Formalizing *ad hoc* Practices in Pragmatic Clinical Trials

Issues of Consent and Implementation

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Issues to consider

- Trial setting
  - Disease/problem (acute, chronic)
  - Location (single-center, multi-center, national)
  - Randomization (individual vs cluster, balanced vs unbalanced)
  - Intervention (pharmacologic, behavioral)
  - Comparison (placebo, usual care, “active” control)
  - Outcomes (clinical, self-reported, claims-based)
- My experience: oncology vs behavioral economics
Background

**Behavioral economics**

- Integrate theories of economics and psychology
- *Standard* economics
  - rational beings maximize expected value
- *Behavioral* economics
  - decision errors are common
    - present bias
    - (mis)understanding of probability
    - loss aversion
  - harness these errors to improve decision-making
  - defaults are powerful
Potential interventions

Daily lotteries for daily behaviors

- large chance of small reward
- small chance of large reward
- only receive reward if desired behavior occurred
- BE principles
  - variable reinforcement
  - regret aversion
  - entertainment
Potential interventions

Deposit contracts

- put down money in advance
- get money back (plus match) if meet goal
- BE principles
  - endowment effect
  - loss aversion
Potential interventions

Social incentives

- identify support partner
- partner receives information on progress
- BE principles
  - cheerleading
  - actions are witnessable
  - social norming
  - competition
Randomized trial of behavioral economic interventions to reduce CVD risk

1. RC4 PIs Asch/Volpp

   - **Population**: 1,500 patients with high cardiac risk and elevated LDL
   - **Interventions**: financial incentives
     - control
     - patient incentives: lottery for daily statin adherence
     - physician incentives: payments for meeting quarterly goals
     - shared incentives: each at half value

   - **Randomization**: cluster-randomized by physician
     balanced by arm
     stratified by study site (Penn, Geisinger, HVMA)

   - **Outcomes**: change in LDL over 12 months
     daily adherence
     statin initiation/intensification

   - **Analysis**: longitudinal mixed effects model for LDL

   - **Side study**: compare different consent approaches in diabetics
### Two Examples

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**Troxel UPenn**

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Two Examples

Rapid cycle approach to improving medication adherence for CAD patients

2. HS PIs Volpp/Asch

- **Population**: 1,500 patients discharged post-AMI
- **Interventions**: financial and social incentives
  - usual care
  - daily lottery, support partner, engagement advisor
- **Randomization**: individual
  - 2:1 ratio for intervention:control
  - stratified by insurance provider/type
- **Outcomes**: repeat cardiac events
daily adherence
insurance claims
- **Analysis**: Cox PH model for time to repeat cardiac event
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**Troxel UPenn**

**Pragmatic Trials**
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Pragmatic Trials
Standard opt-in consent

- Default is **non-participation**
- Participation requires active engagement
- Small proportion of target population enrolls
- Highly selected population
  - Demographics
  - General health awareness
  - Motivation/engagement
  - Healthy worker effect
  - Hawthorne effect
- Mechanism of effect matters
  - drug trials
  - behavioral intervention trials
- Efficacy vs effectiveness
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Opt-in Consent

RC4 experience

- Logistic regression analysis of probability of consent
- Population of subjects expected to be eligible based on EHR (n=25,690)
- 4,751 (18%) consented
- Variation in consent rates by study site
  - Geisinger rates significantly higher
  - Geisinger demographics significantly different
RC4 experience

- Less likely to consent
  - non-whites
  - men
  - uninsured patients
- More likely to consent
  - those with more office visits in the last year
- Additional factors that were not predictive
  - age
  - public vs private insurance
  - presence of coronary artery disease
  - Framingham risk score
  - baseline LDL
- Consenting participants differ in important ways that may also affect the performance of the interventions
Opt-out consent

- Change the default from non-participation to **participation**
- Participants are automatically enrolled
- Participants must actively *decline* or withdraw consent
  - provide contact information enabling this
- Requires waiver of consent
Waiver of consent

• DHHS Common Rule
  1. research involves minimal risk to participants
  2. waiver will not adversely affect rights/welfare of participants
  3. research cannot practicably be conducted without the waiver
  4. subjects will be given additional information about the research upon completion

• Distinct from HIPAA waiver
Waiver of consent

- Research cannot practicably be conducted without the waiver
  - operational considerations
  - scientific considerations
    - generalizability is a fundamental goal of pragmatic trials
    - loss of generalizability invalidates resulting conclusions
A middle ground

- Full-fledged opt-out consent may be challenging
- Instead, change framing and default
  - “you have been enrolled in a new program”
  - include package of study materials
- May still obtain written or verbal consent
RC4 opt-out side study

- Participants
  - adults with diabetes
  - hemoglobin A1c > 8%
- Opt-in arm
  - standard letter offering participation
- Opt-out arm
  - letter stated that they have been enrolled
  - would be contacted within ten days
  - could decline participation at that time
- Unbalanced randomization
  - initially 5:1 ratio
  - later 9:1 ratio
**RC4 opt-out side study**

- **Same interventions in both arms**
  - free wireless glucometers and BP cuffs
  - automated messages about glycemic control
  - ongoing NP support
  - daily lottery for glucometer usage

- **Primary outcome**
  - participation rate
  - defined as attendance at baseline visit

- **Secondary outcomes**
  - attrition at 3 and 6 months
  - daily glycemic monitoring
RC4 opt-out side study

Preliminary results

<table>
<thead>
<tr>
<th></th>
<th>Opt-in</th>
<th>Opt-out</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 569</td>
<td>496</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>participation</td>
<td>61 (12%)</td>
<td>28 (38%)</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>3-month attrition</td>
<td>0%</td>
<td>18%</td>
<td>$p = 0.002$</td>
</tr>
<tr>
<td>6-month attrition</td>
<td>13%</td>
<td>32%</td>
<td>$p = 0.04$</td>
</tr>
<tr>
<td>median glucometer adherence</td>
<td>91%</td>
<td>66%</td>
<td>$p = 0.006$</td>
</tr>
<tr>
<td>decline in glucometer usage</td>
<td>-0.01</td>
<td>-0.03</td>
<td>$p = 0.02$</td>
</tr>
</tbody>
</table>
Experience

RC4 opt-out side study

![Graph showing RC4 opt-out side study results]
HeartStrong opt-out side study

- Overall enrollment rate of 8%
- UPHS patient enrollment rate of 15%
- 50 UPHS patients received HeartStrong program materials
  - letter of introduction to program
  - four GlowCap electronic pill bottles
  - called by staff, given chance to opt out
## HeartStrong opt-out side study

### Preliminary results

<table>
<thead>
<tr>
<th></th>
<th>HeartStrong UPHS patients</th>
<th>Opt-out UPHS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailed</td>
<td>235</td>
<td>50</td>
</tr>
<tr>
<td>Unreachable</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Declined</td>
<td>41%</td>
<td>26%</td>
</tr>
<tr>
<td>Ineligible</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Enrolled</td>
<td>16%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Statistical issues

- Efficacy vs effectiveness
- Opt-out approaches should lead to
  - ↑ generalizability
  - ↑ accrual rates and sample size
  - ↓ effect size
  - ??? power
- Characterize overall impact of these components
  - continuum along spectrum from opt-in to opt-out
  - define “generalizability metric” as a function of sample representativeness
  - define expected effect size as a function of “motivation”
  - derive “power surface” as a function of these components
# Trial features of relevance

- Cluster randomization
- Randomization ratio
- Rapid-cycle innovation / learning health systems
- Source of outcome data (EHR, claims)
- Interim monitoring: safety and efficacy
- Common Rule 4: information to participants
Tensions exist

- Continuum of strength of evidence
  - “standard” RCT
  - “pragmatic” RCT
  - pseudo-experimental designs
  - observational studies
  - demonstration projects
- Require randomization-based evidence
- How to relax RCT restrictions while maintaining validity?
Rapid-Cycle Innovation

Evidence-based evolutionary testing


- Adaptive approach with multiple phases
- Allows learning and adaptive implementation
- Multiple versions of the same intervention (V1.0, V2.0, . . .)
- Progress is expected to be incremental
**EBET framework**

The EBET framework is a rapid-cycle innovation approach developed by Troxel UPenn. It involves an initial main intervention and subsequent iterations informed by side experiments. The timeline is divided into phases such as enrollment and follow-up, with iterations V 1.0, V 2.0, and V 3.0. Side experiments include incentives, social influence, and consumer experience. The time duration is marked in months, with phases spanning from 0 to 36 months.
Statistical issues

- Define time frame for different phases
- Define randomization ratio
- Primary comparison: “overall” intervention vs control
- Secondary comparisons
  - V1.0 vs control
  - V2.0 vs control
  - V2.0 vs V1.0 (temporal confounding?)
- Define Type I error for each comparison
HeartStrong design

- Two-year trial
  - one year each for V1.0 and V2.0
- 2:1 randomization ratio
  - 500 control
  - 500 V1.0
  - 500 V2.0
- Outcome: time to repeat cardiac event
- Statistical power

<table>
<thead>
<tr>
<th>Contrast</th>
<th>HR</th>
<th>α</th>
<th>Power</th>
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<tbody>
<tr>
<td>Int vs ctrl</td>
<td>0.7</td>
<td>0.05</td>
<td>0.8</td>
</tr>
<tr>
<td>V1.0 vs ctrl</td>
<td>0.5</td>
<td>0.05</td>
<td>0.8</td>
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<tr>
<td>V2.0 vs ctrl</td>
<td>0.5</td>
<td>0.05</td>
<td>0.8</td>
</tr>
<tr>
<td>V2.0 vs V1.0</td>
<td>0.62</td>
<td>0.25</td>
<td>0.8</td>
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HeartStrong implementation

- Took more than one year before V2.0 implemented
- Changes in V2.0
  - promotional items in initial mailing
  - improved public web presence
  - improved patient dashboard
- Finished recruitment in December 2014 \((n = 1,509)\)
- Intervention will conclude December 2015
- Final claims data available early 2016
Summary

- “Ethical” vs “statistical” issues: a false dichotomy
- All statistical issues have ethical implications
- Find creative ways to enhance trial value while protecting rights and welfare of participants

Each trial must be designed to have a high probability of finding the right answer to a question of importance to patients
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Devon Taylor
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and

our patients and their physicians