Adaptive Trial Designs
Ross Upshur
All the facts of science aren't enough to understand the world's meaning. For this, you must step outside the world!

Without language or thought, how can you understand anything?
Truth

• The truth cannot be told so as to be understood but not believed.
William Blake
Randomized Control Trial

- Inception Cohort
  - Sample Of Persons
  - Random Allocation
  - Treatment
  - Control

Measure outcomes

Sampling is done here

Time
Adaptive Designs for Clinical Studies

Model-based/Continual Assessment Designs
- Used in dose finding to assign patients to more informative doses

Group Sequential/Sample-Size Re-Estimation Designs
- Allow increases in sample size after interim analysis

Group Sequential/Response Adaptive Designs
- Increase possibility of success by allocating more patients to successful treatments, select patient subgroups more responsive to treatment, drop non-efficacious doses, switch from superiority to non-inferiority or modify primary endpoint

Adaptive Randomization Designs
- Modify randomization on the basis of prognostic factors to balance study groups
Characteristics of Adaptive Designs

- Streamlined
- Flexible
- Optimised
- Data-driven
- Systematic
- Decision-oriented
- Dynamic
- Sequential learning
- Cost-efficient
- Robust
- Real-time
- Bayesian
- Simulation

Adaptive Design

Figure 3
Table 2. Eight Common Types of Adaptations

- Stopping early (or late, i.e., extending accrual) with a conclusion of superiority or futility
- Adaptively assigning doses to more efficiently assess the dose-outcome relationship
- Adding or dropping arms or doses
- Seamless phases of drug development within a single trial
- Changing the proportion of patients randomized to each arm
- Adaptively identifying in on an indication or responder population
- Changing accrual rate

Interim analysis at ~187 events:

Interim Analysis

Planned End

Efficacy
Favorable
Promising Zone (add 225 patients)
Unfavorable
Futility

CP = Conditional power
The probability of success (statistical significance) at the end of the trial given current data trend

Interim outcome partitioned into unfavorable, promising, and favorable zones

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Interim outcome partitioned into unfavorable, promising, and favorable zones
Patient hospitalized with COVID-19 (conventional unit or Intensive Care Unit)

Randomization

- Standard of care (SoC)
  - SoC + Remdesivir IV
    - 200 mg D1 + 100 mg 9 days
  - SoC + Lopinavir/ritonavir PO
    - 400/100 mg BID 14 days
  - SoC + Lopinavir/ritonavir PO + IFN-β-1a SC
    - 400/100 mg BID 14 days
    - 44 μg D1 D3 D6
  - SoC + Hydroxychloroquine PO
    - 400 mg BID D1 (600 mg BID if nasogastric tube) + 400 mg 9 days
<table>
<thead>
<tr>
<th>Component</th>
<th>Traditional</th>
<th>Flexible</th>
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<tbody>
<tr>
<td>Interim Analyses</td>
<td>Limited (1 to 2)</td>
<td>Frequent</td>
</tr>
<tr>
<td>Randomization</td>
<td>Fixed (1:1, 2:1)</td>
<td>Variable</td>
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<td>Number of Arms</td>
<td>Limited (2 to 3)</td>
<td>Few to Many</td>
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<td>Use of Incomplete Data</td>
<td>Imputation at Final Analysis</td>
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<tr>
<td>Philosophy</td>
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<td>Control of Error Rates</td>
<td>Via Theoretical Calculation</td>
<td>Via Extensive Simulation</td>
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Fig. 2. Probabilistic models further refined.
Cartwright’s Causal Criterion

• C causes E if and only if \( P(E/C) +/- \{F_1 + F_2...F_N\} > P(E/-C) +/- \{F_1 + F_2...F_N\} \) where \( F_1...F_N \) are a complete set of covariates.

• An idealized model that sets out precise ceteris paribus conditions.