Clinical Trial Design
Statistical Approaches and Considerations

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Disclosures

- Industry grants to Duke Clinical Research Institute
- Consulting fees from Pamlab Inc
Outline

- Numerous statistical and design approaches exist to increase trial efficiency
- Many have been tried in cardiology, oncology and other areas
- We review a selection here including
  - Event driven trials
  - Composite outcome
  - Adaptive designs
  - Enrichment designs
  - Borrowing of controls
  - Opportunities in era of big data
Event driven trials

- In time-to-event outcome studies power depends on the number of events observed
- Efficiency is increased by stopping when minimum necessary number of events is reached
- All follow-up is included in the analysis
- Blinded interim monitoring of event count allows increasing or decreasing planned study duration or increase in enrolled sample
Composite Outcomes

- Number of primary outcome events can be increased by combining different outcome types
- For example, major adverse cardiovascular events (MACE) consist of cardiovascular death, myocardial infarction and stroke
- Time to first event or hierarchical composite used
- They should be of similar severity
- Analysis of individual components always conducted as sensitivity
Example: Time to MACE composite

<table>
<thead>
<tr>
<th></th>
<th>Study Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (saxagliptin vs. placebo)</td>
<td>613/8280 (7.4%)</td>
<td>609/8212 (7.4%)</td>
<td>1.00</td>
<td>0.89, 1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>EXAMINE (alogliptin vs. placebo)</td>
<td>305/2701 (11.3%)</td>
<td>316/2679 (11.8%)</td>
<td>0.96</td>
<td>NA, 1.16</td>
<td>0.315</td>
</tr>
<tr>
<td>TECOS (sitagliptin vs. placebo)</td>
<td>745/7332 (10.2%)</td>
<td>746/7339 (10.2%)</td>
<td>0.99</td>
<td>0.89, 1.10</td>
<td>0.844</td>
</tr>
<tr>
<td>SAVOR + EXAMINE + TECOS</td>
<td>1663/18313 (9.1%)</td>
<td>1671/18230 (9.2%)</td>
<td>0.99</td>
<td>0.92, 1.06</td>
<td></td>
</tr>
</tbody>
</table>

Example: TAVI in aortic stenosis

- The Placement of Aortic Trans-catheter Valves (PARTNER) trial used Finkelstein-Schoenfeld hierarchical composite

- All-cause mortality first in hierarchy, hospitalization for heart failure second

- Multiple pairwise comparisons performed for all patient pairs, first with respect to time to death and then with respect to time to repeat hospitalization

- Method more powerful if some outcomes continuous

Adaptive Designs

- Key study features (sample size, study duration, number of treatment arms) can be adapted based on information obtained at interim.
- Blinded interim looks focus on combined parameters (event rate, overall mean, variance) and usually do not trigger alpha penalty.
- Unblinded interim looks incorporate effect size observed at interim and usually trigger alpha penalty.
- Decision often based on conditional power.
Example: drop-the-losers design

- In stage A, k experimental and one control treatment administered
- Data unblinded and analyzed and only the best treatment or any treatment exceeding pre-specified threshold proceed to stage B along with control
- Final summary statistic based on sample size-weighted combination of effect versus placebo from stages A and B
Biomarkers

• FDA’s Qualification process for drug development tools:

  • A *prognostic* biomarker is a baseline patient or disease characteristic that categorizes patients by degree of risk for disease occurrence or progression. A prognostic biomarker informs about the natural history of the disorder in that particular patient in the absence of a therapeutic intervention.

  • A *predictive* biomarker is a baseline characteristic that categorizes patients by their likelihood for response to a particular treatment. A predictive biomarker is used to identify whether a given patient is likely to respond to a treatment intervention in a particular way (favorable or not).
## Example: Predictive biomarkers

### Effect of L-Methylfolate 15 mg/d vs Placebo on Pooled Mean Change From Baseline for HDRS-28 Stratified by Baseline Level of Plasma Marker

<table>
<thead>
<tr>
<th>Marker</th>
<th>N</th>
<th>Pooled Mean Change vs. Placebo</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAM/SAH ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2.71 mg/L</td>
<td>36</td>
<td>0.07</td>
<td>-3.33, 3.48</td>
<td>0.966</td>
</tr>
<tr>
<td>&lt; 2.71 mg/L</td>
<td>37</td>
<td>-4.57</td>
<td>-7.73, -1.41</td>
<td>0.005</td>
</tr>
<tr>
<td>4-HNE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3.28 µg/mL</td>
<td>37</td>
<td>-4.55</td>
<td>-7.61, -1.50</td>
<td>0.003</td>
</tr>
<tr>
<td>&lt; 3.28 µg/mL</td>
<td>36</td>
<td>-0.11</td>
<td>-3.67, 3.46</td>
<td>0.953</td>
</tr>
</tbody>
</table>
Adaptive Enrichment Designs

- $G_0$ – all eligible subjects
- $G_1$ – subset of all eligible subjects who possess non-wild-type alleles on either genotype A and B
- $G_2$ – subset of eligible subjects who possess non-wild-type alleles on both genotype A and B
- Conditional power calculated at interim based on effect size in each set
- Opportunity to enrich by recruiting only to subset $G_1$ or $G_2$
Sequential Parallel Comparison Design

- Developed to reduce impact of placebo response
- In stage A, individuals randomized to treatment versus placebo (usually more to placebo)
- Stage A placebo non-responders re-randomized to treatment versus placebo
- Final summary statistic based on weighted combination of effects from stages A and B
- Particular choice of weights enables interpretation as effect after accounting for placebo response

Chi G. Contemporary Clinical Trials Communications 2 (2016): 34-53
ADAPT-A: Aripiprazole Augmentation of SSRIs
Source: Fava et al, Psychotherapy and Psychosomatics 2012

Response rate

<table>
<thead>
<tr>
<th></th>
<th>Drug</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPCD Phase 1</td>
<td>18.5%</td>
<td>17.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>SPCD Phase 2</td>
<td>18.0%</td>
<td>7.9%</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

Phase 1:
- Drug Response 18.5%

Phase 2:
- Drug Response 18.0%

Randomize
n = 221
Borrowing Controls

- All or some controls are borrowed from “historical” data

Numerous options:
  - Pooling: adds historical controls to randomized controls
  - Performance criterion: uses historical data to define performance criterion for current, treated-only trial to beat
  - Test then pool: test if controls sufficiently similar for pooling
  - Power priors: historical control discounted when added to randomized controls
  - Hierarchical modeling: variation between current vs. historical data is modeled in Bayesian fashion
Opportunities in era of big data

- We might be able to run very large simple trials for fraction of cost
  - EHR-enabled trials
    - pcornet ADAPTABLE – trial of aspirin doing in secondary prevention with 20,000 patients with EHR as primary source of data capture
  - Registry-based trials
    - SAFE-PCI in women – comparing access site (radial vs. femoral) in 1800 PCI or angiography with possible PCI women
    - Several ongoing Registry-RCTs in Sweden
ADAPTABLE Study Design
Patients with known ASCVD + ≥1 “Enrichment Factor”

- Identified through EHR screening and electronic patient contact by CDRNs/PPRNs (PPRN patients would need to connect through a CDRN to participate)

- Patients contacted electronically with trial information and e-consent via web portal
  Treatment assignment will be provided directly to patient

- ASA 81 mg QD
- ASA 325 mg QD

Randomized Electronic Follow-Up: 3 vs 6 months
Supplemented with EHR/CDM Data Queries

- Duration: Enrollment over 24 months; maximum follow up of 30 months

- Primary Endpoint: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

- Primary Safety Endpoint: Hospitalization for major bleeding

*Enrichment Factors
- Age > 65 years
- Creatinine > 1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF<50% by echo, cath, nuclear study
- Current smoker
Methods - SAFE-PCI for Women Workflow

Randomization

Demographics
Medical History
Procedural data

Autopopulate trial
database with registry
“big” data

Unique pages for trial

Analytic Database

NCDR®
National Cardiovascular Data Registry

CathPCI Registry®

ORACLE®

DCRI
Conclusions

- Numerous study designs and statistical approaches intend to approve trial efficiency
- Different approaches at different stages of adoption and different potential for application in neuroscience studies
- In general, regulators more open to innovative approaches in smaller studies and/or earlier stages of development (II vs. III)
- Careful consideration and appropriate statistical expertise in the planning stage needed to identify approaches most likely to succeed