Clinical Trial Simulation

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Introduction

1. Definition of clinical trial simulation

Generation of virtual patient data by approximating human, disease and drug behaviors with proposed trial designs using mathematical models and numerical methods. Based on prior experiences or data informed assumptions.

2. Why Do Simulation?

Too many trials fail or un-imformative. Almost 50% of all clinical trials FAIL

Some trials are unfeasible

Clinical trials are expensive and getting more and more expensive

Gap identification, better grasp of consequences. Get more competitive when close the knowledge gap between empiricism and information

3. Why clinical trials fail?

Drug is lemon (poor PK etc)

Inadequate trial design

Wrong study population

Wrong dose

Wrong statistical analysis

Wrong effect being studied

Low statistical power

Modeling vs simulation

1. Differences

Modeling looks back in time; Simulation looks forward

Modeling uses data; Simulation uses models based on data

In modeling, random variability is a nuisance variable; Random variability is the basis for simulation

2. Similarities

Sensitive to 'black box' criticism
Useful method for data summarization
Can identify which variables are important in an experiment
Sensitive to assumptions

Where CTS fits into drug development

1) During drug development process, we encounter many incidences we can not realize what would be the outcome of the decision made on several assumptions. Many times decisions are made based on a few experts' comprehensive understanding and experience. Drug development team members with diverse expertise can combine their experiences into a common knowledge base.
2) When experiment is not possible (like simulation of nuclear bomb explosion)
3) When the system is so complex that it cannot be easily described by a simple set of mathematical equations. Clinical trial design fall into this class
4) When "what-if" questions about a system are needed to be answered.

Steps to simulation

1) Understand the problem and the user
2) Understand the science and the system
3) Build the model within the right context
4) Verification and validation
5) Use the model

What is needed for acceptance of simulation?

1) Better understanding of link between PK and PD
2) Better surrogate marker for drug effect
3) Better understanding of compliance pattern
4) Better understanding of disease progress

Clinical Trial Simulation

1) Complex system, often nonlinear
2) No simple parametric solution
3) Application of an old technology (Monte Carlo) to a new field
4) The Virtual Trial; created at a level of detail appropriate for needs
5) Virtual patients
6) Virtual doses
7) Virtual visit to virtual center
8) Virtual biological and clinical event / outcome (e.g. virtual AEs, surrogates, efficacy, compliance, dropout, etc)

What can CTS provide?

1) Produce a range of possible outcomes
2) Exposes and quantifies unspoken assumptions and working beliefs; uncertainties, links among inputs, covariates, responses, etc.
3) Forces to identify what is know an what is unknown - mutual understanding
4) Allows to identify the impact of uncertainty on trial outcome
5) May result in cheaper, more cost effective studies
6) Can answer "what-if" questions; evaluate performance under differing primary themes

1. Phase 1
   1) Starting dose for first time in human
   2) Prediction of multiple dose PK from single dose
   3) Potential impact of drug interactions on PK/PD
   4) Potential impact of renal/hepatic dysfunction on PK
2. Phase2/3
   1) Dose selection
   2) Number of subjects
   3) What is most powerful statistical test
   4) Comparison of outcome to different experimental design

Examples

1. Guidance for Industry:
   1) Population Pharmacokinetics, CDER, FDA, February 1999 - "Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed design and analysis."
   2) Statistical Approaches to Establishing Bioequivalence - "The number of subjects for BE studies based on either the population or individual BE approach can be estimated by simulation if analytical approaches for estimation are not available."

2. MMF RCCT (CPT 1998)
   1) Problems and Questions
      Study feasibility
      Power?
      Can blinding maintained?
      Dose adjustment algorithm performance etc
   2) Conclusions
      PK can be controlled (AUC)
      Sample size; 3 groups of 40 patients gave 80% power (worst case)
      Proposed data analysis conservative (true alpha < 0.05)

3. Others

The Feb 2000 issue of "Pharmaceutical Approvals Monthly" contains an article entitled "SB Revised Compazine Formulation Cleared Via Computer Simulation Data"

"FDA accepted computer simulation data in lieu of a multiple-dose study to assess bioequivalence of SmithKline Beecham' s new formulation of extended-release Compazine (prochlorperazine maleate) Spansule capsules, according to FDA review documents."

Anatomy of a Clinical Trial Simulation

Clinical Trial Simulation Questions
Confirming: Power
Learning: Power, Bias and Precision
Simulation Model
  Input-Output Model
  Structural Model
  Covariate Model
  Pharmacoeconomic Model
  Stochastic Models
    The IO model includes stochastic components that include:
    Population Parameter Variability
    Residual Unknown Variability
  Covariate (Demographic) Distribution Model
  Trial Execution Model
Analysis of Simulated Data
Analysis of a Single Trial Replication
Analysis of the Simulation Experiment

Table 1. Simulation in Drug Development Good Practices (Table of Contents)

Table 2. Terminology for Models Involved In Clinical Trial Simulation

Model	Components	Partially Descriptive Synonyms
IO Model	Pharmacokinetics (PK) Pharmacodynamics (PD) * Disease Progress (DP) Placebo Response (PL) Covariate Model (CM) relating covariates to typical parameter values Population Parameter Variability (PPV) that includes Between (BSV) and Within Subject (WSV) Variability Residual Unexplained Variability (RUV) that includes Measurement error and Model Misspecification Error Pharmacoeconomics (PEC)	Structural Model Variance Model Pharmacostatistical Model Outcome Model PKPD Model Drug Intervention Model
Covariate Distribution Model	Demographic covariates (e.g. age, weight, gender, disease severity, concurrent treatment) Distribution and Covariance of demographic covariates	Population Model Demographics Trial Subject Inclusion/Exclusion Criteria
Trial Execution Model	Nominal design (protocol) Deviations from nominal protocol	Trial Design Deviation from Protocol Model Compliance Model Subject Withdrawal Missing Observations Adaptive design model

* Pharmacodynamics includes drug effects on biomarkers, surrogate endpoints and clinical endpoints and outcomes.