Innovative Trial Designs

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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 a 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 requires 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.

	HAPVAP	UTI	IA
Control Data	5/12=42%	9/25=36%	14/22=64%
Treatment Data	10/13=77%	23/25=92%	13/15=87%
Pr(trmt better) with separate analyses	0.972	1.000	0.945

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.

	HAPVAP	UTI	IA
Control Data	5/12=42%	9/25=36%	14/22=64%
Treatment Data	10/13=77%	23/25=92%	13/15=87%
Pr(trmt better) with separate analyses	0.972	1.000	0.945

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Statistical Innovation

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.

	HAPVAP	UTI	IA
Control Data	5/12=42%	9/25=36%	14/22=64%
Treatment Data	10/13=77%	23/25=92%	13/15=87%
Pr(trmt better) separate	0.972	1.000	0.945
Pr(trmt better) sharing information	0.997	1.000	0.995

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

	HAPVAP	UTI	IA
Control Data	5/12=42%	7/18=39%	25/29=86%
Treatment Data	18/21=86%	24/25=96%	11/19=58%
Pr(trmt better) separate	0.997	1.000	0.014
Pr(trmt better) sharing information	0.995	1.000	0.038

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