Innovative Trial Designs

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July 18, 2016
Disclosures and Acknowledgements

• Kert Viele is an employee of Berry Consultants, a consulting firm specializing in innovative trials with multiple clients.
• Work presented here largely the result of discussion funded by ARLG
  – co-PIs Roger Lewis and Brad Spellberg
  – discussion included academics, pharmaceutical companies, FDA, BARDA, Berry Consultants
Standard Trial

• Here focus is on treatments for resistant pathogens.
• Multiple body sites
  – HAPVAP (combined), UTI, IA
  – others possible
• Generally standard trials, even enriched for resistance, encounter relatively low rates of resistant pathogens.
  – Small samples makes inferences difficult
Standard Trial

• Standard trials focus on one drug versus control at one body site.
• This is then repeated across the industry, with lots of trials occurring, each with small sample size of resistant pathogens
Innovations

• We consider three innovations in this talk
  – Platform trials
  – Early stopping
  – Sharing information across body sites

• Each has the potential to produce significant savings compared to collections of “one drug, one body site” trials.
Platform Trials

• Trials which incorporate multiple drugs all once, sharing control information.

• I-SPY 2 (breast cancer) is a long running platform trial, has explored implementation issues in a practical setting.
  – See July 7, 2016 NEJM for 4 articles on ISPY2

• Other examples in preparation or waiting for implementation
  – IMI EPAD (Alzheimers), PREPARE (influenza), GBM-AGILE (GBM), Gates Foundation Ebola
Platform Trials

• Sharing of control information is a key efficiency gain
  – If we run 40 standard trials on control:treatment with 24,000 subjects, we allocate 12,000 to control and 300 to each novel treatment.
  – Sharing control reduces the sample size required to evaluate all novel treatments.

• Combined with early stopping, drugs which fail (or succeed) early free up space for new drugs, “investing” the savings forward.
Platform advantages

• Savings of 35% of sample size or more
• More details/rigor in Saville and Berry in slightly different context (Clinical Trials 2016, “Efficiencies of platform clinical trials: A vision of the future” currently online ahead of print)
Early Stopping of Body Sites

• Futility (and success) stopping allows drugs to be discarded (or approved) prior to their maximum sample size.
  – can be body site specific. If a drug performs poorly in HAPVAP, can eliminate that drug from HAPVAP only

• Sample size savings can often be 15-20%
  – can be larger or smaller depending on true effect
Early Stopping of Body Sites

• Early stopping has synergies with platform trials. Saved subjects for one drug can be used to test other drugs.

• For example, instead of being able to test 40 drugs in a platform, could test 48 (if 20% savings occur) with the same number of subjects.
Sharing Information Across Body Sites

- Often we expect antibiotics to work across body sites
  - not a guarantee, depends on penetration
  - some counterexamples, but trends are common
- Would like a method which recognizes general trends while having good chance of recognizing outlying body sites.
Sample Data Set

• In the data set below, we see a nice general trend across all 3 body sites, but only 1 meets p=0.025 threshold on its own.

<table>
<thead>
<tr>
<th></th>
<th>HAPVAP</th>
<th>UTI</th>
<th>IA</th>
</tr>
</thead>
<tbody>
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<td>Control Data</td>
<td>5/12=42%</td>
<td>9/25=36%</td>
<td>14/22=64%</td>
</tr>
<tr>
<td>Treatment Data</td>
<td>10/13=77%</td>
<td>23/25=92%</td>
<td>13/15=87%</td>
</tr>
<tr>
<td>Pr(trmt better) with separate analyses</td>
<td>0.972</td>
<td>1.000</td>
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Sample Data Set

• Context matters. The data in IA, for example, is more convincing when paired with strong results in the other body sites — would look like a potential spurious high if the drug had failed in HAPVAP and UTI.

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Sharing information

• Hierarchical models incorporate the context of each individual result.
  – point estimates are “pushed together”
  – effective sample size increased through the analysis.

• Good models do this dynamically.
  – More sharing when common effects are observed
  – If a group appears to be an true outlier, share less.
Sample Data Set

• In our sample dataset, the model sees common effects in all three body sites.
• Adjusted results are successful in all three sites.

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Sample Data Set 2

• Here IA appears to have a significant problem.
• The successes in HAPVAP and UTI do not “pull up” the negative story in IA, results are still negative there.
  – due to huge group difference, model shares little"
Sharing information

• Over a population of drugs, particularly when we expect many to have general trends across body sites, sharing information can increase effective sample size 30-45%.

• Primary driver of conclusion for each body site is the data in that site
  – sharing augments the sample size, doesn’t replace data in that site
Sample size savings
(for a plausible scenario)

• Adding early stopping to borrowing can reduce sample sizes
  – standard design requires 400-425 per arm
  – borrowing alone reduced sample sizes to 300 per arm.
  – early stopping as well reduces that to 230-275 per arm.

• A platform trial structure produces further advantages
  – sharing control information
  – utilizing subject savings to accelerate investigation of future drugs.
  – average 325/drug (not arm)
Summary

• Potential for significant innovation in clinical trial design.
  – platform trials
  – early stopping
  – sharing of information

• The three innovations here can be used separately or in combination
  – synergies exist in the combinations, particularly with early stopping and platform trials.

• Each innovation has been implemented in areas outside antibiotics