R, Simulations, and Complex Innovative Trial Designs

A Presentation for R in Pharma

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent the FDA's views or policies.

Outline

1. Complex Innovative Trial Design Pilot
2. Simulation Studies
3. Sizing Simulations appropriately
4. App Demo
5. Use of R for simulations

CID Pilot Program

Complex **I**nnovative Trial **D**esign Pilot Program

Federal Register, Vol. 83, No. 169, Thursday, August 30, 2018, Notices pp 44274-44277

"In connection with the sixth iteration of PDUFA, FDA committed to conduct a pilot program for highly innovative trial designs for which analytically derived properties (e.g., Type I error) may not be feasible, and simulations are necessary to determine trial operating characteristics."

CID Pilot, Design Features

Examples of Innovative Features

- Use of simulations to determine operating characteristics
- Seamless adaptive designs
- Hierarchical modeling
- Bayesian designs
- Use of an informative prior distribution (possibly based on historical controls)
- Response-adaptive randomization, etc.

Therapeutic need
(*i.e.*, therapies being developed for use in disease areas where there are no or limited treatments)

CID Pilot Meeting Program

- Joint CDER/CBER effort
- Five year duration
- Sponsors
  - submit designs
  - have the opportunity to engage with regulatory staff on designs via two meetings
- Agency
  - will select up to 2 submissions per quarter
  - uses the design as a case study for continuing education and information sharing
- Meetings led by OB (CDER) with participation from all relevant disciplines

Benefits for Sponsors and FDA

- Ensure safe and effective therapeutic options for patients
- Provide a path forward for challenging problems benefitting from innovative thinking
- Acknowledge one size does not fit all
- Enhance and advance expertise with innovative designs with both regulators and regulated industry

CID, Statistical Analysis and Simulations Plans

Sponsors will be expected to submit detailed plans:

- "Description of study design,including study schema with treatment arms, randomization strategy, and endpoints."
- "Key features of the statistical analysis plan including, but not limited to, the analyses, models, analysis population, approach to handle missing data, and decision criteria. These should include aspects of the design that may be modified and the corresponding rules for decisions, if adaptive."
- "Simulation plan, including the set of parameter configurations that will be used for the scenarios to be simulated and preliminary evaluation and discussion of design operating characteristics. Preliminary simulation results of the operating characteristics (e.g., type 1 error, power, etc.) should include several hypothetical, plausible scenarios." (Federal Register)

CID, Simulation Report

Sponsors whose meeting requests are granted as part of the pilot program will be expected to submit a detailed simulation report that includes:

a. "Example trials in which a small number of hypothetical trials are described with different conclusions.

b. Description of the set of parameter configurations used for the simulation scenarios, including a justification of the adequacy of the choices.

c. Simulation results detailing the simulated type I error probability and power under various scenarios.

d. Simulation code that is readable, adequately commented on, and includes the random seeds. **The code should preferably be written in widely-used programming languages such as R or SAS to facilitate the simulation review.**" (emphasis added)

CID Presentation Requirements

The Federal Register also states presentation requirements:
"Overall conclusions including a brief summary of the simulated operating characteristics based on design features and analyses and a discussion of the utility of the CID given the simulation results."

CID Page

Complex Innovative Trial Design Pilot Program

Simulation Studies

What should go into simulations studies, plans and reports such as those in the CID Pilot Meeting Program?

Two references:

- Burton A, Altman D, Royston, P and Holder, R. The design of simulations studies in medical statistics, *Statistics in Medicine*, 2006; 25: 4279-4292
- Morris T, White I, Crowther M. Using simulation studies to evaluate statistical methods, *Statistics in Medicine*, 2019;38:2074–2102

Burton *et al*

0. "Detailed protocol of all aspects of the simulation study
    a. Justifications for all decisions made
1. Clearly defined aims and objectives
2. Simulation procedures
3. Methods for generating the datasets
4. Scenarios to be investigated
5. Statistical methods to be evaluated
6. Estimates to be stored for each simulation and summary measures to be calculated over all simulations
7. **Number of simulations to be performed**
8. Criteria to evaluate the performance of statistical methods for different scenarios (assessments of bias, accuracy, coverage)
9. Presentation of the simulation results" (don't claim more precision than your simulation can support)

Morris *et al*

Embrace the "ADEMP" structured approach

- Aims
- Data-generating mechanism
- Methods
- Estimands
- Performance measures

Morris *et al*, continued

Morris *et al* echo many of the same concerns of Burton *et al*.

- Planning
  - ADEMP
- Coding and Execution
- Analysis
- Reporting
  - Include Monte Carlo SE
  - Publish code to execute simulation study

Morris et al do not explicitly address the issue of determining the appropriate number of simulations.

How Many Simulations Should be Performed?

Hauck and Anderson, A Survey Regarding the Reporting of Simulation Studies, *American Statistician*, 1984, 38, No. 2, pp 214-216

"For example, many of the studies chose 500 or 1,000 iterations so as to have a suitably 'large' number without any consideration as to whether that number is sufficient (or possibly excessive) for accomplishing the purposes of the planned study. As Hoaglin and Andrews noted, statisticians should be expected to pay attention to their own principles. "

Hoaglin and Andrews, The Reporting of Computation-Based Results in Statistics, *American Statistician*, 1975, 29, No. 3, pp 122-126.

Determining the appropriate number of simulations

Estimand θ, estimator $\hat{\theta}$,
δ is the margin of error
$1 - \gamma$ is the significance level
n is the number of simulations
Assume that $\lim_{n \to \infty} \hat{\theta}(n) = \theta$,

Fundamental Estimation Inequality (FEI):

$$P\left(\left|\theta - \hat{\theta}(n)\right| \leq \delta\right) \geq 1 - \gamma$$

Fundamental Estimation Inequality, continued

If $\hat{\theta}(n)$ is approximately normal then $\theta - \hat{\theta} \sim N(0, \frac{\sigma_\theta}{\sqrt{n}})$, so from the FEI we may obtain

$$P\left(Z \leq \frac{\delta}{\sigma/\sqrt{n}}\right) \geq 1 - \frac{\gamma}{2}$$

where $Z \sim N(0, 1)$, and hence

$$n \geq \left(\frac{z_{1-\frac{\gamma}{2}}\sigma_\theta}{\delta}\right)^2.$$

Exact Approach

From the FEI, we may also obtain

$$P\left(-\delta \leq \theta - \hat{\theta}(n) \leq \delta\right) \geq 1 - \gamma,$$

which yields,

$$P\left(\theta - \delta \leq \hat{\theta}(n) \leq \theta + \delta\right) \geq 1 - \gamma,$$

and hence,

$$F_{\hat{\theta}(n)}(\theta + \delta) - F^{-}_{\hat{\theta}(n)}(\theta - \delta) \geq 1 - \gamma,$$

This provides a way to estimate the number of simulations needed to attain a desired level of significance.

Shiny App

Using these methods, Waleed, Torres and Schuette (2019) have obtained methods for determining the number of simulations for binomial outcomes, such as those associated with Type I error, and power. Furthermore, these methods have been extended to exponential, Weibull and Gompertz distributions, so that time to event designs can also be considered.

Using R for Simulations

Simulations that require a large number of iterations/replications will also require greater computing resources. Efficient coding and efficient resource utilization may be increasingly important in order to provide timely results and contain costs.

- Vectorization. Replace loops with vectors and matrices. RAM can be an issue.
- Parallelization. Even on a single machine, multiple cores may be utilized.
- High Performance/Throughput Computing. Use of computing clusters and grid engines to distribute jobs to many machines. Typically requires the use of Linux environments.
- Consider rewriting critical components in C and using the Rcpp package.

Potential R advantages

Open source software such as R have some distinct advantages over commercial packages:

1. Cost
2. Scalability and Random number generation
3. Flexibility

As Eric Nantz has demonstrated, it's possible to use shiny with HPC environments.

Summary and Conclusions

- The CID Pilot Program offers new opportunities for FDA and regulated industry to advance the state of the science, promote innovative methods, and thereby improve public health.
- Use a learn and confirm approach with simulations; limited simulations can be used for learning, but confirming results requires planning and resources.
- Develop a simulation plan.
- Determine the number of simulations to be run a priori. Commonly used values such as 500, 1000, 5000, and 10000 may be inadequate.
- Write a detailed simulation report, if only for your future self. Don't claim more precision for your results than your simulations can statistically support.
- Simulations are yet another use case for R. R is now referenced by the Federal Register.

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Questions?

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