Best Practices for Efficient CDISC-Compliant PK NCA

Presented by Mitchikou Tseng, OCS Life Sciences

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Meet the Speaker

Mitchikou Tseng

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Organization: OCS Life Sciences

For more than 9 years, Mitch has been working as a SAS programmer in the pharmaceutical research industry. Her initial five years of experience were primarily in Phase 2 and 3 studies, while in recent years, her involvement has been in early development stage/Phase 1 and nutrition research studies.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

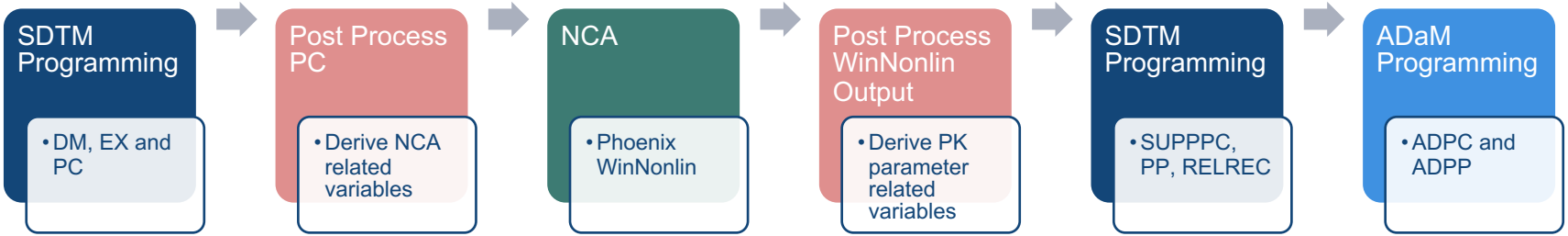
1. NCA Workflow
2. ADaM IG for NCA Input Data
3. Workflow Details
4. Conclusion

Pharmacokinetic Non-Compartmental Analysis (PK NCA)

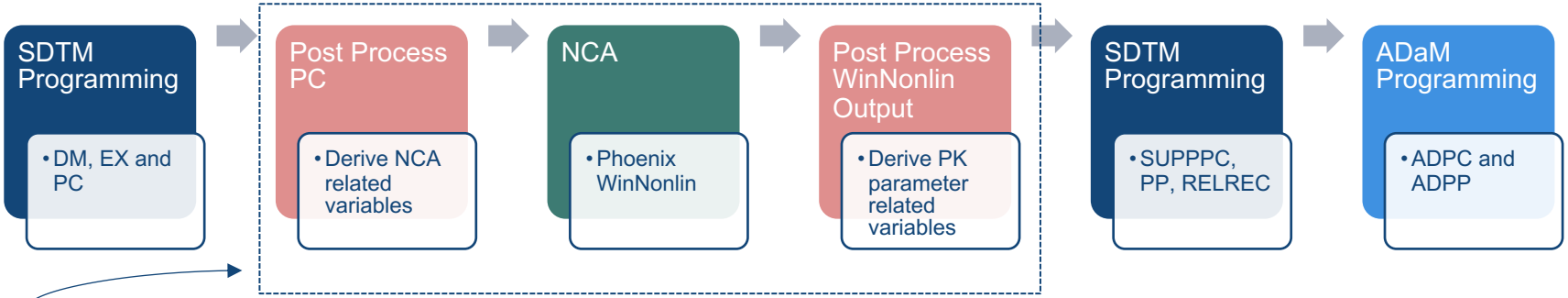
Model independent approach to estimate PK parameters which describe the absorption, distribution, metabolism, and excretion of a drug

NCA Workflow

NCA Workflow – Old version

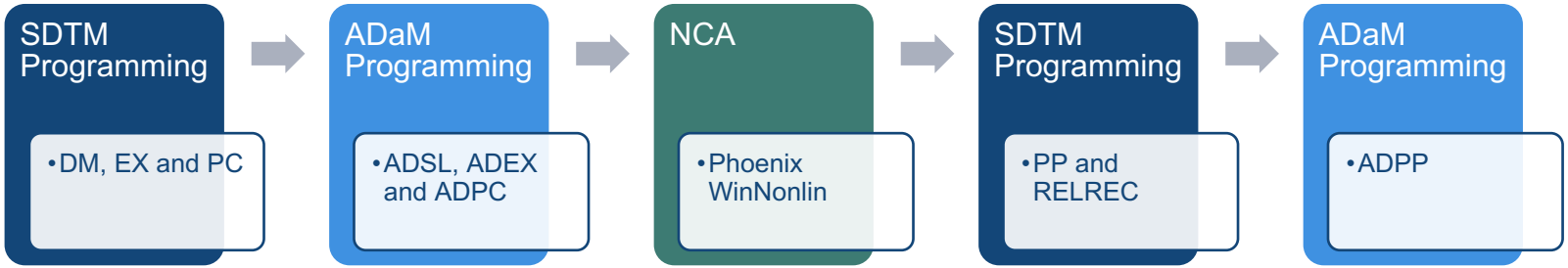


NCA Workflow – Old version



- Solely implemented by the pharmacokineticist
- NCA related data
  - Post process PC variables are stored as part of SUPPPC
  - PP contains the post processed data from WinNonlin
  - Treated as import files in SDTM programming
    - Derivations are not detailed in specifications nor define.xml
    - Creates confusion on which is the final “SUPPPC”
- More steps and intermediate files = more QC effort

NCA Workflow – New version



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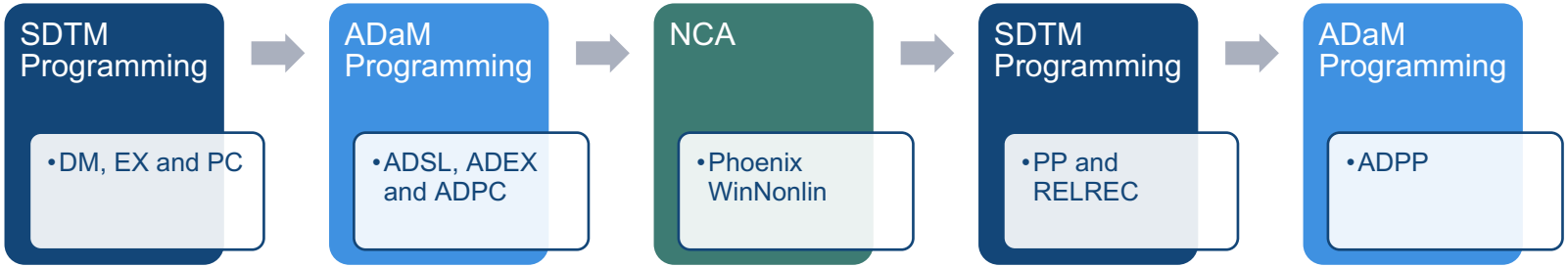
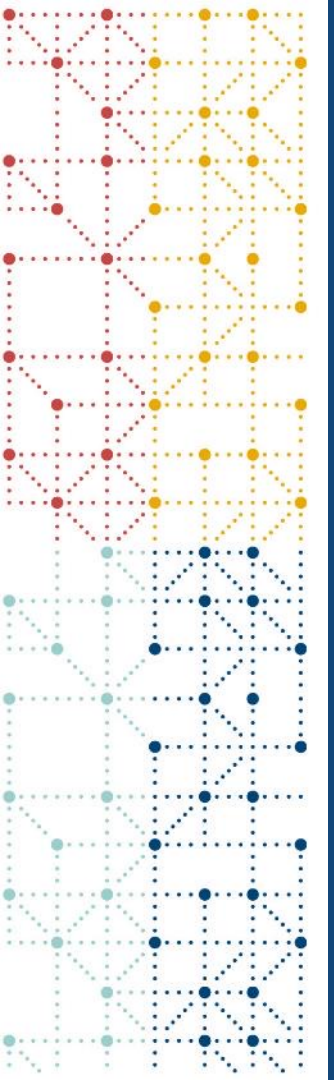


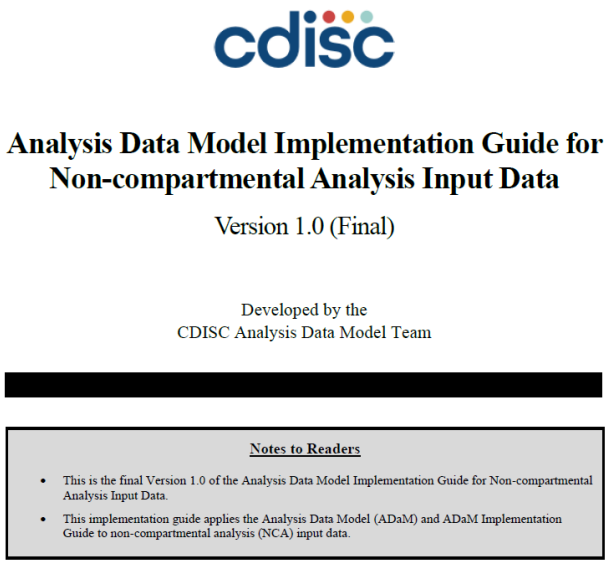
- NCA is done after ADSL, ADEX and ADPC is ready
- ADPC is the input to NCA
- Derivations are detailed in the specifications and define.xml
  - NCA related variables are derived in ADPC directly
  - PK parameter related variables/records are derived in PP/ADPP directly
  - ADPC and PP can be developed by programmers with guidance of the pharmacokineticist
- Less steps and intermediate files = less QC effort



ADaM IG for NCA Input Data

ADaM IG for NCA Input Data

- Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data v1.0 (29 Nov 2021)
- Basic Data Structure (BDS) as the specification for the input dataset for NCA
- Supports commonly structured NCAs, and measurements from collections over time intervals (typical for urine)
  - new standard NCA variables
  - required variables for NCA



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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.

New Standard NCA Variables

Variable Name	Variable Label	Notes
NCAXFL	PK NCA Exclusion Flag	Flag for exclusion of a record into a PK NCA calculation (Y = exclusion, Null = inclusion) *Important for Phoenix WinNonlin filtering. Examples are placebo records, daily pre-dose concentrations in between full profile collection days, excluded records.*
NCAwXRS	Reason w for PK NCA Exclusion	This variable is used to explain why the record is not included in the PK NCA.
PKSUMXF	PK Summary Exclusion Flag	Flag for exclusion of a record from a PK summary (1 = exclusion, Null = inclusion) *We use PKSUMXF**L**.*
METABFL	Metabolite Flag	Flag to designate if observations within a subject are associated with a metabolite. Required if parent drug and metabolites are present in the dataset. *Not often used. We thought adding ANALYTE to represent the name of the parent drug or metabolites is more useful.*
NRRLT	Nominal Rel. Time from Ref. Dose	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	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	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).
TMPCTDF	Percent Diff. Nominal vs. Actual Time	This is the percent difference between nominal and actual time. It is derived by using the standard percent difference formula: 100*(NRRLT - ARRLT)/(NRRLT). In addition, we use TMDF for Difference Nominal vs Actual Time.

Workflow Details

Analysis ready ADPC

- All variables needed for NCA
- May be used to create TLFs for observed concentration time data, but this is not the primary purpose of the dataset
- In practice, we do use it for TLFs
  - PCSTRESC is retained
  - AVAL is the variable used in Phoenix WinNonlin
  - AVALTLF is created when graphical presentation is different than PCSTRESC/NCA rules
  - Variable to indicate notes about the PK collection (e.g. vomiting, time deviation)
  - Derived records/DTYPE are added for urine calculation

DTYPE
CONVERSION
CUMULATIVE
CUMULATIVE PERCENTAGE

Exclusion of data in ADPC

- Excel file which lists the records to be excluded
  - Created by the pharmacokineticist
  - Agreed with the sponsor
- Automatic reading/importing of the file
  - Filename with default prefix and date e.g. STUDY1_PART_A_PC_EXCL_YYYYMMDD.xlsx
  - Contains record identifiers e.g. STUDYID, USUBJID, VISIT, PCDTC, PCTESTCD, PCCAT
  - Exclusion notes are included in the file
  - Implement a macro to:
    - automatically select the latest exclusion file
    - flag the excluded records
    - And attached the exclusion notes to the records
- ADPC is rerun once new exclusion file is available

NCA

- Phoenix WinNonlin
- Import to WinNonlin is ADPC
  - Lean ADPC – only crucial variables needed for NCA are included for accuracy and efficiency
- Results export via CDISC functionality – PP.XPT including RELREC.XPT

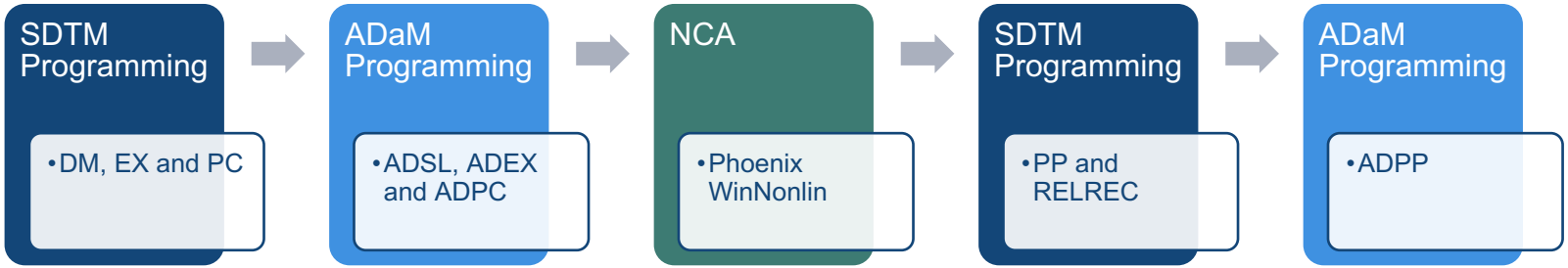
PP and ADPP

- PP program processes the Phoenix WinNonlin PP.XPT
  - Automatic import of the XPT files via macro
  - Create additional variables related to the PK parameters
    - Flags and notes related to lambda-z and span rules satisfaction
    - Other CDISC SDTM variables not initially available

- ADPP program uses PP as input
  - Create additional parameters (records) not part of PP

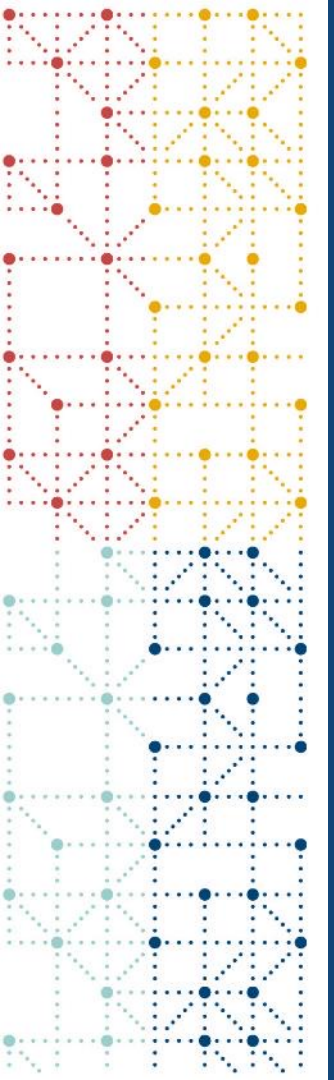
    Such as:
    - Parameter ratios between 2 profiles (e.g. CMAX, AUC)
    - Concentration trough levels
    - Renal clearance and other urine parameters
    - CSF to plasma ratio

NCA Workflow – New version



What's the best practice?

- Where should the NCA flags (e.g. lambda-z or span rules) be derived?
- Where should the derived parameters be placed, PP or ADPP?
- Impact on RELREC
  - Currently program processes the Phoenix WinNonlin RELREC.XPT
  - When there are PK parameters from Phoenix WinNonlin RELREC.XPT that are not part of the final PP
  - When there are additional parameters not derived from Phoenix WinNonlin
    - Example: When CTROUGH is derived at PP level, we added a supplemental variable CTROUGH_LNKID to easily create RELREC between PP and PC



Conclusion

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- Standardization is the most important impact of the ADaM IG for NCA Input Data

- Continuous learning process to discover the efficient workflow for NCA
  - Gaps on where to derive NCA related flags and derived parameters
  - Efficient way to implement exclusion of records and importing of files

- How do you implement your NCA workflow?

Thank You!

For questions and comments, please visit the OCS Booth or contact me at Mitchikou.Tseng@ocs-consulting.com