Development and Evaluation of a Simulation Platform for Malaria Volunteer Infection Study (VIS) Designs

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ABSTRACT

Background: Previous work[1] demonstrated viability of adaptive reduced trial designs for VIS in malaria, reducing traditional three single-dose-level, 8 subject cohorts (n = 24) to a three-dose-level single-cohort (n=8) design. The prior proof of concept work used a single cohort, single subset (n=8), favoring the optimal dose (2-2-4). The goal of this work is to select cohort data stochastically to assess performance under uncertainty as to the optimal dose. A simulation-analysis platform was developed for rapid iterative model performance assessment and refinement in support of malaria research.

Methods: An R based platform was developed to rapidly simulate, estimate, and summarize VIS study results for alternate designs. The platform generates analysis datasets and NONMEM control files for estimation with NONMEM 7.3 using KIWI 3. The platform was tested with a literature model for quinidine (3). Ten traditional design studies (8 subjects at each of 3 single dose-level cohorts (n=24)) were simulated from which 100, 2-2-4 (low-middle-high dose) and 4-4-8 single-cohort design trials were selected and evaluated for bias and imprecision of parameter estimates.

Results: Central tendency of PD parameter estimates was comparable between full and reduced study designs. Parameter bias was small and comparable across designs [e.g., Gordi Model, mean transit time (MTT) of parasite life-cycle: -3.0 & -3.3% for reduced vs full-design, respectively]. Precision was rank order for 2-2-4 and 4-4-8 versus traditional 8/8/8 designs (MTT: 2.35, 0.791, & 0.511 %RSD, respectively)

Conclusions: Simulations demonstrated similar accuracy, but reduced precision of PK/PD model parameters at a much reduced trial cost and duration. Further clinical assessment of single cohort design is warranted.

INTRODUCTION

Traditional malaria volunteer infection studies have three consecutive single-dose cohorts. Work was done to show the ability of a single cohort with multiple-dose levels to estimate PK/PD parameters. A simulation platform was developed to stochastically test different trial designs and compare across malaria PD models and asses need and feasibility of additional cohort with additional doses across the dosing range.

METHODS

Developed a platform for simulation and analysis of traditional and adaptive VIS designs (**Figure 1**).

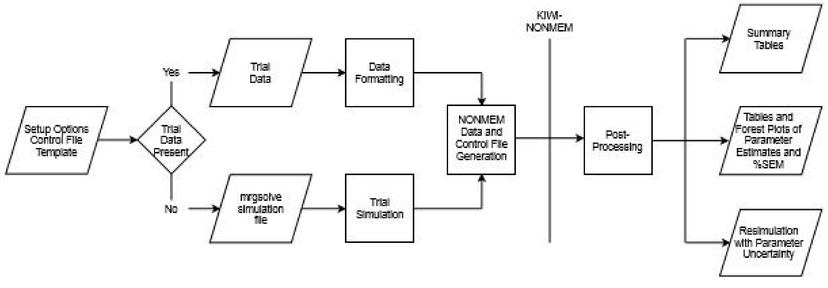

Figure 1: The platform is a series of R scripts that simulates trials with *mrgsolve* v.0.9.0, generates necessary NONMEM control files and datasets, and runs post-processing for tables and plots of parameter estimates. Estimation was done with NONMEM7.3 within KIWI3.0 shell. User provides models and design specifications to be evaluated by the program.

Data was simulated from modified quinidine PK/PD model.[3] In the simulation patients received rescue doses when an increase in $\log_{10}$ parasite was detected over three time points or patients whose parasite count fell below LOQ (0.003) became detectable within observation period.

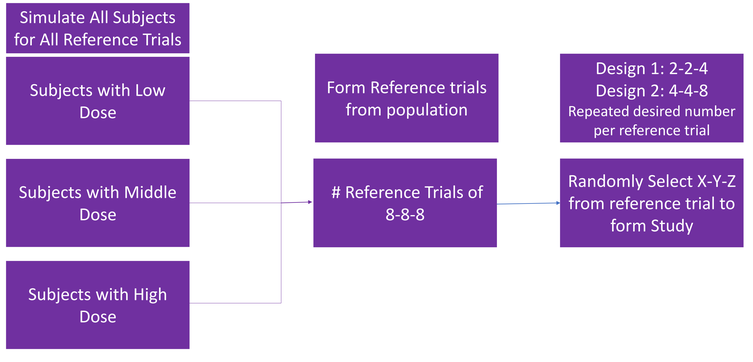

Figure 2: 10 Trials of a traditional design (8 low, 8 middle, and 8 high dose per trial) were simulated. From each 'reference' trial, 10 subsets of 2 designs, 2-2-4 (Design 1) and 4-4-8 (Design 2) ,were randomly selected to compare back to the reference trial

RESULTS

Central tendency of the fixed parameter estimates were comparable between the full and reduced; percent difference was less than 25% from simulation values for all fixed estimates.(**Table 1 and 2**). Precision of the estimates (%SEM) was rank order (**Figure 3**) for the adaptive versus the traditional design, fixed parameter estimate %SEM less than 20% for all parameters (**Table 1**). Estimated PK/PD parameters were then used to re-simulate expected parasite curves without regard to rescue dose for doses tested.

Parameters	Simulation Values	Reference Estimates	Reference %SEM	Design 1 Estimates	Design 1 %SEM	Design 2 Estimates	Design 2 %SEM
MTT (1/h)	0.8	0.774 (0.748 - 0.795)	0.511 (0.0979 - 0.75)	0.776 (0.74 - 0.807)	2.35 (0.894 - 9.37)	0.773 (0.741 - 0.8)	0.791 (0.231 - 1.35)
KPINJ (ng/(mL*h))	0.24	0.281 (0.211 - 0.497)	2.08 (0.696 - 5.93)	0.267 (0.186 - 0.468)	10.6 (3.01 - 39.5)	0.267 (0.198 - 0.481)	3.4 (0.997 - 8.7)
KINJ (1/h)	0.09	0.111 (0.0844 - 0.161)	0.6 (0.0809 - 1.68)	0.111 (0.0824 - 0.188)	3.74 (0.821 - 23.8)	0.111 (0.0844 - 0.169)	1.03 (0.222 - 3.93)

Table 1: Pharmacodynamic Fixed Parameter estimates and %SEM with median and 90% Confidence Interval

Parameters	Reference	Design 1	Design 2
MTT	3.3%	3%	3.4%
TVKPINJ	17.1%	11.3%	11.3%
TVKINJ	23.3%	23.3%	23.3%

Table 2: Percent difference of Fixed Parameter estimate from Simulation Values by trial design

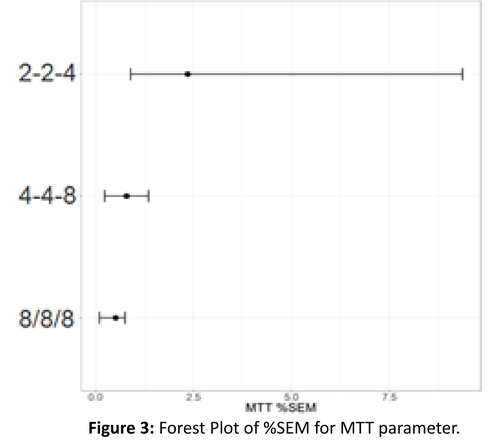

Figure 3: Forest Plot of %SEM for MTT parameter.

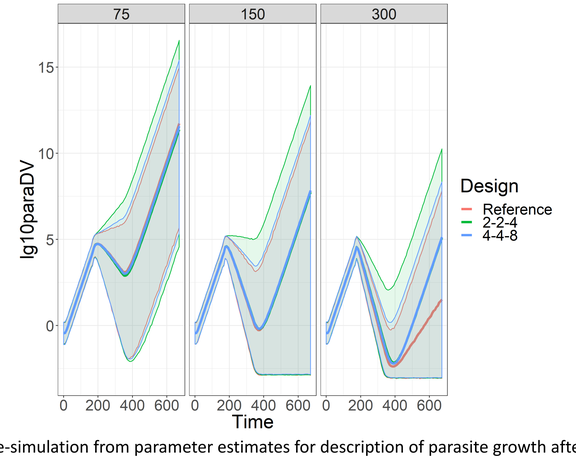

Figure 4: Re-simulation from parameter estimates for description of parasite growth after one dose of trial medication, lines represent median, 90% Confidence interval for parasite growth

CONCLUSIONS

A scalable simulation platform was developed that rapidly and efficiently compares study designs in adaptive VIS studies or Phase 2 clinical trials for Malaria. The platform can evaluate numerous adaptive designs and compare back to the traditional reference. It was shown that fixed PD estimates are comparable and precision is reasonable even with eight patients compared to twenty-four. We were also able to simulate similar malaria growth profiles with parameter uncertainty. Work is being done in parallel to optimize dose selection for additional cohorts.

REFERENCES

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2. Baron, K, et al. 2015. JPKPD 42:S84-S85
3. Gordi T, et al. 2005. BJCP. 60(6):594-604