Cracking the Code on NCA: Where Programmers Take On Drug Data, with a Dose of Adaptability

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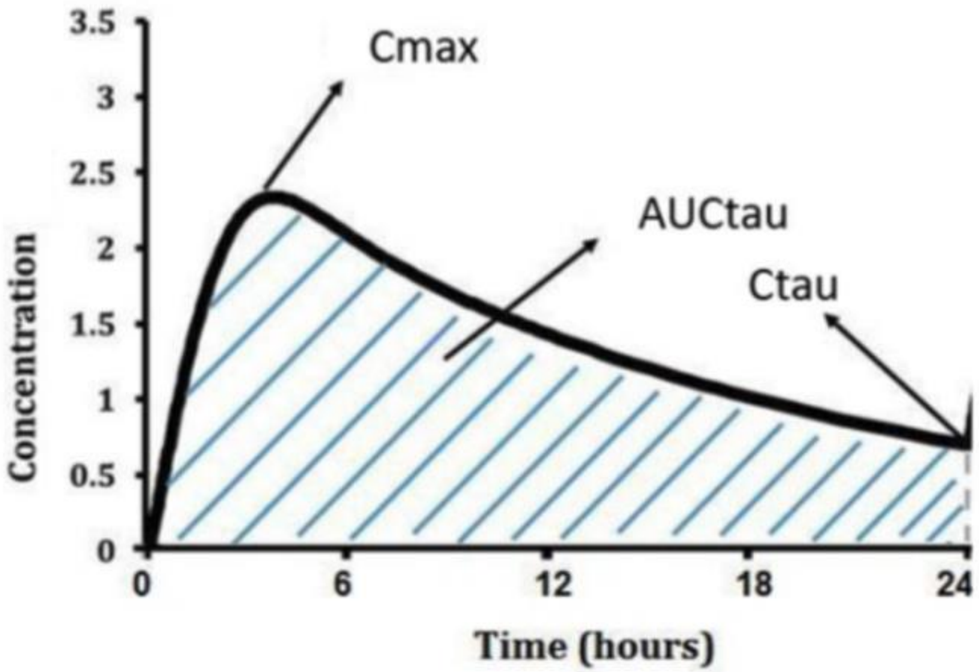
Introduction

- Pharmacokinetics (PK) is the study of the effect of the body on a drug.
- Different mathematical methods are used to calculate PK parameters that describe, characterize, and quantify this effect.
- Non-compartmental analysis (NCA) is one class of mathematical methods for studying the level of exposure following administration of a drug.

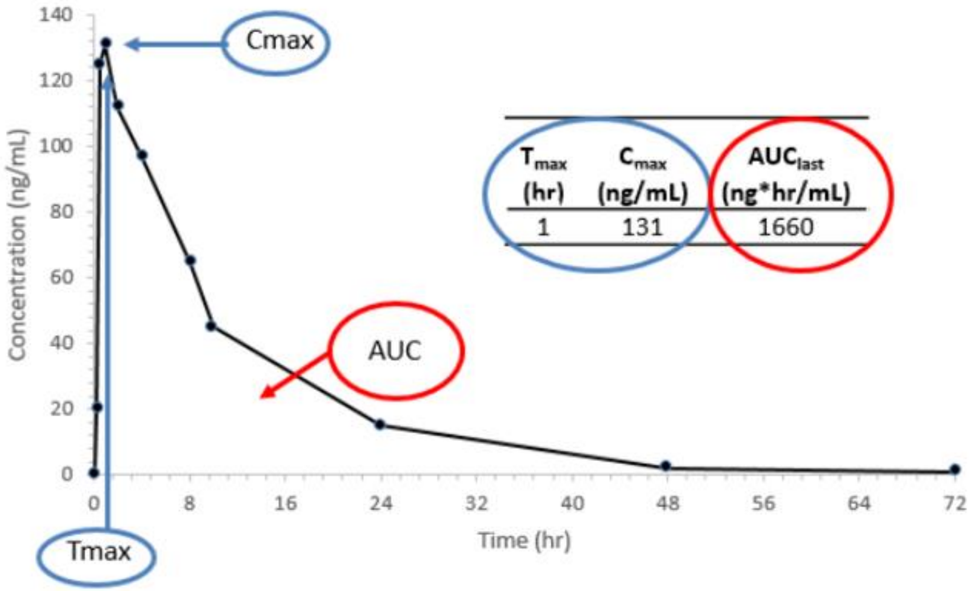


General Objective of Non-Compartmental Analysis

Pharmacokinetic (PK) non-compartmental analysis (NCA) is primarily a time-from -event- based analysis that derives multiple parameters from time-concentration profiles for individual subjects

These parameters can include:

- Cmax - Maximum Concentration
- Tmax - Time to Cmax
- AUC - Area Under Curve
- LAMZHL - Half-Life Lambda z



Analysis Data structure

CDISC defines “NCA as one class of mathematical methods for studying the level of exposure following the administration of a drug and is commonly used to analyze serial drug concentration data from clinical trials by individual subjects.” *

The ADNCA dataset structure is designed to support commonly structured NCAs, including analyses with both discrete time-point measurements (typical for plasma or serum) and measurements from collections over time intervals (typical for urine).

The dataset format is developed to support the more common structures for NCA programs but does not prevent additional variables to accommodate more complex variants of or programming for NCA.

*https://www.cdisc.org/system/files/members/standard/foundational/ADaMIG_for_Non-compartmental_Analysis_Input_Data_v1.0_1.pdf

Analysis Data structure

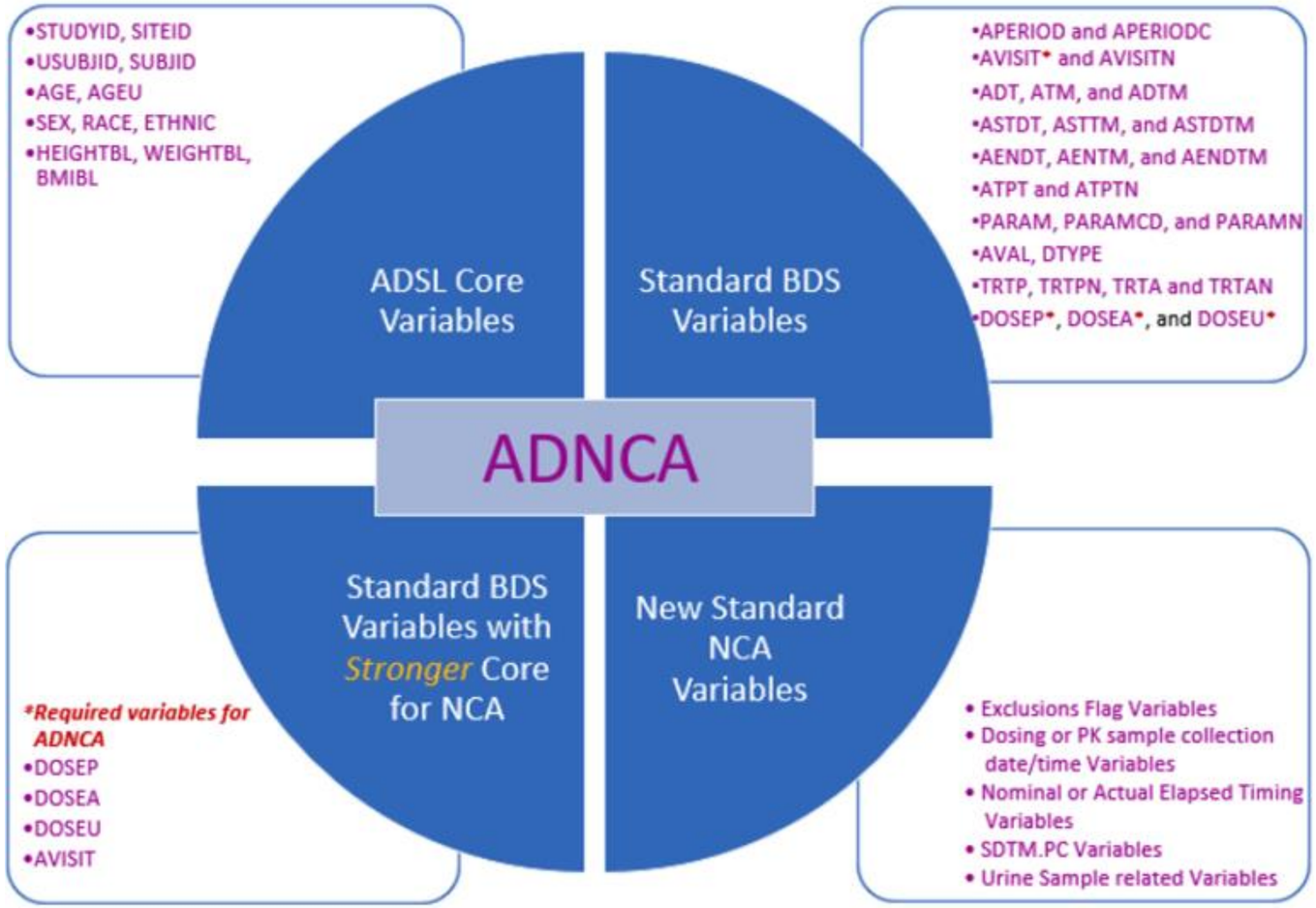
The ADaM NCA dataset is not intended to be used for graphical and tabular presentations of results from NCA (e.g., PK parameters such as maximum concentration and area under the curve) that are tabulated in the SDTM z Parameters (PP) domain.

ADNCA datasets should be “analysis-ready”: This means they should contain the variables needed for the intended use of performing non-compartmental analysis (NCA).

Data Structure Name	Data Structure Description	Class of Dataset	Subclass 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.

Analysis Data structure

ADNCA is comprised of a combination of dose information and concentration results. These data are combined to facilitate the creation of both nominal and actual timing variables. The ADNCA dataset will also include timing variables that relate to the most recent dose as well as the very first dose given to the subject. This structure will therefore facilitate the analysis of data from single dose and multiple dose studies.



Programming Solutions

The development of ADNCA follows the BDS data structure with additional NCA variables intentionally formatted to support basic NCA. Programmatically, while the ADNCA domain does not restrict other variables for non-basic NCA, proper implementation is difficult to achieve and requires multiple rounds of review and feedback from the PK scientist to ensure the ADNCA is robust enough to account for study-specific complexities and variants.

In general, for complex study of raw concentration data and extensive derivations, ADNCA serves well for NCA analysis purposes. For PK concentration standard analysis, ADPC is the appropriate dataset.

Specifications for ADNCA should be drafted collaboratively by the PK scientist and statistical programmer (with review by the biostatistician).

Programming Solutions

Additionally, beyond emerging trends related to using Non-compartmental Analysis Input Data (ADNCA), the common challenges associated with NCA programming include:

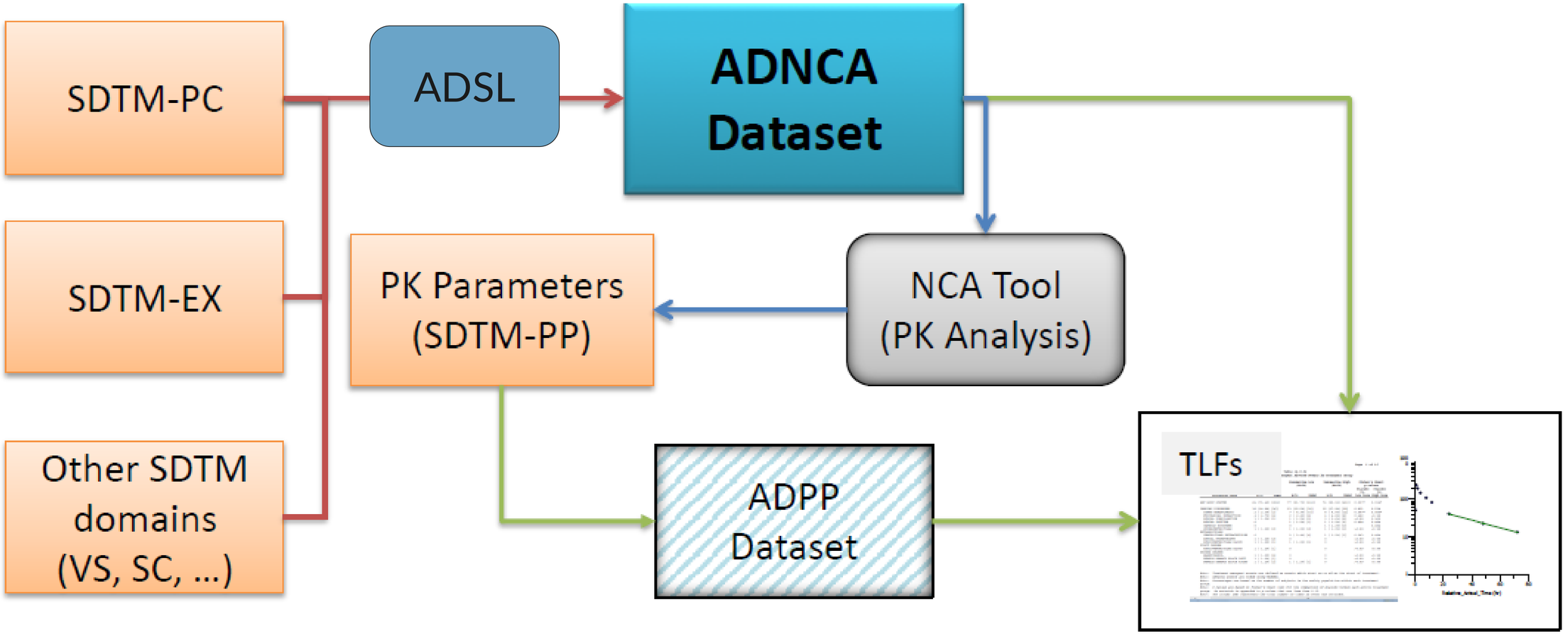
Managing missing sampling or concentration data.

- BLQ values.
- Exclusions.
- Project specific analysis flags
- Using actual vs. planned sampling time points.
- Concentration data review.
- Baseline definition and adjustment.
- *Individual subject plots*.
- *Descriptive tables*.

Challenges

The challenges often arise in clinical trial studies containing NCA, which can be exacerbated early on in the study. Recurrent examples include when roles and responsibilities are not well defined, timelines do not account for multiple review cycles between the biostatistics and PK teams, and unclear DTAs with insufficient detail are put in place specifically related to the raw concentration data. Once the study begins, continued challenges include differing opinions among the biostatistician, PK scientist, and statistical programmer, raw concentration data timing and adherence to the DTA, study timelines, frequent communication, review cycles, data issues, and staying within budget.

Conclusion


SDTM-PC
SDTM-EX
Other SDTM domains (VS, SC, ...)
ADSL
ADNCA Dataset
PK Parameters (SDTM-PP)
NCA Tool (PK Analysis)
ADPP Dataset
TLFs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Thank you!