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Improving the Efficiency and Ensuring the Quality of Data Assembly for Pharmacometric Analysis

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COGNIGEN

ABSTRACT

Purpose. Better tools and processes can improve the efficiency of data assembly and the quality of analysis-ready datasets for pharmacometric analyses.

Methods. A systematic analysis of unstructured e-mails generated during data assembly was performed to uncover the most frequently discussed issues. These issues were categorized into knowledge domains and used to develop a series of formal programming specification forms.

Results. Issues pertaining to dose were most common. The specification forms were deployed in conjunction with a collaborative website to capture semi-structured communications. Subsequent review of these team communications will enable future refinement and expansion of the specification forms.

Conclusions. The development of these specification forms is anticipated to improve the performance characteristics of data assembly in terms of consistency, reliability, timeliness and quality of the work product.

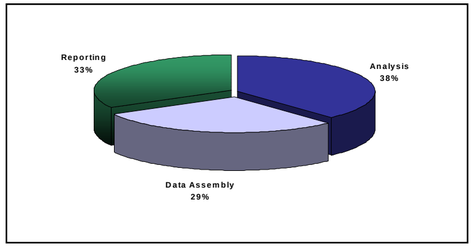
INTRODUCTION

- Quality of analysis and the appropriateness of recommendations based on the model are contingent upon the quality of the analysis dataset.[1,2]
- Efforts to improve requirements for the NONMEM® dataset creation may improve the efficiency and quality of pharmacometric analysis.
- The creation of an analysis-ready dataset for NONMEM (typically) consists of preparing a time-ordered sequence of events for each subject, based on a statement of clear and concise specifications for the analyses.
- Once data programming begins, the programmer is likely to face a host of issues that arise from deficiencies in the requirements or inconsistencies between the requirements and raw data.
- These issues typically spawn a series of discussions between the stakeholders, generating more specific questions as the team members clarify issues and resolve uncertainties.
- This iterative cycle of questioning and discussion is a valuable source of information on how to improve requirements and reduce the time and effort required for data assembly.

GOALS

- Improve the efficiency of data assembly for pharmacometric analyses
- Improve the quality of the pharmacometric analysis-ready datasets

Resource Allocation for Pharmacometric Analyses

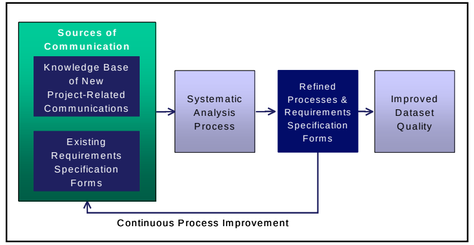


OBJECTIVES

- Formalize the requirements specification process based on an understanding of the information required for unambiguous communications between pharmacometrician and programmer
  - To identify common sources of miscommunication between team members regarding pharmacometric dataset assembly
  - To develop formalized programming specifications for NONMEM data assembly
  - To implement a strategy for continually refining and expanding the scope of these programming specifications
- Implement a strategy and feedback loop for continuous improvement

METHODS

Overview



Systematic Analysis Process

- Identifying data assembly related communication problems
  - Project e-mail folders were created to automatically capture all project-related team communications
  - E-mail communications for three historical Cognigen projects were selected for systematic analysis
    - 1100 e-mails were manually scanned to build a knowledge base of project-related questions
    - These questions were categorized into the root causes of confusion and uncertainty between pharmacometrician (requirements provider) and programmer (requirements receiver)
  - Text mining tools were then utilized to extract relevant information from two additional historical Cognigen projects (1500 e-mails) in order to search for relationships heretofore unappreciated in the previous manual scanning process
    - e.g., a strong correlation between the words 'Dose' and 'recreate' was revealed, indicating a frequent need to recreate the dataset based on a dose-related issue

Formalization Process

- Designing the Prototype Requirements Specification Forms
  - Conducted interviews with stakeholders to ascertain the importance of each communication issue from the various perspectives
  - Began to formulate new requirements that would address the gaps in existing requirements specification process
  - Identified key informatic elements that link together scientific knowledge and dataset structure and content of NONMEM-specific variables
    - Route of Administration → Depot / No Depot → Compartment definitions
  - Developed prototype form aligning the pharmacometrician needs for completing the form, with the programmer needs for processing the form
  - Implemented a pilot test on previously completed projects

Continuous Process Improvement

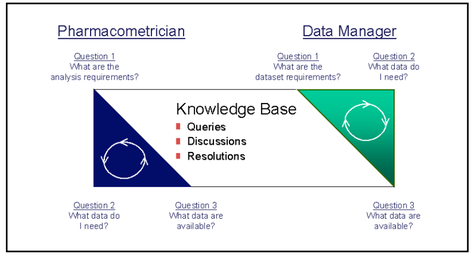
- Managing and capturing future project communications
  - Pharmacometrician, programmer, and information technology representatives met to discuss possible solutions for improving project team communications
  - A web-based solution (wiki) was implemented to facilitate communication and collaboration
  - Wiki templates were created to provide structure for issue-specific project communication needs, as well as the information extraction process for future systematic analyses

RESULTS

Systematic Analysis Process

- Examples of e-mail questions after initial requirements had been communicated to programmer
  - *How many doses prior to sample should be included in the analysis dataset? And what if subjects don't have sufficient doses prior to samples?*
  - *If a subject has three missed doses, can I still assume steady state?*
  - *How should the weight-based dosing be calculated? Is there a cap?*
  - *Is time since last dose calculated based on start or end of the infusion?*

Building The Knowledge Base[3]



- Common sources of confusion and error
  - The most common sources of confusion and errors related to the NONMEM dataset creation process included instructions for:
    - Creating dosing records
    - Composition of analysis population
    - Management of concentration records
    - Handling the timing of concomitant medications and setting concomitant medication flag variables
    - Imputation of missing data

Formalization Process

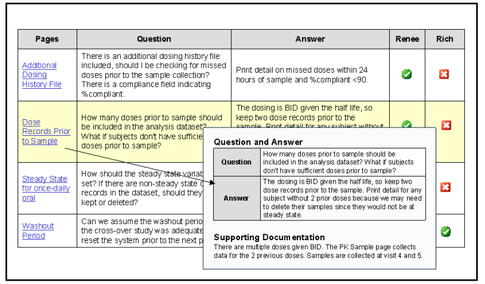
- Prototype Requirements Specification Forms
  - New forms were designed based on logical organization
    - Characterization of base PK model
    - Definition of analysis population
    - Dose specification
    - Concentration specification
    - Subject covariates, labs, conmeds, and PD endpoints: TBD
    - Simulation dataset specification

Example of Prototype Requirements Specification Form

Consideration	Options
How many doses prior to sample should be included?	
How should non-compliant subjects be managed if they don't have sufficient doses prior to sample?	• Keep • Delete • Impute Dose
If using Steady-State flag: 1. When is a subject considered to be at steady state?	
2. Keep or delete non-steady-state doses?	• Keep • Delete
3. How should missed doses that could impact steady state be handled?	

Continuous Process Improvement

- Managing and capturing future project communications
  - Utilization of the new forms will entail a continuous learning process
    - Practical application will reveal better information to include in and improve on the form
  - Need a way to track, monitor, and create a feedback loop with the ongoing questions
    - Continue to reduce rework by further refining requirements
    - Continue to improve quality and efficiency through more effective communications
- Wiki as a communication tool
  - A wiki[4] (Hawaiian word for 'quick') is an open, collaborative community website where authorized users can easily add, remove, edit, and search content using a web browser
  - Simple, efficient tool for information sharing, collaboration, and knowledge management
  - Content is centralized so knowledge doesn't get lost, buried in e-mails, or scattered into file systems
  - Security features include granular permissions, audit trail, and revision history
- Communication requirements
  - The programmer poses question using question template
    - Documents question, details, supporting documentation, and question category
  - Collaborators provide feedback to question
  - Programmer implements decision as necessary, and confirms completion of task
  - Metadata, inherent to each question page, enables
    - Creation of individual's "To Do" list
    - Automatic generation of a question and answer list
  - Questions are subsequently reviewed for content to integrate into specification template
- Improved Communication/Collaboration Tools



Pages	Question	Answer	Renee	Rich
Additional Dosing History File	There is an additional dosing history file included, should I be checking for missed doses prior to the sample collection? There is a compliance field indicating %compliant.	Print detail on missed doses within 24 hours of sample and %compliant <90.	✓	✗
Dose Records Prior to Sample	How many doses prior to sample should be included in the analysis dataset? What if subjects don't have sufficie doses prior to sample?	The dosing is BID given the half life, so keep two dose records prior to the sample. Print detail for any subject without	✓	✗
Steady State for once-daily oral	How should the steady state variab set? If there are non-steady state records in the dataset, should they kept or deleted?	The dosing is BID given the half life, so keep two dose records prior to the sample. Print detail for any subject without 2 prior doses because we may need to delete their samples since they would not be at steady state.		✗
Washout Period	Can we assume the washout perio the cross-over study was adequat reset the system prior to the next p			✓

Question and Answer

Question	How many doses prior to sample should be included in the analysis dataset? What if subjects don't have sufficient doses prior to sample?
Answer	The dosing is BID given the half life, so keep two dose records prior to the sample. Print detail for any subject without 2 prior doses because we may need to delete their samples since they would not be at steady state.

Supporting Documentation
There are multiple doses given BID. The PK Sample page collects data for the 2 previous doses. Samples are collected at visit 4 and 5.

NEXT STEPS

- Supplement configuration management process for tasks with revolving requirements, e.g., the creation of ad hoc figures and tables
- Monitor the ongoing project-related communications and create a repository for future analytical efforts
- Periodically analyze repository for insight enabling continuous improvement and further refinement of the requirements specification forms
- Continually refine taxonomy to improve the performance characteristics of automated text mining procedures
- Direct future research efforts at quantifying the value of the formalized process

SUMMARY

- Formalization of requirements specification is critical to ensuring the quality and consistency of the pharmacometric data assembly process
- Improvement to existing tools and processes can be realized through systematic analysis, formalization, and continuous process improvement
- Analysis of e-mail communications was integral to formalization efforts for the data assembly process employed at Cognigen
- Limitations in the systematic analysis of e-mail communications prompted implementation of a wiki solution for project communications
- Impact of these formalization efforts on team productivity and quality are yet to be determined, but of major importance

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