

Challenges in Data Standardization and Completeness for the Development of a Renal Impairment Tool in Clinical Pharmacology

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Introduction

The Office of Computational Sciences (OCS) in collaboration with Office of Clinical Pharmacology (OCP) has developed and piloted a Renal Impairment Tool to evaluate clinical pharmacology data from subjects with varying degrees of renal insufficiency to inform decision making regarding dosing recommendations. During development, OCS has found that inconsistencies in usage of CDISC data standards and incomplete datasets has made it difficult to import submitted data into the tool for analysis. The findings include (1) input datasets were not compliant with CDISC standards or were missing required features, including glomerular filtration rate (GFR), pharmacokinetics parameters category (PPCAT), and appropriate laboratory units; (2) ADaM datasets did not clearly label duplicate records with distinct flags, which are important for baseline measurements and end of treatment measurements; (3) Supplemental Demographics datasets did not contain treatment grouping information in circumstances when it was not present in Demographics (DM or ADSL) datasets, which creates a conditional requirement that mandates manual review. The improvement of data quality in the clinical pharmacology space, has a significant potential to produce efficiencies in the analytical process and evaluation of renal impairment and other related areas

Objectives for Renal Impairment Tool

- Provide a flexible and customizable tool that facilitates Renal Impairment analyses across a variety of study designs and user needs
- Allow users to upload CDISC-compliant sponsor datasets in SDTM or ADaM format
- Design user interface to empower users to iteratively refine analysis outputs in real time in the FDA-CDER intranet
- Simplify parameter selection process by automatically detecting recommended variable:value pairs from uploaded datasets

Requirements for Renal Impairment Tool

- Intuitive user interface that enables detailed analyses with minimal user input
- Tool accommodates variation in study design
- Tool permits import of SDTM and ADaM datasets:
 - Demographics, Laboratory, PK Concentrations, PK Parameters datasets are all required
- User may freely specify custom parameters for all analysis variables and values
- User may easily export the full analysis to Microsoft Word format to enable collaboration and sharing
- Users can select, filter, and tune pharmacokinetic, demographics, and laboratory inputs to meet specific analytical needs

Description of Datasets and Issues

STUDY 001

- All SDTM and ADaM datasets are sufficiently complete and require no modifications
- ADaM ADPC is missing PCSPEC (Specimen) and PC unit variables, which are optional for the analysis
- Renal impairment analysis is complete
- Analysis outputs using SDTM and ADaM inputs are identical

STUDY 002

- No SDTM Laboratory dataset (LB) provided by sponsor
- Insufficient data to perform renal impairment analysis

STUDY 003

- DM and SUPPDM datasets do not include treatment groupings information
- Treatment groupings must be derived and mapped manually into DM
- No records for GFR under CDISC standard variable (Lab Test Code LBTESTCD)
- Missing units in PC and PP datasets
- Partial outputs for Renal Impairment analysis possible
- Insufficient data to perform complete renal impairment analysis

STUDY 004

- SUPPDM uses SET as treatment grouping variable
- Renal impairment analysis is complete
- Analysis outputs using SDTM and ADaM inputs are identical

STUDY 005

- All SDTM and ADaM datasets are sufficiently complete and require no modifications
- PC is missing PPCAT (Category) variable, which is option for the analysis
- Renal impairment analysis is complete
- Analysis outputs using SDTM and ADaM inputs are identical

STUDY 006

- All SDTM and ADaM datasets are complete and require no modifications
- Renal impairment analysis is complete
- Analysis outputs using SDTM and ADaM inputs are identical

STUDY 007

- No valid treatment grouping information in Demographics data (DM or SUPPDM)
- Treatment groupings must be derived from Laboratory (LB) dataset
- No AUCIFO in PK data – derivation required
- Datasets not appropriate for use in Renal Impairment Tool without modifications

STUDY 008

- No records for GFR under CDISC standard variable (Lab Test Code LBTESTCD)
- Partial outputs for Renal Impairment analysis possible
- Insufficient data to perform complete Renal Impairment analysis
- Missing units in PC and PP datasets

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Results

- Design principles aligned with key design specifications
- Stable tool accessible by CDER users, currently available to limited testing group
- Tool deployed as web application in CDER RAPID environment (AWS GovCloud)
- Studies with sponsor datasets conforming to minimum requirements are successfully ingested and processed in the Renal Impairment Tool
- Analyses are successfully performed on SDTM and ADaM datasets with identical statistical outputs

Study	Full Analysis?	No manual data modifications?	Not missing key data?
STUDY 001	✓	✓	✗
STUDY 002	✗	✓	✗
STUDY 003	✗	✗	✗
STUDY 004	✓	✓	✓
STUDY 005	✓	✓	✗
STUDY 006	✓	✓	✓
STUDY 007	✗	✗	✗
STUDY 008	✗	✓	✗

Conclusion

The pilot Renal Impairment Tool developed by OCS-OCP partnership was designed to be a flexible and user-friendly platform for conducting statistical analyses. Improving the analytical coverage of the Renal Impairment Tool to accommodate additional study designs requires high quality data submissions with improved adherence to CDISC data standards and data requirements. Renal impairment analyses integrates data from several domains. Therefore, a single missing record or variable in one domain can impact the integrative analyses and yield faulty or absent results. Submission of high-quality data will facilitate tool development and statistical programming across FDA centers and offices.

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