPW-s002	2	2	h	114	ug/L							
CPW	CPW-s002	5	4	h	72	ug/L			Y	1		Late Sample	
CPW	CPW-s002	8	8	h	59.15	ug/L							
CPW	CPW-s003	0	0	h	0	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	0.4	0.25	h	19.8	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	0.75	0.5	h	126	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	1.33333	1	h	131.25	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	2	2	h	114	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	4	4	h	97.85	ug/L	Y	0.083333	Y	1			Vomiting
CPW	CPW-s003	7	8	h	68.25	ug/L	Y	0.083333	Y	1			Vomiting

Standard Approach with ADNCA

Dosing or PK sample collection date/time Variables :

- These are key variables to establish relationship between dosing and corresponding PK sample collection data for respective analyte.
- Some of these variables are further used in calculating actual duration of treatment, analysis relative time from first or most recent dose, deviation from planned time etc.

Variable Name	Variable Label
FANLDT	First Date of Dose for Analyte
FANLTM	First Time of Dose for Analyte
FANLDTM	First Datetime of Dose for Analyte
PCRFTDT	Reference Date of Dose for Analyte
PCRFTTM	Reference Time of Dose for Analyte
PCRFTDTM	Reference Datetime of Dose for Analyte

USUBJID	PCTESTCD	AVISIT	PCTPT	PCDTC	FANLDT	FANLTM	FANLDTM	PCRFTDT	PCRFTTM	PCRFTDTM
XYZ123-01-1001	XYZ123P	DAY 1	Predose	2011-09-09T08:28	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	1H	2011-09-09T10:02	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	2H	2011-09-09T10:58	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	4H	2011-09-09T12:58	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	6H	2011-09-09T15:02	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	12H	2011-09-09T20:47	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	13H	2011-09-09T21:57	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 1	14H	2011-09-09T22:55	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 2	16H	2011-09-10T00:48	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 2	18H	2011-09-10T02:51	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 2	24H	2011-09-10T08:40	09SEP2011	9:00	09SEP2011:09:00:00	09SEP2011	9:00	09SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 3	Predose	2011-09-11T08:37	09SEP2011	9:00	09SEP2011:09:00:00	11SEP2011	9:00	11SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 4	Predose	2011-09-12T09:00	09SEP2011	9:00	09SEP2011:09:00:00	12SEP2011	9:10	12SEP2011:09:10:00
XYZ123-01-1001	XYZ123P	DAY 5	Predose	2011-09-13T08:45	09SEP2011	9:00	09SEP2011:09:00:00	13SEP2011	9:00	13SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 6	Predose	2011-09-14T08:45	09SEP2011	9:00	09SEP2011:09:00:00	14SEP2011	9:00	14SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	Predose	2011-09-15T08:47	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	1H	2011-09-15T10:00	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	2H	2011-09-15T10:58	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	4H	2011-09-15T13:00	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00

Standard Approach with ADNCA

Nominal or Actual Elapsed Timing Variables :

- Planned and Actual Elapsed Time from reference exposure to Study Treatment Variables and percent difference of Nominal v/s Actual Time are vital variables for PK NCA.
- This information is essential for interpreting PK data accurately, particularly when assessing parameters such as time to maximum concentration (Tmax) and time-related areas under the concentration-time curve (AUC).

Variable Name	Variable Label
NRRLT	Nominal Rel. Time from Ref. Dose
ARRLT	Actual Rel. Time from Ref. Dose
MRRLT	Modified Rel. Time from Ref. Dose
TMPCTDF	Percent Diff. Nominal vs. Actual Time
TMDEV	Time Deviation (h)
CLKDEV	Clock Deviation (hh:mm)

USUBJID	PCTESTCD	AVISIT	PCTPT	ADTM	SCHDTM	PCRFTDTM	NRRLT	ARRLT	MRRLT	TMPCDTF	TMDEV	CLKDEV
XYZ123-01-1001	XYZ123P	DAY 1	Predose	09SEP2011:08:28:00	09SEP2011:09:00:00	09SEP2011:09:00:00	0	-0.53	0.00	.	-0.53	-0:32
XYZ123-01-1001	XYZ123P	DAY 1	1H	09SEP2011:10:02:00	09SEP2011:10:00:00	09SEP2011:09:00:00	1	1.03	1.03	-3.3	0.03	0:02
XYZ123-01-1001	XYZ123P	DAY 1	2H	09SEP2011:10:58:00	09SEP2011:11:00:00	09SEP2011:09:00:00	2	1.97	1.97	1.7	-0.03	-0:02
XYZ123-01-1001	XYZ123P	DAY 1	4H	09SEP2011:12:58:00	09SEP2011:13:00:00	09SEP2011:09:00:00	4	3.97	3.97	0.8	-0.03	-0:02
XYZ123-01-1001	XYZ123P	DAY 1	6H	09SEP2011:15:02:00	09SEP2011:15:00:00	09SEP2011:09:00:00	6	6.03	6.03	-0.6	0.03	0:02
XYZ123-01-1001	XYZ123P	DAY 1	12H	09SEP2011:20:47:00	09SEP2011:21:00:00	09SEP2011:09:00:00	12	11.78	11.78	1.8	-0.22	-0:13
XYZ123-01-1001	XYZ123P	DAY 1	13H	09SEP2011:21:57:00	09SEP2011:22:00:00	09SEP2011:09:00:00	13	12.95	12.95	0.4	-0.05	-0:03
XYZ123-01-1001	XYZ123P	DAY 1	14H	09SEP2011:22:55:00	09SEP2011:23:00:00	09SEP2011:09:00:00	14	13.92	13.92	0.6	-0.08	-0:05
XYZ123-01-1001	XYZ123P	DAY 2	16H	10SEP2011:00:48:00	10SEP2011:01:00:00	09SEP2011:09:00:00	16	15.80	15.80	1.2	-0.20	-0:12
XYZ123-01-1001	XYZ123P	DAY 2	18H	10SEP2011:02:51:00	10SEP2011:03:00:00	09SEP2011:09:00:00	18	17.85	17.85	0.8	-0.15	-0:09
XYZ123-01-1001	XYZ123P	DAY 2	24H	10SEP2011:08:40:00	10SEP2011:09:00:00	09SEP2011:09:00:00	24	23.67	23.67	1.4	-0.33	-0:20
XYZ123-01-1001	XYZ123P	DAY 3	Predose	11SEP2011:08:37:00	11SEP2011:09:00:00	11SEP2011:09:00:00	0	-0.38	0.00	.	-0.38	-0:23
XYZ123-01-1001	XYZ123P	DAY 4	Predose	12SEP2011:09:00:00	12SEP2011:09:10:00	12SEP2011:09:10:00	0	-0.17	0.00	.	-0.17	-0:10
XYZ123-01-1001	XYZ123P	DAY 5	Predose	13SEP2011:08:45:00	13SEP2011:09:00:00	13SEP2011:09:00:00	0	-0.25	0.00	.	-0.25	-0:15
XYZ123-01-1001	XYZ123P	DAY 6	Predose	14SEP2011:08:45:00	14SEP2011:09:00:00	14SEP2011:09:00:00	0	-0.25	0.00	.	-0.25	-0:15
XYZ123-01-1001	XYZ123P	DAY 7	Predose	15SEP2011:08:47:00	15SEP2011:09:00:00	15SEP2011:09:00:00	0	-0.22	0.00	.	-0.22	-0:13
XYZ123-01-1001	XYZ123P	DAY 7	1H	15SEP2011:10:00:00	15SEP2011:10:00:00	15SEP2011:09:00:00	1	1.00	1.00	0.0	0.00	0:00
XYZ123-01-1001	XYZ123P	DAY 7	2H	15SEP2011:10:58:00	15SEP2011:11:00:00	15SEP2011:09:00:00	2	1.97	1.97	1.7	-0.03	-0:02
XYZ123-01-1001	XYZ123P	DAY 7	4H	15SEP2011:13:00:00	15SEP2011:13:00:00	15SEP2011:09:00:00	4	4.00	4.00	0.0	0.00	0:00

Automation of Standard Variables in ADNCA

- Now that we have looked at to the standard list of variables and overall framework of ADNCA, Next step is how we can automate the derivations using simple SAS macros to increase reproducibility.
- Each organization has a global library for their standard macros to facilitate Datasets/TLFs programming which can be updated to accommodate changes as per ADNCA requirements for standard BDS variables and some of the new macros can also be included for new standard ADNCA variables in global library to facilitate macro driven programming.
- These SAS macros, scripts, or tools are widely used to automate the routine programming derivations for Datasets and TLFs. Variables metadata and source datasets used are quite standard with this approach and thus it is easy to convert these derivations into macro programs.
- Such automation can reduce the overall development and maintenance time of a program and at the same time makes it consistent between different studies and submissions.


%INIT

Automation of Standard Variables in ADNCA

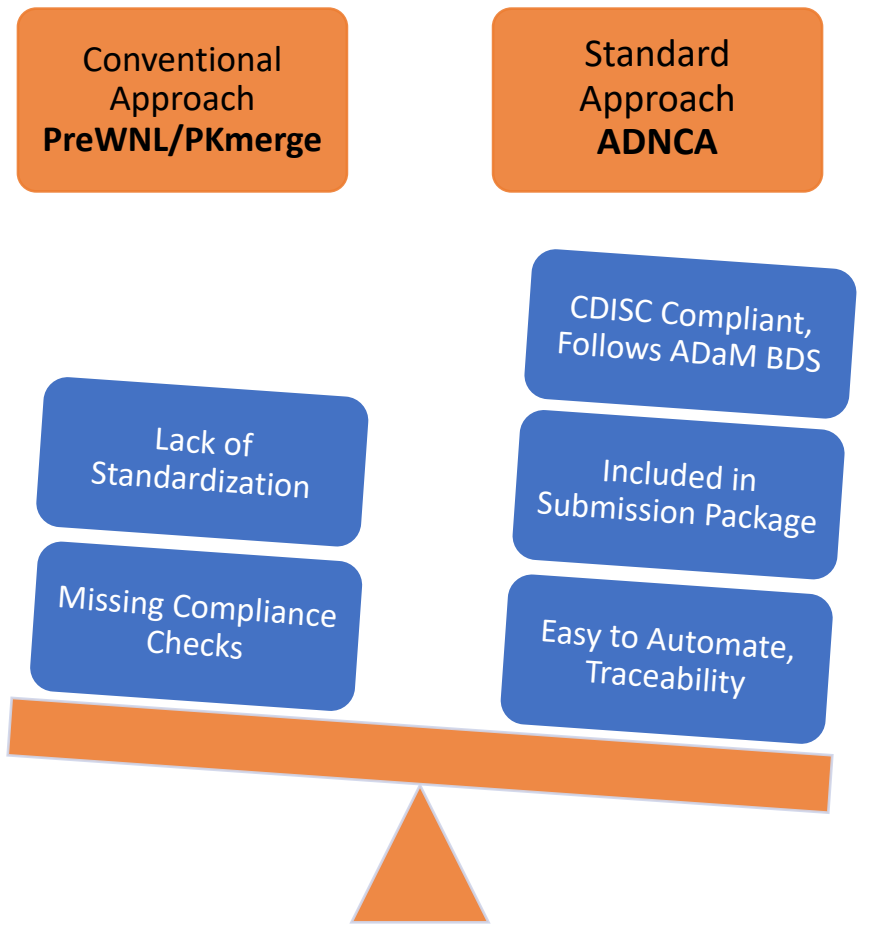
Sample SAS Macro Program %NCADTM

```
/*Macro Program to create ADNCA standard Date/Time and Elapsed Time related Variables*/
%macro ncadtm(trt=,analyte=) ;

/*Bring in the First Dosing Date/Time from Exposure Data*/
proc sort data = sdtm.ex out = ex ;
  by usubjid exstdtc ;
  /*Make Sure to filter non-missing or non-zero dosing records*/
  where extrt = "&trt" and exdose ne 0 and exstdtc ne "" ;
run ;

data ex1 (keep=usubjid extrt exdose exdosu exdosfrq exstdtc exendtc);
  set ex ;
  by usubjid ;
  if first.usubjid ; /*Select the first record for Treatment*/
run ;

/*Merge this first exposure date/time with PC records*/
proc sort data = sdtm.pc out = pc ;
  by usubjid pcdtc ;
  where pctestcd = "&analyte" ; /*Filter data for required analyte*/
run ;

data pc_ex ;
  merge sdtm.pc(in=a) ex1 ;
  by usubjid ;
  if a ;
run ;

/*Derive required variables*/
/*Creating Macro to separate Date and Time*/

%macro datetime(var=,date=,time=,dt=) ;

    if length(&Var)>=10 then &date = input(substr(&var,1,10),is8601dt.) ;
    if length(&Var)>10 then &time = input(substr(&var,12),time5.) ;
    if length(&Var)>11 then &dt = input(&var,is8601da.) ;

%mend datetime ;
```

```
/*Creating Standard NCA Date/Time Variables*/
data pc_ex1 ;
  set pc_ex ;

  /*Calling Macro for separating Date/Time*/
  %datetime(var=EXSTDTC, date=FANLDT, time=FANLTM, dt=FANLDTM)
  %datetime(var=EXENDTC, date=FANLEDT, time=FANLETM, dt=FANLEDTM)
  %datetime(var=PCRFTDTC, date=PCRFTDT, time=PCRFTTM, dt=PCRFTDTM)
  %datetime(var=PCDTC, date=ADT, time=ATM, dt=ADTM)

  format FANLDT FANLEDT PCRFTDT ADT date9.
         FANLTM FANLETM PCRFTTM ATM time5.
         FANLDTM FANLEDTM PCRFTDTM ADTM datetime19. ;
run ;

data pc_ex2 ;
  set pc_ex1 ;

  /*Pre-processing PCTPTNUM to have values in Hour Format*/
  if pctpt = "Predose" then pctptnum = 0 ;
  else pctptnum = input(compress(pctpt,"H"),best.) ;

  NRRLT = PCTPTNUM ;                          /*To be converted into hours if not already*/
  ARRLT = (ADTM - PCRFTDTM)/3600 ;            /*Actual Elapsed Time from dosing*/
  if NRRLT = 0 and ARRLT < 0 then MRRLT = 0 ; /*Set negative Elapsed Time to Zero*/
  else if NRRLT > 0 and ARRLT < 0 then MRRLT = NRRLT ;
  else MRRLT = ARRLT ;

  /*Percent difference Nominal v/s Actual*/
  if NRRLT not in (.,0) then TMPCDTF = ((NRRLT-ARRLT)/NRRLT)*100 ;

  SCHDTM = PCRFTDTM + (NRRLT*3600) ;        /*In Date-time Format*/
  if nmiss(NRRLT,ARRLT)=0 then TMDEV = ARRLT - NRRLT ;
  if nmiss(ADTM,SCHDTM)=0 then CLKDEV = Put((ADTM - SCHDTM),time5.) ;

  format ARRLT MRRLT TMDEV 10.2 TMPCDTF 5.1
         SCHDTM datetime19. ;
run ;

%mend ncadtm ;

/*Calling Macro*/
%ncadtm(trt= XYZ123, analyte= XYZ123P)
```

Summary and Conclusion

- Non-compartmental pharmacokinetic analysis plays a pivotal role in providing critical information about a drug's behavior in the body, supporting decision-making during various stages of clinical research and regulatory submissions.
- The submission of data in non-standard formats not only extends the review time but also poses challenges in establishing relationships and traceability.
- CDISC standards have evolved over the time and are widely used for submissions of clinical data to regulatory authorities such as FDA and PMDA. Now is a good time to replace traditional PK programming approaches with standard ADNCA. While the current ADaM Implementation Guide (IG) for NCA (v1.0) represents the initial standard guidance, it may not comprehensively cover all potential variables or scenarios for PK input data standardization but similar to other recommended guidelines, it is anticipated that ADNCA will undergo further enhancements to align with industry requirements.



| Namaste |

Thank You !

Any Questions ?