Title: Facilitating the Pharmacometrics Work-Flow with the MItools R Package

Authors: William Knebel*(1), Tim Bergsma (1), Jeannine Fisher (1), George Georgalis (1), Leonid Gibiansky (1), Bill Gillespie (1), Matt Riggs (1), and Marc R. Gastonguay (1)

Institutions: (1) Metrum Institute, Tariffville, CT, USA

Objectives: A pharmacometrician's typical work-flow requires access to a variety of software tools for different stages (data preparation, exploration, modeling, post-processing and reporting) of the strategic modeling and simulation process. This process requires reliable, reproducible and traceable inter-operability between software tools. No single tool capable of managing and performing these tasks is publicly available. To this end, we have developed an R software (version 2.4.0; www.r-project.org) package, MItools, to facilitate the pharmacometrics work-flow.

Methods: All necessary system (operating system, R, Sun Grid Engine) software tools were installed via a set of shell scripts under version control. NMQual 6.1.1 (Metrum Institute) was used to install, qualify, and track all code patches/options for NONMEM® Version V and VI (ICON Development Solutions). All R scripts and functions were maintained under version control.

Results: The MItools R package development successfully met functional requirements including utilies for: common data preparation tasks, stratified bootstrap resampling of data sets, NONMEM® control stream creation/editing, NONMEM® model execution as single or batch runs, creation of standard and user-defined diagnostic plots, execution and summary of bootstrap and predictive check results, implementation of simulations from posterior parameter distributions, reporting of output tables suitable for import into word processing software, and creation of a detailed analysis log. All data preparation prior to the utilization of MItools is performed in R via scripts customized for a given analysis. MItools runs on single worksation computers (Windows XP or Mac OSX) with R version 2.2 or above and across computer grids utilizing the Sun Grid Engine distributed computing software running on the NetBSD operating system. The utilization of MItools with Sun Grid Engine allows for distributed computing and easy sharing and management of computing resources between multiple users and projects. Little or no knowledge of scripting (shell, Perl, etc.) beyond some basic R-language proficiency is required of end-users. Functions within the MItools package can be readily exposed, customized and extended using standard methods available in the R base package. Funtional requirements for MItools have recently been revised to include utilities for control and automation of WinBUGS/OpenBUGS software and a prototype has been developed.

Conclusions: The MItools package allows the pharmacometrician to work within one easily scriptable environment (R software) for data preparation, analysis, and reporting tasks. (The MItools package is available for download from Metrum Institute at http://metruminstitute.org/downloads).