Pharmacokinetic / pharmacodynamic modeling and simulation in the design and analysis of Randomized Concentration-Controlled Trials (RCCTs)

N. Seth Berry, PharmD
Senior Scientific Advisor
Quantitative Decision Strategies & Analytics
Overview

• The Causal Chain in Clinical Pharmacology

• What is a Randomized Concentration-Controlled Trial (RCCT)?
  › How does it differ from a fixed-dose, randomized dose-response controlled trial (RDCT)?
  › What is the difference between Concentration-Response (C-R) and Dose-Response (D-R) analyses?

• What impact does PK variability have on response?
  › High vs. Low PK variability
  › Minimizing Confounding Overlap

• What is the role of a RCCT in a Drug Development Program?
Carl Peck, MD
The Champion of the Randomized Concentration-Controlled Trial
The Causal Chain

From Dose to Clinical Endpoint

Dose
- Represents the basic amount of drug being administered to a patient
- Often a static assignment that does not change over time

Concentration
- The amount of drug that is observed in the body
- Varies within a subject over time due to the effect of absorption, distribution, metabolism, and elimination (ADME) of the drug
- Additionally can vary between subjects due to differences in the ADME

Response
- In basic clinical pharmacology receptor theory, the effect the drug has on the body
- Varies within a subject over time due to the concentration of drug available to elucidate an effect
- Additionally can vary between subjects due to differences in the receptors / genetics
- Is not always quantifiable

Clinical Endpoint
- The observed patient outcome or assessment.
- Can vary both within and between patients over time.
Population PK Models
*Nonlinear Mixed Effects Modeling*

- Create Basic Structural Model
  - 1-, 2-, 3-Compartment
  - Route of Administration (Oral, IV)
  - Estimate PK Parameters
    - Absorption Rate Constant
    - Volume of Distribution
    - Clearance
- Create Error Model
  - Between Subject Variability
    - Exponential Error Model
  - Within Subject Variability
    - Proportional Error Model
    - Additive Error Model
What is a Randomized Concentration-Controlled Trial (RCCT)?

- Terminology
  - **RDCT (Randomized Dose-Controlled Trial)**
    - Objectives: Dose-Response; Effectiveness
    - Design: Randomization to 2+ fixed doses (including placebo)
      - Parallel or cross-over
    - Analysis: Relationship between the assigned fixed-doses and the observed effect(s) is analyzed
  - **RCCT (Randomized Concentration-Controlled Trial)**
    - Objectives: Concentration-Response; Effectiveness
    - Design: Randomization to 2+ pre-defined concentration ranges (including zero)
      - Achieved, if necessary, via adaptively individualized doses
    - Analysis: Relationship between the achieved concentrations and the observed effect(s) is analyzed
  - **Concentration Drives Clinical Response (R)**
    - A Concentration-Response (C-R) relationship always exists somewhere
    - Concentration is a confirmed measure of exposure in contrast to uncertain exposure after assigned dosage in a Dose-Response (D-R) analysis
Dose- vs Concentration-Response

*Design and Analysis*

- Dose-Response

  - $D_1$
  - $D_2$
  - $D_3$
  - $O$ (Placebo)

- Concentration-Response

  - $C_1$
  - $C_2$
  - $C_3$
  - $O$ (Placebo)
Implications of Low PK Variability in a RDCT

Low PK Variability = No Confounding or Little Overlap

Dose vs Maximum Concentration

Dose vs Response

Maximum Concentration vs Response
Implications of High PK Variability in a RDCT

High PK Variability = Confounding Overlap

Dose vs Maximum Concentration

Dose vs Response

Maximum Concentration vs Response
Implications of High PK Variability in a RDCT

Confounding Overlap Worse in Narrow Dose Range

Dose vs Maximum Concentration

Dose vs Response

Maximum Concentration vs Response
Concentration-Response Analysis:
*The Confounding Effect of High Correlation between PK and Response*

- **RDCT**
  - $D_1$
  - $D_2$
  - $D_3$
  - $O$ (Placebo)

- **RCCT**
  - $C_1$
  - $C_2$
  - $C_3$
  - $O$ (Placebo)

A RCCT Protects Against the Disease and Pharmacokinetic Confounders That Cause the Down Bias
Consequences of High PK Variability and/or PK-R Correlation in D-R & C-R Analyses

• RDCT: valid D-R analysis may be biased by
  › High PK variability
    » Reduces power unless fixed doses are far apart
  › High correlation between PK and R
    » May downwards bias D-R relationship unless covariate analysis is employed

• RDCT: valid post-hoc C-R analysis relies on
  › Low PK variability
    » High PK variability reduces power
  › Low correlation between PK and R
    » High correlation downwards biases C-R relationship

• RCCT: valid C-R analysis
  › Independent of PK variability
    » High PK variability is controlled via individualized dosing
  › Resistant to downwards bias due to high correlation between PK and R
    » Further benefits from covariate modeling
The Uses of a Randomized Concentration-Controlled Trial

• Efficient, unbiased estimation of the C-R Relationship\(^1^3\)

• Establishment of Effectiveness\(^4^6\) of a Drug with
  › Narrow Therapeutic Range, and/or
  › High PK Variability

• Safe trial of a drug with a narrow therapeutic index w/serious toxicities &/or serious consequences of under-exposure\(^7^9\)

• Examples:

  1. Hale, Michael D, and Russell Reeve. “Planning a randomized concentration controlled trial with a binary response (Mycophenylate mofetil).” *Proceedings of the Biopharmaceutical Section, 1994 Joint Statistical Meetings*
  
  2. Reeve, Russell and Michael D Hale. “Results and efficiency of Bayesian dose adjustment in a clinical trial with binary endpoint.” *Proceedings of the Biopharmaceutical Section, 1994 Joint Statistical Meetings*
  
  
  
  
  
  
  
Randomized Concentration-Controlled Trials in Drug Development

- **When Should a RCCT be Considered?**
  - **Usually in Phase I/II**
    - To Define the Therapeutic Range / Therapeutic Index
      - Concentration – Effect Reduction Relationship
    - Concentration – Adverse Reaction Frequency/Severity Relationship
  - To Undertake a Safe Trial
    (if ADR = severe)
  - **In Phase III (rarely)**
    - If Therapeutic Drug Monitoring (TDM) is Contemplated
    - If Dose Adjustment is the Only Way to Achieve Safe and effective Exposures in the Effective Range
    - If C-R information is required by a regulatory agency which is concerned about high PK variability or safety

- **When Should a RCCT NOT be Applied?**
  - Wide Therapeutic Range
  - Low Inter-individual PK Variability
  - Very Large PD Variability
  - No correlation between PK and Clinical Response
Randomized Concentration-Controlled Trials in Drug Development

Other Factors

• Demanding Design
  › Complex Dose-Concentration Titration Procedures
  › Blinding / Drug Packaging
  › Drug Product / Dosage Forms
  › More Costly, Possibly Longer Trial

• Opportunities
  › Mobile web applications to help guide PK concentration assignments via Bayesian dosing adjustments
  › Large molecules with narrow therapeutic windows

• Labeling
  › Could Lead to a Requirement for Concentration Monitoring (Therapeutic Drug Monitoring)
Questions?