Paper SI04

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

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ABSTRACT

In pharmacokinetic data analysis, standardizing input data for non-compartmental analysis (NCA) has historically been challenging due to varying approaches across companies which makes it difficult and time consuming for reviewers and auditors to understand the data flow and lineage. For statistical programmers, conveying these details in the Analysis Data Reviewer's Guide to establish traceability and relationships with SDTM and other PK ADaM datasets such as ADPC/ADPP is also challenging. This paper introduces ADNCA (ADaM NCA input Dataset), utilizing CDISC ADaM IG to convert clinical study PK, Exposure, Exclusions and Disposition data into NCA input data for pharmacokinetic analysis and PK parameters calculation. ADNCA seamlessly integrates with CDISC ADaM IG, simplifying PK data preparation, ensuring data quality, consistency, traceability, and compliance to industry standards. This paper demonstrates methods to automate standard variables derivations using the SAS® Macro programs. These macros reduce ADNCA dataset creation time, making it analysis and submission ready.

INTRODUCTION

Pharmacokinetic Non-Compartmental Analysis is a critical part of pharmacokinetics, which is the study of how the body absorbs, distributes, metabolizes, and eliminates drugs or substances. In most of Phase 1 studies, PK NCA focuses specifically on analyzing pharmacokinetic parameters such as the area under the concentration-time curve (AUC), maximum concentration (Cmax), time to reach Cmax (Tmax), elimination rate constant (Ke), and half-life (t1/2) using non-compartmental methods. These parameters provide crucial insights into how a drug behaves in the body.

Now a days most of the companies are utilizing CDISC standards such as CDASH, SDTM and ADAM for organizing and formatting clinical data to streamline processes in collection, management, analysis, and reporting. Some of these standards are also one of the required standards for data submission to regulatory authorities such as FDA (U.S.) and PMDA (Japan).

The statistical programming team plays a pivotal role in generating input dataset for pharmacokinetic (PK) analysis. This input dataset is commonly known as PKmerge or PreWNL dataset/file. Currently, different organizations are using different conventional names for this dataset. Using this dataset as input, PK scientist calculates different required PK parameters using specialized software such as Phoenix WinNonlin® or NonMEM®. Some studies may require additional covariates to be included in this PK input dataset from different source datasets (SDTM/ADAM) including biomarker or laboratory datasets. While the CDISC implementation guides (SDTM/ADAM IG) provide detailed instructions for SDTM PC/PP and ADaM ADPC/ADPP, we now also have an additional implementation guide for creating standard PK input dataset (ADNCA).

This paper aims to introduce the Analysis Data Model (ADaM) Basic Data Structure (BDS) as the designated specification for developing the PK input dataset for Noncompartmental Analysis (NCA). The ADaMIG for NCA dataset outlines numerous variables essential for calculating PK parameters using NCA and provides general naming conventions applicable for supplementary variables. As certain variables follow standard derivation rules, their automation through simple SAS macros can expedite the overall programming process.

Analysis Dataset Metadata for ADNCA dataset is specified as follows:

Data Structure Name	Data Structure Description	Class of Dataset	Sub-Class of Dataset	CDISC Notes
ADNCA	Basic Data Structure Non-Compartmental Analysis	BASIC DATA STRUCTURE	NON-COMPARTMENTAL ANALYSIS	Dataset designed to support NCA. Primarily sourced from SDTM PC and supplemented by information from the EX, EC, or other relevant domains.

CONVENTIONAL APPROACHES

Presently, most of the companies involved in PK/PD programming have different approaches for the creation of PK input dataset for NCA. Some create this dataset directly using raw datasets extracted from eCRF data combined with external PK concentrations laboratory data while others create this dataset using SDTM/ADaM datasets as source. Creating PK input dataset requires lot of data transformation, new derivations and flagging record or subject level exclusions. For any statistical programmer, having correct and up to date specifications for programming this input dataset is essential. Usually, PK scientists work closely with programmers to create or update specifications file as per study's requirements and available source data. This file is usually created as separate Microsoft® excel file like creating SDTM or ADAM specification. In this process, naming conventions used for the key variables and supplementary variables are non-standard and differs from one company to other.

SAMPLE PKMERGE / PREWNL SPECIFICATION TEMPLATE

Domain Structure:	One record per subject per analyte per analysis visit per analysis timepoint
Program Name:	prewnl.sas
Source Data Used:	SDTM : PC, EX, DS, DV, AE, ML ADaM : ADSL
Sort Order:	STUDYID, USUBJID, ANALYTE, PKDAY, NOMTIME

Variable	Variable Label	Type	Controlled Terms Or Formats	Conversion Definition / Programming Comments/ Algorithm
SUBJID	Subject ID	Char		ADSL.SUBJID
PLNTRT	Planned Treatment	Char		Planned treatment as per Protocol. Combination of Treatment name, dose and frequency Ex. ABC 10 mg QD
ACTTRT	Actual Treatment	Char		Actual treatment as per Exposure Domain. Combination of Treatment name, dose and frequency. Concatenate EX.EXTRT, EX.EXDOSE and EX.EXDOSFRQ Ex. TEST 20 mg BID
MATRIX	Specimen Material Type	Char		PK Sample specimen type collected as per protocol. Ex. Plasma, Serum, Urine
ANALYTE	Analyte	Char		Parent Drug or Metabolite name to be assigned from PC.PCTEST
AVISIT	Analysis Visit	Char		Analysis Visit as per Protocol Ex. Day 1, Day 2, Day 7 etc. This is different from PK DAY
PKDAY	PK Day	Num		PK DAY is derived as reference dosing day for respective collected PK samples Ex. AVISIT = Day 2, ATPT = 24 h while PKDAY = 1 and ATPT = 24 h
NOMTIME	Nominal Time	Num		Planned PK Sample collection timepoint in hours. Mostly assigned from PC.PCTPTNUM Ex. 0 (Predose), 1, 2, 4,..24, 48
DOSEDT	Dosing Date	Num	DATE9.	Dosing Date assigned from EX.EXSTDTC corresponding to respective PK Sample
DOSETM	Dosing Time	Num	TIME5.	Dosing Time assigned from EX.EXSTDTC corresponding to respective PK Sample
SCHDT	Scheduled PK Sample Collection Date	Num	DATE9.	Scheduled date of PK sample collection is calculated using exposure drug date/time and nominal time. Convert EXSTDTC in numeric. Add respective Nominal Time (in seconds) to numeric exposure date/time. Convert result value to SAS date/time. Extract date part and assign as Scheduled Date
SCHTM	Scheduled PK Sample Collection Time	Num	TIME5.	Derive same as scheduled date. At the end extract time part and assign as Scheduled Time
PCDT	Actual PK Sample Collection Date	Num	DATE9.	Date part from PC.PCDTC
PCTM	Actual PK Sample Collection Time	Num	TIME5.	Time part from PC.PCDTC
AET	Actual Elapsed Time (h)	Num	DATE9.	Calculated as (PCDTC - EXSTDTC)/3600 in hours
TMDEV	Time Deviation (h)	Num		Calculated as difference between Actual Elapsed time and Nominal Time of PK Sample
CLKDEV	Clock Deviation (hh:mm)	Char	TIME5.	Calculated as difference between PK Sample collection date/time and Scheduled Date/time in HH:MM
PCTDEV	Percent Time Deviation	Num		Calculated as ((AET - NOMTIME)/NOMTIME)*100
WINDOW	Window	Char	Y	Flag to identify PK collections outside of Protocol defined window
PKEXFL	PK Exclusion Flag	Num		PK Exclusion flag for excluding records from PK NCA or summary
PKEXCMT	PK Exclusion Reason	Char		PK Exclusion reason for excluding records from PK NCA or summary

CHALLENGES WITH CONVENTIONAL APPROACHES

- **Lack of Standardization and Reusability:** Conventional methods may lack standardized naming conventions for the variables for merging PK data, making it difficult to establish a consistent and reproducible process across different studies or projects.
- **Limited Automation:** The derivations of variables with conventional approach limit the automation of PK merge file creation. This can result in inefficiencies, especially when dealing with large datasets or frequent updates.
- **Issues with data mapping and traceability:** Difficult and time consuming to explain relationship and traceability in Analysis Data reviewer's guide.
- **Issues with data submission:** Difficulty in submitting non-standard intermediate data to regulatory authorities.
- **Missing Compliance check:** As this dataset does not follow specific defined structure with standard variables, there are no methods to check the compliance of this dataset with industry standards such as CDISC.
- **Time Consuming Review:** As the structure of PK input dataset submitted to regulatory for review are different in structure with custom variable naming conventions, it takes more time to review the data and conclude results.

NEW STANDARD APPROACH WITH ADNCA DATASET

As described in the Introduction section, 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). The following flow chart explains the mapping of CRF or External PK raw data to create standard SDTM.PC domain. Using this SDTM dataset along with other essential datasets such as DM, EX, DS, DV, AE, ML, required analysis datasets are created as per ADaM IG. All required subject-level core variables are mapped from ADSL while other information is merged from essential SDTM datasets. ADPC is created using ADSL and SDTM.PC to facilitate PK concentration related TLFs programming. ADNCA plays a key role as input dataset to perform PK analysis by PK Scientist (Pharmacokineticist) using specialized software such as Phoenix WinNonlin®. After PK NCA is done, PK parameters file is generated and provided to SDTM mapping team to create SDTM.PP. PK parameters analysis dataset (ADPP) is created to generate PK parameters related TLFs as per Protocol and SAP.

OVERALL CLINICAL PK DATA WORKFLOW WITH ADNCA:

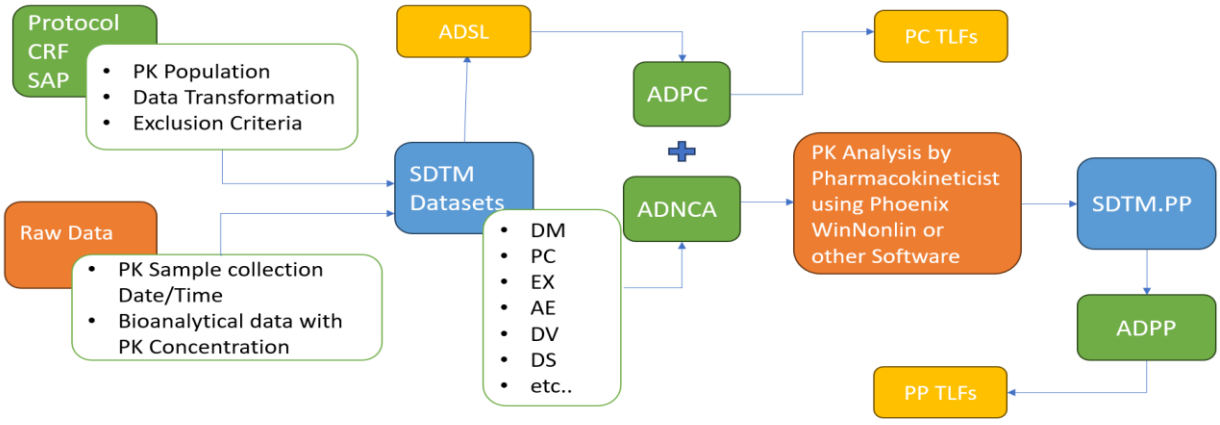

Figure 1

Since ADNCA follows the BDS, most of the core variables can be found in ADaMIG v1.3, Section 3.3. Standard subject-level (ADSL) and BDS variables that are commonly used in NCA are as per following.

ADSL CORE VARIABLES:

- STUDYID
- USUBJID and SUBJID
- SITEID
- AGE and AGEU
- SEX
- RACE

BDS CORE VARIABLES:

- APERIOD and APERIODC
- AVISIT* and AVISITN
- ADT, ATM, and ADTM
- ASTDT, ASTTM, and ASTDTM
- AENDT, AENTM, and AENDTM
- ATPT and ATPTN
- PARAM, PARAMCD, and PARAMN
- AVAL
- DTYPE
- TRTP and TRTPN
- TRTA and TRTAN
- DOSEP*, DOSEA*, and DOSEU*

*BDS Variables DOSEP, DOSEA, DOSEU, and AVISIT have a different core value for NCA which will be discussed later in this paper.

Other baseline characteristics variables can be added in ADNCA from ADSL dataset as per the study or analysis requirements. Ex. HEIGHTBL, WEIGHTBL, BMIBL etc.

NEW STANDARD NCA VARIABLES:

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	Type	Codelist/ Controlled Terms	Core	CDISC Notes
NCAXFL	PK NCA Exclusion Flag	Char	Y	Perm	Flag for exclusion of a record into a PK NCA calculation (Y = exclusion, Null = inclusion)
NCAXFN	PK NCA Exclusion Flag (N)	Num	1	Perm	Numeric flag for exclusion of a record into a PK NCA calculation (1 = exclusion, Null = inclusion). NCAXFN can only be included if NCAXFL is also included.
NCAwXRS	Reason w for PK NCA Exclusion	Char		Perm	This variable is used to explain why the record is not included in the PK NCA.
NCAwXRSN	Reason for PK NCA Exclusion of w (N)	Num		Perm	This variable is used to explain why the record is not included in the PK NCA.
PKSUMXF	PK Summary Exclusion Flag	Char	Y	Perm	Flag for exclusion of a record from a PK summary (1 = exclusion, Null = inclusion)
PKSUMXFN	PK Summary Exclusion Flag (N)	Num	1	Perm	Numeric flag for exclusion of a record from a PK summary (1 = exclusion, Null = inclusion). PKSUMXFN can only be included if PKSUMXFL is also included.
METABFL	Metabolite Flag	Char	Y	Cond	Flag to designate if observations within a subject are associated with a metabolite. Required if parent drug and metabolites are present in the dataset.

Dosing or PK sample collection date/time Variables – These are key variables to establish relationship between dosing and corresponding PK sample collection data. All these variables are created considering 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	Type	Codelist/ Controlled Terms	Core	CDISC Notes
FANLDT	First Date of Dose for Analyte	Num		Perm	Date of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. Note that FANLDT may not match TRTSDT or any of TRxxSDT values.
FANLTM	First Time of Dose for Analyte	Num		Perm	Time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the start time of the first dose.
FANLDTM	First Datetime of Dose for Analyte	Num		Perm	Date and time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the start date and time of the first dose.
FANLEDT	First End Date of Dose for Analyte	Num		Perm	End date of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. Note that FANLEDT may not match TRTEDT or any of TRxxEDT values.
FANLETM	First End Time of Dose for Analyte	Num		Perm	End time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the end time of the first dose.
FANLEDTM	First End Datetime of Dose for Analyte	Num		Perm	End date and time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the end date and time of the first dose.
PCRFTDT	Reference Date of Dose for Analyte	Num		Req	Date of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFTTM	Reference Time of Dose for Analyte	Num		Req	Time of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFTDTM	Reference Datetime of Dose for Analyte	Num		Req	Date and time of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFEDT	Reference End Date of Dose for Analyte	Num		Cond	The end date of reference exposure to treatment associated with PARAM and ANALYTE. Must be related to the time recorded in PC.PCRFTDTC and to the analyzed profile. If dosing occurs over an interval, this should be populated. If populated, ADOSEDUR and DOSEDURU are required to be filled out.
PCRFETM	Reference End Time of Dose for Analyte	Num		Cond	The end time of the reference exposure to treatment associated with PARAM and ANALYTE. Must be related to the time recorded in PC.PCRFTDTC and to the analyzed profile. If dosing occurs over an interval, this should be populated. If populated, ADOSEDUR and DOSEDURU are required to be filled out.
PCRFEDTM	Ref. End Datetime of Dose for Analyte	Num		Cond	The end date and time of the reference exposure to treatment associated with PARAM and ANALYTE. Must be related to the time recorded in PC.PCRFTDTC and to the analyzed profile. If dosing occurs over an interval, this should be populated. If populated, ADOSEDUR and DOSEDURU are required to be filled out.

Nominal or Actual Elapsed Timing Variables – These variables determine planned v/s actual elapsed time with respect to first or most recent exposure to treatment for respective analyte. TMPCTDF highlights the percent difference between nominal v/s actual time. These variables are necessary components in PK analysis, enabling accurate characterization of drug concentration profiles, precise parameter estimation, and informed decision-making in clinical research and drug development.

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
NFRLT	Nom. Rel. Time from Analyte First Dose	Num		Perm	This is the planned elapsed time (for sample point or start of sampling interval) from first exposure to treatment associated with PARAM and ANALYTE. For studies with an extended duration infusion,use the define to document if this is from the start or end of the infusion.
AFRLT	Act. Rel. Time from Analyte First Dose	Num		Perm	This is the actual elapsed time (for sample point or start of sampling interval) from first exposure to treatment associated with PARAM and ANALYTE. Note that this is referring to the first dose available for a particular drug. It is useful in multiple-dosing situations.
NEFRLT	Nom. Rel. End Time from First Dose	Num		Perm	This is the planned elapsed end time of sampling interval from first exposure to study treatment.
AEFRLT	Act. Rel. End Time from First Dose	Num		Perm	This is the actual elapsed end time of sampling interval from first exposure to study treatment.
FRLTU	Rel. Time from First Dose Unit	Char	(PKUNIT)	Perm	This is the unit for all elapsed times from first dose.
NRRLT	Nominal Rel. Time from Ref. Dose	Num		Req	This is the planned elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.
ARRLT	Actual Rel. Time from Ref. Dose	Num		Req	This is the actual elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.
MRRLT	Modified Rel. Time from Ref. Dose	Num		Perm	This variable could be used to modify the ARRLT variable based on analysis needs (e.g., setting negative values to zero or having a mix of nominal and actual time based of TMPCTDF).
NERRLT	Nominal Rel. End Time from Ref. Dose	Num		Perm	This is the planned elapsed end time of sampling interval from reference exposure to study treatment.
AERRLT	Actual Rel. End Time from Ref. Dose	Num		Perm	This is the actual elapsed end time of sampling interval from reference exposure to study treatment.
MERRLT	Modified Rel. End Time from Ref. Dose	Num		Perm	This variable could be used to modify the AERRLT variable based on analysis needs (e.g., setting negative values to zero or having a mix of nominal and actual time based on TMPCTDF).
RRLTU	Rel. Time from Ref. Dose Unit	Char	(PKUNIT)	Req	This is the unit for all elapsed times from reference dose.
TMPCTDF	Percent Diff. Nominal vs. Actual Time	Num		Perm	This is the percent difference between nominal and actual time. It is derived by using the standard percent difference formula: 100*(NRRLT - ARRLT)/(NRRLT).

Urine Sample related Variables – Urine PK samples are usually collected in intervals such as Predose (-4 to 0), Post dose 0 – 4 h, 4 – 8 h etc. Volume and Specimen weight data are important for the calculation of Urine PK parameters.

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
VOLUME	Volume Value	Num		Cond	PC.PCSTRESN from a PC volume record. This is the volume related to AVAL. Conditionally required if sample is interval-based collection, such as urine.
VOLUMEU	Volume Value Unit	Char	(UNIT)	Cond	PC.PCSTRESU from a PC volume record. Conditionally required if VOLUME is present.
SPWEIGHT	Specimen Weight Value	Num		Cond	PC.PCSTRESN from a PC specimen weight record, adjustment based on LLOQ rules possible. This is the specimen weight associated with AVAL. Conditionally required if sample is interval based collection, such as a potential non-fluid matrix (e.g., feces).
SPWEIGHU	Specimen Weight Value Unit	Char	(UNIT)	Cond	PC.PCSTRESU from a PC weight record. Conditionally required if SPWEIGHT is present.

Above are most of the new standard NCA variables to be included in ADNCA dataset. Apart from these variables, there are other core variables included from ADSL as mentioned earlier in this paper. Essential BDS variables to support the required PK analysis are also included in this dataset. Since ADNCA follows BDS class, it is easy to perform compliance checks on this dataset using Pinnacle 21. The typical structure of the dataset is one record per subject per parameter (analyte) per analysis visit per analysis timepoint. ADNCA is included in ADaM define.xml with proper explanation in analysis data reviewers guide. ADNCA helps in establishing lineage and traceability between SDTM/ADaM datasets and PK parameter file received from PK scientist. This detailed description and standard process helps reviewer to understand the data better and faster. At the same time, statistical programmers can create standard macros to automate the derivations of required key variables which increases the reproducibility of the dataset for other projects in a short time.

The following are some key variables which can be carried forwarded from SDTM.PC into ADNCA to provide supporting information to PK scientist while performing NCA.

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
PCGRPID	Group ID	Char		Perm	Used to tie together a block of related records in a single domain to support relationships within the domain and between domains. Must be a direct copy of PC.PCGRPID.
PCSEQ	Sequence Number	Num		Cond	PC.PCSEQ associated with AVAL.
PCSPEC	Specimen Material Type	Char	(SPECTYPE)	Perm	Defines the type of specimen used for a measurement (e.g., SERUM, PLASMA, URINE). This column must be a direct copy of PC.PCSPEC.
PCSTRESC	Character Result/Finding in Std Format	Char		Cond	Character results/findings in a standard format. The purpose of this column is to capture whichrecords are BLQ or LLOQ in the AVAL column. This column must be a direct copy of PC.PCSTRESC.
PCSTRESU	Standard Units	Char	(UNIT)	Cond	Standardized unit associated with AVAL. Units associated with AVAL are needed for clear NCAs. This column must be a direct copy of PC.PCSTRESU.
PCLLOQ	Lower Limit of Quantitation	Num		Cond	Indicates the lower limit of quantitation for an assay. Must be a direct copy of PC.PCLLOQ.

In summary, **Figure 2** below provides a clear and accessible representation of the composition of the ADNCA dataset.

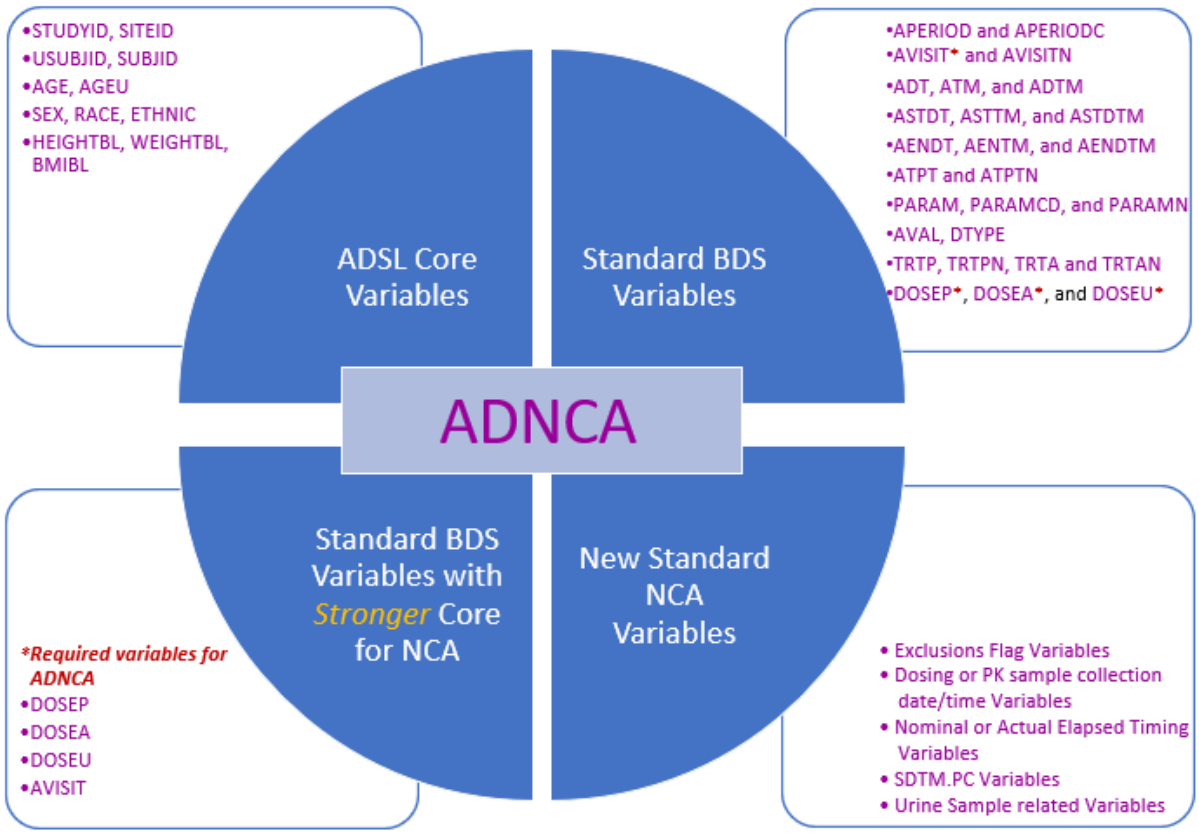

Figure 2

AUTOMATION OF ADNCA WITH EXAMPLES

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 which can be updated to accommodate changes as per ADNCA requirements for standard BDS variables or some of the new macros can also be included 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. Creating ADNCA with a new standard approach can also adopt creating SAS macros for derivations of certain essential variables. Since variables metadata and source datasets used are quite standard with this approach, it is easy to convert these derivations into macro programs. This can reduce the overall development and maintenance time of a program and at the same time makes it consistent between different studies and submissions.

Below are few examples on how certain standard NCA variables look like with their values in the final dataset and then later we also have proposed SAS macro program to automate the derivation of these variables. Note that there could be several other ways to create/automate certain key variables based on study or therapeutic area requirements.

Example 1

First Dosing details or date/time of the reference time point for PK sample records plays a key role in performing NCA. Creating SAS macro for deriving these variables will reduce the repetitive data transformations. In the dataset below we have merged PC and EX SDTM datasets to derive First Dosing and Reference Dosing date/time related variables (highlighted in red) for corresponding PK concentrations records. Further in this paper, the proposed macro program is presented to derive these variables for ADNCA.

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
XYZ123-01-1001	XYZ123P	DAY 7	6H	2011-09-15T15:00	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	12H	2011-09-15T20:56	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	13H	2011-09-15T22:03	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 7	14H	2011-09-15T22:58	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 8	16H	2011-09-16T00:58	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 8	18H	2011-09-16T02:45	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 8	24H	2011-09-16T09:43	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 8	36H	2011-09-16T21:05	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 9	48H	2011-09-17T09:02	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00
XYZ123-01-1001	XYZ123P	DAY 10	72H	2011-09-18T09:15	09SEP2011	9:00	09SEP2011:09:00:00	15SEP2011	9:00	15SEP2011:09:00:00

Example 2

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).

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
XYZ123-01-1001	XYZ123P	DAY 7	6H	15SEP2011:15:00:00	15SEP2011:15:00:00	15SEP2011:09:00:00	6	6.00	6.00	0.0	0.00	0:00
XYZ123-01-1001	XYZ123P	DAY 7	12H	15SEP2011:20:56:00	15SEP2011:21:00:00	15SEP2011:09:00:00	12	11.93	11.93	0.6	-0.07	-0:04
XYZ123-01-1001	XYZ123P	DAY 7	13H	15SEP2011:22:03:00	15SEP2011:22:00:00	15SEP2011:09:00:00	13	13.05	13.05	-0.4	0.05	0:03
XYZ123-01-1001	XYZ123P	DAY 7	14H	15SEP2011:22:58:00	15SEP2011:23:00:00	15SEP2011:09:00:00	14	13.97	13.97	0.2	-0.03	-0:02
XYZ123-01-1001	XYZ123P	DAY 8	16H	16SEP2011:00:58:00	16SEP2011:01:00:00	15SEP2011:09:00:00	16	15.97	15.97	0.2	-0.03	-0:02
XYZ123-01-1001	XYZ123P	DAY 8	18H	16SEP2011:02:45:00	16SEP2011:03:00:00	15SEP2011:09:00:00	18	17.75	17.75	1.4	-0.25	-0:15
XYZ123-01-1001	XYZ123P	DAY 8	24H	16SEP2011:09:43:00	16SEP2011:09:00:00	15SEP2011:09:00:00	24	24.72	24.72	-3.0	0.72	0:43
XYZ123-01-1001	XYZ123P	DAY 8	36H	16SEP2011:21:05:00	16SEP2011:21:00:00	15SEP2011:09:00:00	36	36.08	36.08	-0.2	0.08	0:05
XYZ123-01-1001	XYZ123P	DAY 9	48H	17SEP2011:09:02:00	17SEP2011:09:00:00	15SEP2011:09:00:00	48	48.03	48.03	-0.1	0.03	0:02
XYZ123-01-1001	XYZ123P	DAY 10	72H	18SEP2011:09:15:00	18SEP2011:09:00:00	15SEP2011:09:00:00	72	72.25	72.25	-0.3	0.25	0:15

SAS Macro Program

```
/*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)
```

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. This paper represents ADNCA data structure and talks about its benefits over the conventional approach for creating NCA input data for PK analysis. Further, it is also suggested that creating simple SAS macros for the derivations of standard NCA input variables can enhance the consistency and reproducibility of this dataset. The inclusion of the ADNCA dataset as part of the ADaM submission package, embedded in define.xml and the reviewers' guide, significantly reduce the burden on statistical programmers, streamlining the explanation and integration of non-standard datasets in regulatory submissions.

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