Trial, Interrupted

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Ingram Olkin Forum Series
Trial Disruptions

• Trials can be disrupted so that normal procedures are not possible.
• Disruption can motivate design changes
• Changes should respect the basic tenets of clinical trials
Respect Randomization

- *Randomized clinical trials are the greatest medical invention ever*
- Respect randomization
  - Keep the groups pristine
  - Keep the intervention pristine
  - Keep the outcome pristine
- Be creative and responsive
- Unplanned blinded adaptations
  - Be careful
  - Use permutation to be sure
Example #1  mAbs for malaria

• Malaria is parasitic disease spread by mosquitoes
• Young children receive daily prophylactic drugs
  • Inconvenient
  • Non-compliance
• Monoclonal antibodies seasonal protection with 1 administration?
• Plan
  • Establish acceptable dose & efficacy in Bethesda
  • Do a field trial in Mali children
VRC 612: Human challenge trial of malaria mAb

- **Part A: Dose Evaluation**
  - 5 mg/kg
  - 20 mg/kg
  - 40 mg/kg

- **Part B: Human challenge**
  - Give volunteer malaria parasites
Correlate of Risk

Fit a logistic regression model $Y=\text{Infection Indicator}$
Identify a mAb level where hardly anyone is infected
VRC 612: Human challenge trial of malaria mAb

• Part A: Dose Evaluation
  • 5 mg/kg
  • 20 mg/kg
  • 40 mg/kg

• Part B: Human challenge
  • Give volunteer malaria parasites

COVID-19
VRC 612: Adaptation

• Part B: Dose Evaluation
  • 5 mg/kg
  • 20 mg/kg
  • 40 mg/kg
  • 40 mg/kg 6 months ago

• Part B: Human challenge
  • Give volunteer malaria parasites
Fit a logistic regression model $Y=\text{Infection Indicator}$
Identify a mAb level where hardly anyone is infected
Example #2:  HIV prevention

• Blinded randomized trial of 3200 women at risk of HIV infection
  • Injectable cabotegravir: every 8 weeks
  • Oral tenofovir: daily

• Accrual 2 years
  • Follow-up 1.6 – 3.6 years

• Analysis
  • Cox model with treatment indicator and stratified by site
  • Intent-to-treat analysis
Follow-up

HIV infection
COVID-19 interruption
COVID-19 interruption

HIV infection

Periods of site disruption

COVID-19
Adaptation based on COVID-19

• Blackout periods = disruption
  • Study product not available
  • Define periods of potential disruption

• An adjudication committee will define the period(s) of disruption for each site. The adjudication committee will be blinded to the number of infection events detected after April 2020.
Cox Model -> Anderson Gill

- Simpler version
  - Estimated treatment effect = \( 1 - \frac{R_I}{R_D} \)
  - \( R_Z = \frac{\text{Number of Events on Arm } Z}{\text{Total Followup on Arm } Z} \)

- Anderson Gill
  - Remove volunteers from the risk set during periods of disruption
  - Re-enter HIV-negative volunteers into the risk set after period of disruption

<table>
<thead>
<tr>
<th>Patient</th>
<th>Start</th>
<th>Stop</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
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</tr>
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<td>0</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2.4</td>
<td>0</td>
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</table>

<table>
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<tr>
<th>Patient</th>
<th>Start</th>
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<tr>
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<td>3.3</td>
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<td>1</td>
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<tr>
<td>3</td>
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<td>2.2</td>
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</tr>
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</table>
FDA Guidance on Adaptation

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

• In general, adequately **pre-specified** adaptations based on non-comparative data have no effect or a limited effect on the Type I error probability.

• [https://www.fda.gov/media/78495/download](https://www.fda.gov/media/78495/download)
Unplanned adaptations before breaking the blind

Martin Posch\textsuperscript{a*†‡} and Michael A. Proschan\textsuperscript{b}

Occasionally, things go so wrong in a clinical trial that a change must be made. For example, the originally planned primary outcome may be measured completely unreliably. Is there any recourse? One may still be able to salvage the trial using a permutation test if a change is made before breaking the treatment blind. The solution is not a panacea; we discuss the limitations and legitimate grounds for criticism. Still, when it is needed, the procedure is preferable to rigid adherence to a design that makes no sense. Published 2012. This article is a US Government work and is in the public domain in the USA.
Crossover trial

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Z</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Control</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>Treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

Data: \( D_1, D_2, D_3, D_4, \ldots, D_{n-3}, D_{n-2}, D_{n-1}, D_n \)
\( Z_1, Z_2, Z_3, Z_4, \ldots, Z_{n-3}, Z_{n-2}, Z_{n-1}, Z_n \)

Analysis: one-sample t-test using
\[ Y = Z D - (1-Z)D = \text{Treatment} - \text{Control} \]

\( D = \text{Period 1 Outcome} - \text{Period 2 Outcome} \)
Blinded adaptation

- Data: $D_1, D_2, D_3, D_4, \ldots, D_{n-3}, D_{n-2}, D_{n-1}, D_n$

Blinded Sample variances

Blinded Adaptive t-test BAT

Use the smaller variance

$$\frac{\bar{Y}}{\sqrt{S_1^2/(n-1)}}$$
The advantage

<table>
<thead>
<tr>
<th>n</th>
<th># cohorts</th>
<th>Type I error rate</th>
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<td>0.08</td>
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<td>2</td>
<td>0.06</td>
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<tr>
<td>640</td>
<td>2</td>
<td>0.05</td>
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<table>
<thead>
<tr>
<th>n</th>
<th># cohorts</th>
<th>Type I error rate</th>
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<td>0.14</td>
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<tr>
<td>160</td>
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<td>0.08</td>
</tr>
<tr>
<td>640</td>
<td>4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Real world example: Pick the ‘most efficient’ Wald test statistic
Numerator unbiased
Pick smallest denominator

Can we save ourselves from well-intentioned adaptations that cheat?
Permutation = Salvation

• Data: \( D_1, D_2, D_3, D_4 = (0.4, -0.3, 0.5, -0.1) \)
  \( Z_1, Z_2, Z_3, Z_4 = (1, 0, 1, 0) \)

• Analysis: Permutation Distribution of BAT

<table>
<thead>
<tr>
<th>Permutation</th>
<th>Mean Difference ( \bar{Y} = ZD - (1-Z)D )</th>
<th>BAT = ( \frac{\bar{Y}}{\sqrt{\frac{S^2_{(1)}}{n-1}}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100</td>
<td>-0.075</td>
<td>-0.036</td>
</tr>
<tr>
<td><strong>1010</strong></td>
<td><strong>0.325</strong></td>
<td><strong>1.56</strong></td>
</tr>
<tr>
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<td>0.025</td>
<td>0.12</td>
</tr>
<tr>
<td>0110</td>
<td>-0.025</td>
<td>-0.12</td>
</tr>
<tr>
<td>0101</td>
<td>-0.325</td>
<td>1.56</td>
</tr>
<tr>
<td>0011</td>
<td>0.075</td>
<td>0.036</td>
</tr>
</tbody>
</table>

\( S^2_{(1)} = 0.13 \)
Permutation Punishes Sneakiness

• Use Drug as proxy for treatment indicator

• ‘Blinded’ adaptations:
  • Pick best of 17 different tests
  • Double the sample size if t-test p-value >0.05.

• Permutation Punishment
  • Null: Treatment has no effect on outcome, drug level

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug Level</th>
<th>Treatment Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.1</td>
<td>?</td>
</tr>
<tr>
<td>3</td>
<td>0.0</td>
<td>?</td>
</tr>
<tr>
<td>9</td>
<td>1.2</td>
<td>?</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>?</td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>?</td>
</tr>
<tr>
<td>1</td>
<td>0.0</td>
<td>?</td>
</tr>
</tbody>
</table>
Blinded unplanned adaptations

- COVID-19 interruptions may lead to unplanned adaptations
  - Respect randomization
  - Be creative
- Unplanned blinded adaptations can be fine
  - Can use permutation distribution for inference
  - Read Posch & Proschan 2011
Summary
PALM Fire and Ice

- Compare 28-day mortality in EVD patients who receive investigational therapeutics relative to Zmapp

- 1:1:1:1 randomization to Zmapp, Mab114, Remdesivir, Regeneron
  Regeneron added in Protocol v.3.0 on 12Dec2018

- Sample size: 500 EVD patients
  85% power to detect a 50% improvement in 28-day mortality from 30% (Control) to 15%

- Multi-outbreak, multi-country
Trial Timeline

- Nov 20: Beni opens
- Dec 14/24: Protocol v3.0 approvals
- Dec 28: Butembo opens
- Jan 25: Katwa opens
- Feb 8: DSMB mtg
- Feb 16: Katwa opens
- Feb 25: Butembo ETC Re-opens
- Feb 27: ~Mar 1
- Mar 30: Additional Sites?
- June: DSMB Mtg?

Events:
- Beni attack
- Katwa Fire
- Butembo Fire
- PALM reopens: in Butembo
  - In Katwa
  - Additional Sites?
Katwa ETC Fire: 25 Feb 2019
Butembo ETC Fire: 27 Feb 2019

4 patients on study
Moved to Butembo ETC

6 patients on study + 4 patients moved from Katwa

CRF binders were here
Data flow in remote, high-conflict region

- CRFs uploads were current up to day of fire.
- Three randomization assignments day of fire.
  - Participant data recovered
- No missing primary outcome data

SITE/North Kivu, DRC

INRB Coordinating Center, Kinshasa, DRC

NIAID/DCR, Bethesda