

PP24: Implementing ADNCA in the PK Process: A Cross-Departmental Approach

PK/PD analysis is an important part of compound development. Implementing results from PK/PD analysis in ADaM datasets requires combining expertise from different stakeholders. In this poster, we will showcase how we collaborated on a cross-departmental process flow leading to datasets that fulfill the requirements on PK/PD analysis and ADaM standards.

Abstract

PK-related data formatted as ADaM datasets are being requested more frequently by health authorities. This requires study teams to prepare submission-ready ADaM PK-related data, on an ad hoc basis without prior planning. Over the years, the International Society of Pharmacometrics (ISoP) & CDISC have partnered closely to standardize Non-Compartmental Analysis (NCA) data formats establishing the new regulatory standards which have been adopted by J&J.

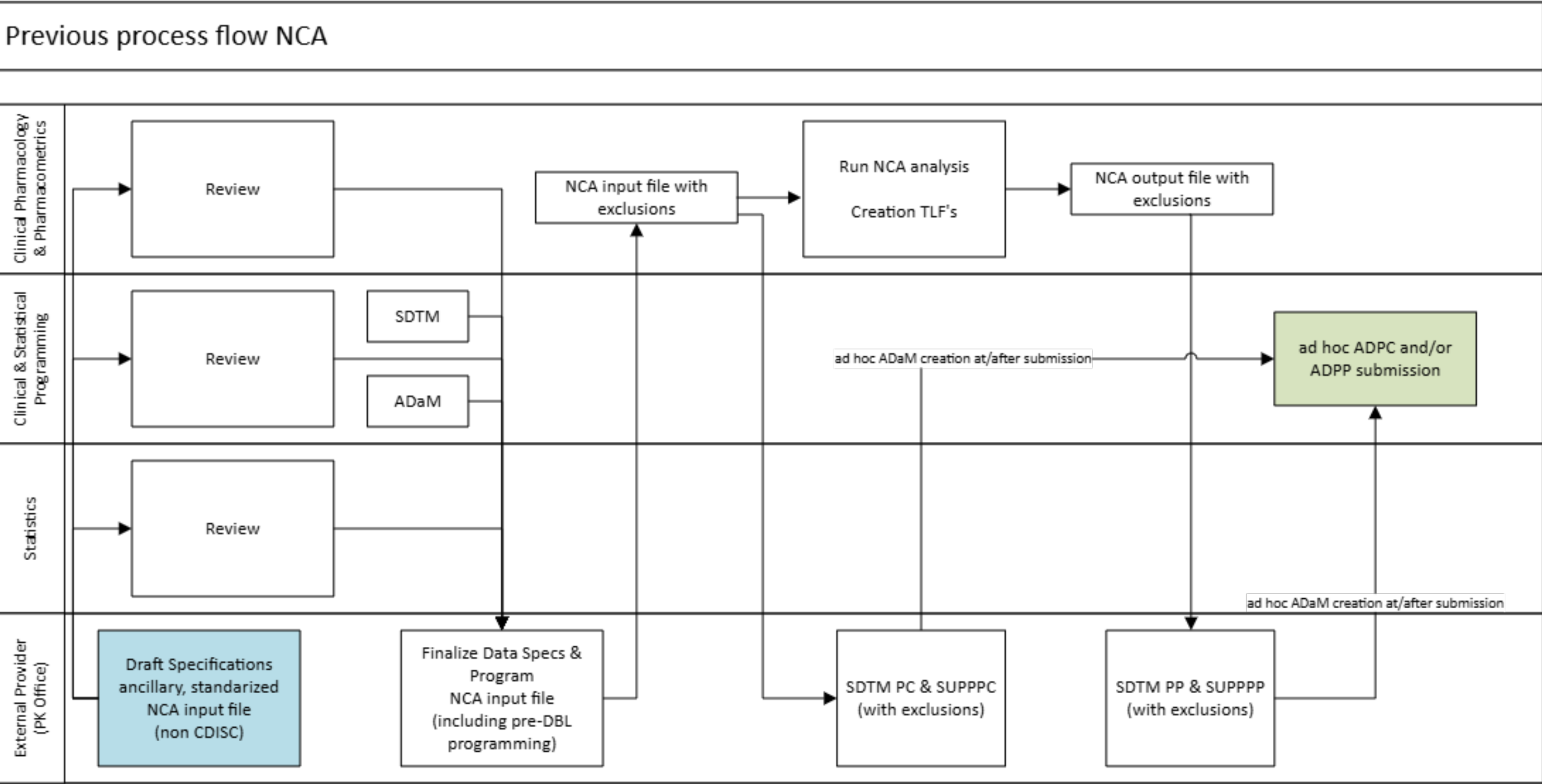
The new ADaM BDS data structure, ADNCA, necessitated process improvements to optimize the delivery of the required datasets. To address challenges and minimize last-minute re-work moving forward, we initiated a collaborative effort across multiple departments to reform our NCA data flow.

This poster presents insights into the modifications we implemented utilizing an ADNCA dataset as input for the NCA analysis. We will outline the steps taken to enhance the rollout of this revised process and discuss the challenges encountered during implementation of the initial studies using this streamlined approach. Through these changes, we aim to improve efficiency and compliance with the latest regulatory standards in our programming efforts.

Previous NCA process flow

- Creation of NCA input specification document, based on input from different stakeholders.
- NCA input file created by PK Office, based on specification document.
- NCA input file updated by PK Scientist and provided back to PK Office for updating SUPPPC and inclusion in SDTM package.
- Performing analysis and creation of TLF's based on NCA input and NCA output file.
- NCA output file provided to PK Office for creation of PP & SUPPPP and inclusion in SDTM package.
- Ad Hoc creation of ADaM datasets based on request from Health Authorities

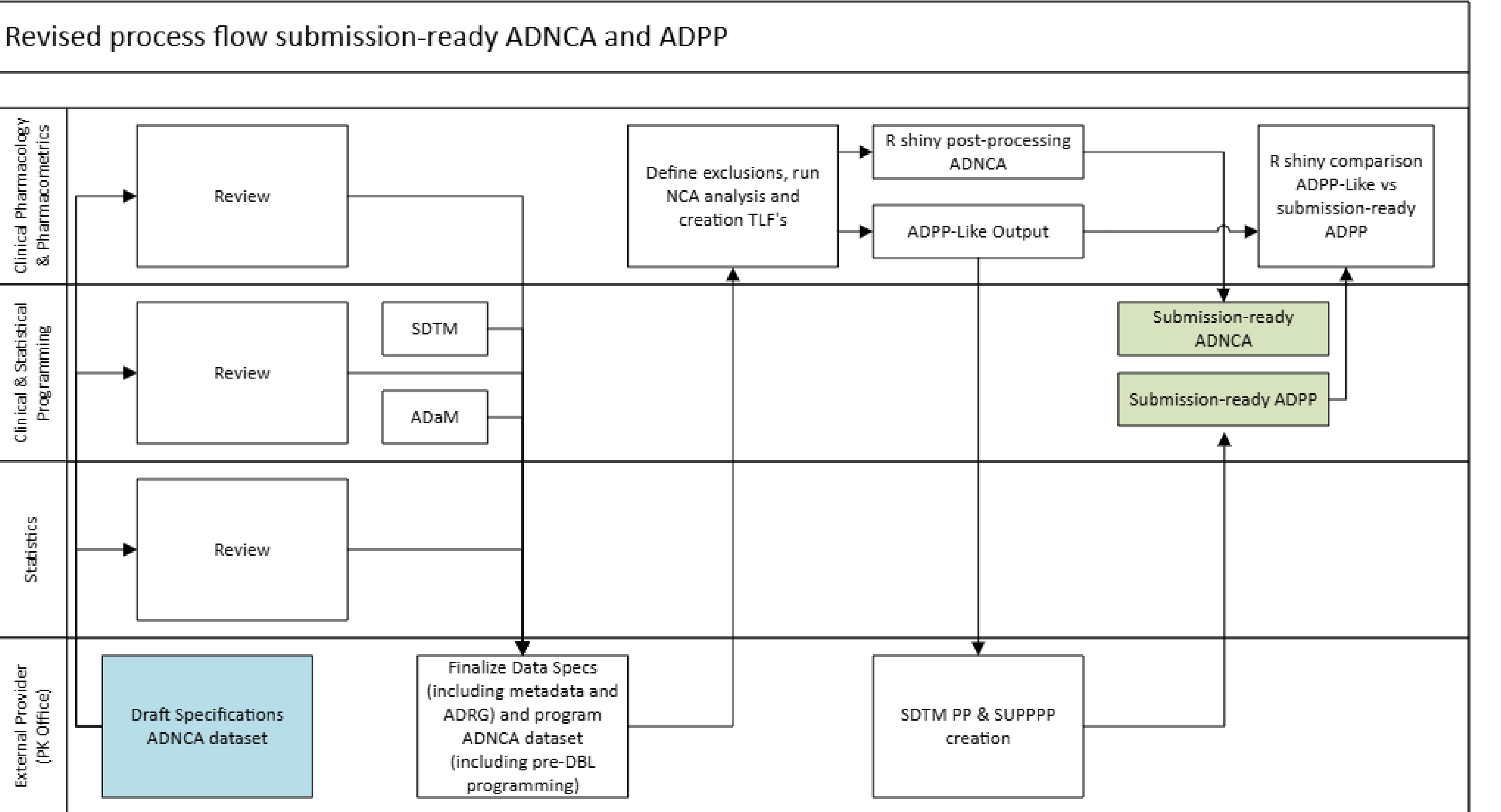
Figure 1. Previous process flow NCA datasets (Non-CDISC format)



Revised NCA process flow

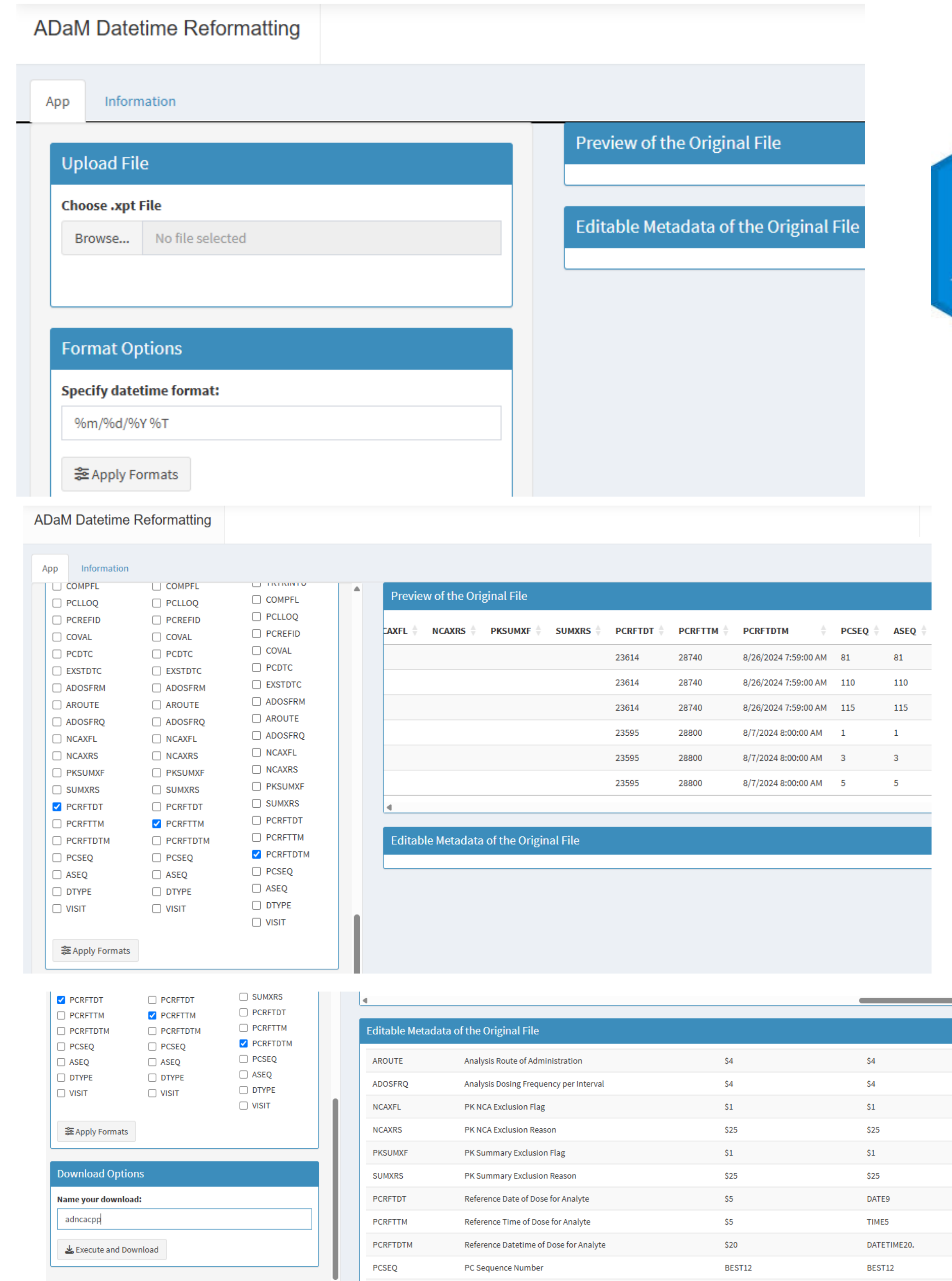
- J&J Clinical Pharmacology & Pharmacometrics, Clinical & Statistical Programming & Clinical Data Standards worked together to create a robust metadata template for ADNCA & ADPP which fulfills requirements from PK perspective to be able to perform the analysis using Phoenix WinNonlin software but also meeting CDISC ADaM requirements.
- Creation of ADNCA input specification document using metadata template, based on input from different stakeholders.
 - ADNCA created by PK Office, based on metadata.
 - ADNCA updated by PK Scientist to define exclusions.
 - NCA analysis performed, creation of ADPP-like dataset.
 - Creation of TLF's based on ADNCA and ADPP-like.
 - ADPP-like provided to PK Office for creation of PP & SUPPPP and inclusion in SDTM package.
 - ADNCA provided to Statistical Programming, together with metadata, programs used to create ADNCA and text to be included in ADRG.
 - ADPP created by Statistical Programming based on PP, SUPPPP and ADSL.
 - Inclusion of ADNCA & ADPP in ADaM eSub package.

Figure 2. Process flow ADNCA datasets (CDISC format)

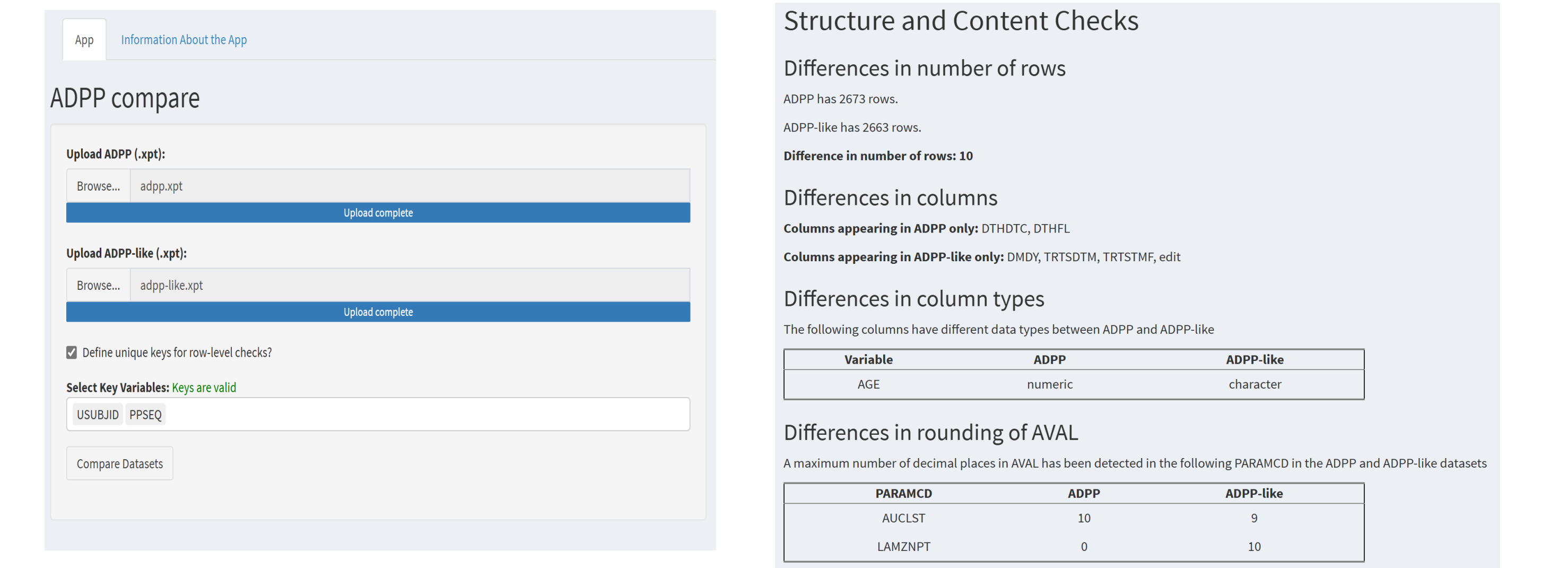


Challenges

- We chose to implement the new process using a trial-and-error approach. We worked out metadata templates and guidance documents as best as possible before the first study would go through the revised flow. We used the first studies as pilot studies and learned from the outcomes to improve the metadata templates and build in additional checks.
- The ADNCA dataset exported from Phoenix WinNonlin had formatting issues with date/time variables. An R Shiny App is now used to check and correct ADNCA before providing to Statistical Programming.



- By going through these initial pilot studies, we also noticed that some of the specifications in our metadata template were leading to P21 issues. Most were resolved by adding or renaming required variables or updating labels in metadata template.
- For NCA analysis, all scheduled samples need to be included in ADNCA (even when not available in PC domain or having PCSTAT = "NOT DONE"). For these records, P21 error AD0196 pops up (Required Variable value is null). In our guidance documents for Statistical Programming, we provided information on how to handle this error in ADRG.
- To make sure the submission-ready ADPP is consistent with ADPP-like, used for TLF creation, an R Shiny app is developed to compare ADPP-like with ADPP dataset.



Conclusion

The roll-out and adoption of the CDISC ADaM BDS dataset structure of ADNCA has been implemented successfully. At study completion, we have submission-ready non-compartmental analysis datasets including exclusions to descriptive concentration-time data, as well as data excluded from PK/PD parameter calculation, available per regulatory requirements.

At this point, we are still including the PK analysis results in PP/SUPPPP as part of the SDTM package. However, once this is no longer required based on CDISC guidelines, we are well-prepared to immediately have the ADPP-like dataset used for the creation of submission-ready ADPP.

References

CDISC Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data v1.0

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