Optimizing Dose Selection Across the Clinical Trials Spectrum

Thoughts on the Morning Session

Ken Cheung
Columbia University

April 2024

Optimizing **Dose Selection** Across the Clinical Trials Spectrum

Selecting the right dose is critical in drug development

- Examples of delayed approval and post-approval changes (Bretz)
- Easy to miss the appropriate dose range (Bretz)
- Optimus: **educate, innovate, collaborate** with patients and oncology community (Cheng)

- What do our (non-oncology) clinical colleagues think?
- Evaluating more doses takes more patients than single arm
- Trials in rare diseases have a limited pool of participants.

Optimizing Dose Selection Across the Clinical Trials Spectrum

An optimal dose ultimately is not defined only by safety, but also efficacy

- Benefit-risk (Cheng)
- Trade-off between efficacy and safety/tolerability (Bretz)
- Optimus/From MTD to OBD (Yuan)
- Dose selection at interim based on multiple endpoints (Jin)
- Dose is multi-dimensional: duration, frequency, dosage form, route of administration (Bretz)

- DLT/MTD is not optimal (outside cytotoxic), but could be a useful upper bound

Optimizing Dose Selection Across the Clinical Trials Spectrum

How to get there efficiently is more complicated

- Combining phases makes sense (Cheng, Yuan, Jin)
- Phase 1b/2
- Are patient populations of different phases comparable?
- Safety and efficacy may be evaluated on different timeline. TITE approach alleviates the issues
- Seamless phase 2/3
- Two-stage design: Using safety and efficacy to select dose and then randomize for final analysis is a pragmatic approach
- **Don't** throw away data if the stage 1 patients are comparable to stage 2 patients.

Optimizing Dose Selection Across the Clinical Trials Spectrum

How to get there efficiently is more complicated

- Treatment combination has unique challenges (Cheng)
- Estimating synergistic effects in trials = a *near i*mpossibility
  = Estimating interactions with a relatively small n in a safe manner

Optimizing Dose Selection Across the Clinical Trials Spectrum

How to get there efficiently is more complicated

- Utility approach is easy to communicate (Yuan)
- Who's utility?
- Lee et al. (2019): nurse's and physician's perception of cancer treatment burden are quite different. How about patient's utility?
- How robust is the approach if a different set of utilities are used?

Optimizing Dose Selection Across the Clinical Trials Spectrum

How to get there efficiently is more complicated

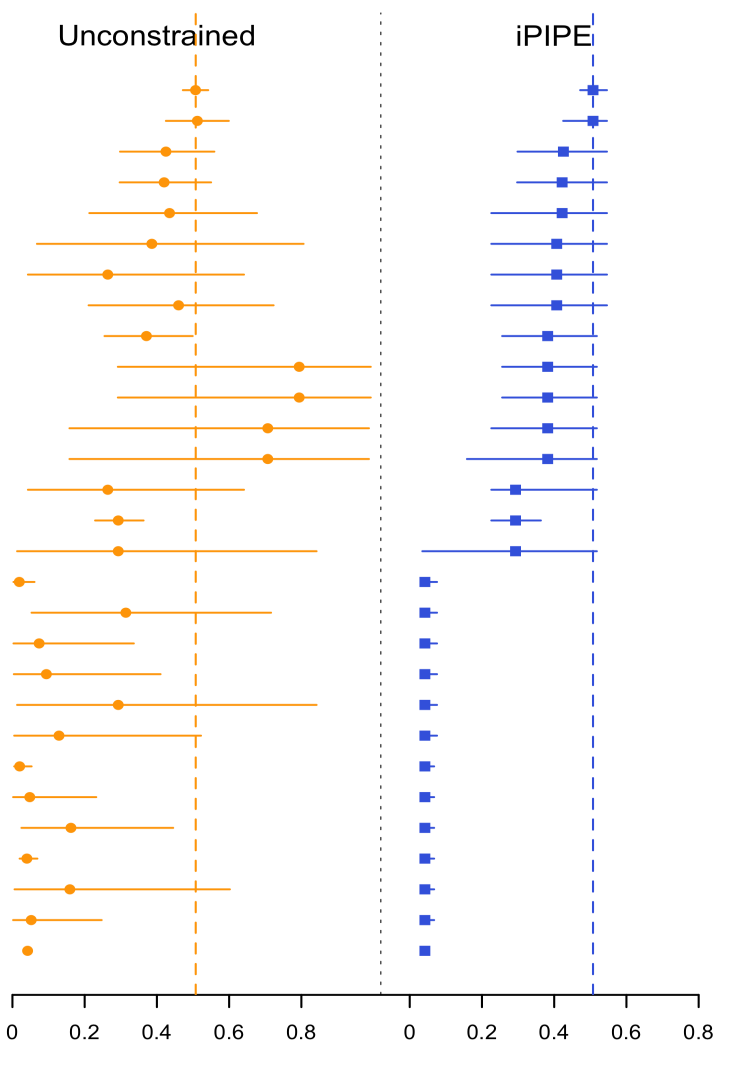
- Phase 2 trial design = everything but the kitchen sink
- MCP-Mod: Randomized phase 2 dose ranging (Bretz)
- Two-stage/efficacy integrated phase 1b/2 (Yuan)
- Adaptive seamless phase 2/3 (Jin)
- Context is important: no one-size-fits-all for dose selection (Cheng)
- Robustness: MCP-mod accounts for model uncertainty; especially important for adaptive design (sensitivity analysis may not be feasible)

Optimizing Dose Selection **Across the Clinical Trials Spectrum**

What about trials of non-drug/non-biologic agents?

- Non-pharmacologic intervention includes behavioral intervention, mobile health in decentralized trials, hybrid telemedicine, etc.
- Hypothetical (but not unlikely) RCT example: medically tailored meals vs weight loss drug in obese/diabetic ACS patients
- An actual trial (BREAK2): 25-armed randomized trial of sedentary break **ClinicalTrials.gov** NCT05353322
- Each participant will have a randomized sedentary break visit and a control visit
- Adaptive dose finding: Efficacy (BP, CGM) and safety-integrated

Optimizing Dose Selection **Across the Clinical Trials Spectrum**



Estimated response rate of 29 four-dimensional mobile interventions. iPIPE (monotone regression) vs observed proportions

Non-drug trial statistical issues

- Combination of intervention components
- Multi-dimensional. BREAK2: type; intensity; **frequency; duration.**
- Adaptive dose finding (many arms)
- Efficacy and safety-integrated
- Difficulties with parametric models: interaction of intervention components; plateau dose-response
- Monotonicity goes a long way. Cheung and Diaz (2023, *JRSS-B*):

Summary/Discussion

- Dose selection is important for the success of a treatment development program
- It is equally important to communicate collaboratively about the importance of dose selection
- How to get to an optimal dose depends on specific context; e.g., human subject considerations, funding constraints, robustness of results, reproducibility, inferential/operational, "white space", etc.
- Statistical inputs are critical to the regulatory process for drug trials
- Non-drug trials share similar statistical considerations

Kudos to the presenters!