Dose Finding & Strategies for Novel Combination Development

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Topics

1. Disclosures: none
2. Dose finding
3. Response surface designs
4. Factorial trials
5. Pipeline design
If he had a needle to find in a haystack he would not stop to reason where it was most likely to be, but would proceed at once, with the feverish diligence of a bee, to examine straw after straw until he found the object of his search. ... I was almost a sorry witness of such doings, knowing that a little theory and calculation would have saved him ninety per cent of his labor.

—New York Times, October 19, 1931 (the day after Thomas Edison died)
Dose (Finding) Escalation

• Designs only a mother could love
  – 3+3 and similar up and down methods
  – Accelerated titration
  – Cohort expansions

• Limitations
  – Poor operating characteristics (i.e., they don’t reflect truth very well)
  – No useful extensions to drug combinations
  – Cannot cope with non-MTD dose finding

• The only true dose titration designs are model guided
Dose Finding Challenges

• New drugs are not so toxic, so what if the MTD is not the right idea?

• How do we explore the joint dose space reasonably fully?

• Can we deal with more than one outcome in dose finding?
More Likable Designs

- Continual reassessment method
- Conditional escalation with overdose control (EWOC)
- Other model guided dose finding

Why?
- Efficiency
- No bias
- Direct extension to combinations
Challenge: 2D MTD


3D MTD


• Combinations
Higher Dimensional MTD

• With therapeutic combinations, the MTD is an infinite set of doses.

• The MTD cannot be found reliably with a restricted search (e.g., 1D) of the joint dose space.

• It requires a more sophisticated search algorithm and a larger number of study participants than ordinary phase I trials.

• In many cases, investigators would have to allow the possibility of dose reductions of standard agents when adding a new agent, if a true MTD is being sought. This always seems to yield an ethics snag.
Beyond the MTD

- MTD is not the right optimization concept for drugs broadly, especially outside of oncology!
- The general dose optimization question has no standard approaches.
- One possible general approach is “Envelope Simulation”, yet to be accepted.
Example

- Find the dose associated with peak response.
- Response is not a probability.
- Unreal but useful model.
- Envelope data gets us started and then their influence disappears when real data arrive.
Response Surface Designs

• Method widely used to optimize a multi-variable industrial or chemical process.
  – Vary each factor while others are held fixed
  – Small number of runs at each combination
  – Model the results with a flexible surface
  – Find the optimum predicted by the surface

• Simple, reliable and flexible.
• Little used in human trials.
• Might be able to get by with 1 subject per design point.

Factorial Designs

• The technique of varying more than one factor or treatment in a single study was used in agricultural experiments in England before 1900.

• The method did not become popular until it was developed further by R. A. Fisher and Yates [1935], but since then it has been used to great advantage in both agricultural and industrial experiments.

• Influential discussions of factorial experiments were given by Cox [1958] and Snedecor and Cochran [1980].

• Factorial designs have been used relatively infrequently in medical trials, except in disease prevention studies.
Factorial Designs

- The only way to study treatment-treatment interactions.

- The essential dichotomy:
  - When interactions are present or suspected, factorials are required
  - When interactions are known to be absent, factorials can be 2:1 efficient

- Why aren’t all trials factorial designs?

Effect Estimates 2x2, No Interaction

- Main effect of treatment A = \( \frac{1}{2} (X_A - X_0 + X_{AB} - X_B) \)

- Main effect of treatment B = \( \frac{1}{2} (X_B - X_0 + X_{AB} - X_A) \)

- Note how the same data yield effects of both treatments when interactions are absent.

- Thus a factorial can be efficient and we can get 2 trials for 1.
Interaction Effect Estimate 2x2

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>$X_0$</td>
<td>$X_A$</td>
</tr>
<tr>
<td>Yes</td>
<td>$X_B$</td>
<td>$X_{AB}$</td>
</tr>
</tbody>
</table>

- AB interaction effect: dose A have the same effect with and without B?
  - Does $(X_A - X_0) - (X_{AB} - X_B) = 0$ ?

- Does B have the same effect with and without A?
  - Does $(X_B - X_0) - (X_{AB} - X_A) = 0$ ?

- Note the two interaction effects are identical.
If each cell has n subjects and the cell mean is estimated with a precision of $\sigma / \sqrt{n}$, where $\sigma$ is the person-to-person std. dev.,

- The std. dev. of a main effect is $\sigma / \sqrt{n}$.
- The std. dev. of an interaction effect is $4\sigma / \sqrt{n}$. 
Factorial Designs

• The design is super efficient (sample size) when interactions are known to be absent.

• The design is inefficient (4x) when we must study interactions
Adaptive Features

• Why haven’t I talked about “adaptive designs”?

• Such designs have nothing uniquely tailored to the problems of combinations.

• To be complete, the CRM, EWOC and related designs are formally adaptive.
Pipeline Design

• The overall development pipeline is a “learning machine”, and as such is described by a Bayesian equation.
  – Seamless or staged pipelines are the same in this regard
  – Is also true of drug combination development
  – This result is a truth of nature

• Consider the odds of a true positive result from the overall development process:

  \[
  \text{output odds} = \text{input odds} \times \text{Bayes Factor.}
  \]
Amplifier

\[ \text{Bayes Factor} = \frac{\text{power}_1 \times \text{power}_2 \times \cdots}{\alpha_1 \times \alpha_2 \times \cdots} , \]

where the subscripts indicate stages, steps, decision points, phases, seams, etc. – they are all the same idea.

Every step has a power and type I error even if they are poor or unacknowledged.

These ideas can be used to design the pipeline just like we design an individual trial.

Not presently being done, even though every treatment is in its own context and should have a unique pipeline.
Implications

• Any step with a zero type I error will cause development to yield 100% true positives.

• The BF is a frequentist term in a Bayesian learning algorithm – indicates we should not be fussing about philosophical differences.

• Anyone who thinks “randomized phase IIs” are a good idea (relaxed type I and II error rates) should realize how they can degrade the overall pipeline performance.

• A sequence of optimal trials does not necessarily make an optimal pipeline.
Final Comments

- Old questions, old designs; new questions, new designs.

- Some old design tools are available for new questions.

- New design methods are also available.

- NIH and FDA will have to motivate and lead pipeline design.