Evaluating antibacterial drugs in unmet need settings

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Outline

- Randomized trials in the resistant pathogen setting:
  - Examples
  - Platform trials
  - Combining subjects with infections at different body sites

- Challenges and options when it is difficult to enroll:
  - Inferential and descriptive statistics
  - Bayesian and frequentist statistics

Examples of randomized trials in the resistant pathogen setting

- Four recently published randomized clinical trials compared colistin monotherapy to combination therapy for life-threatening carbapenem-resistant *Acinetobacter baumannii* infections:

First author	Country	Period	Sample size	Combination
Durante-Mangoni	Italy (5 centers)	11/2008-7/2011	N = 210	Colistin + Rifampicin
Aydmir	Turkey (1 center)	03/2011-03/2012	N = 43	Colistin + Rifampicin
Sirijatuphat	Thailand (1 center)	01/2010-03/2011	N = 94	Colistin + Fosfomycin
Dickstein*	Greece, Israel, Italy (6 centers)	10/2013-Ongoing	N = 240 enrolled N = 360 planned	Colistin + Meropenem

*Carbapenem-resistant *A. baumannii* is the dominant but not exclusive pathogen

Examples of randomized trials in the resistant pathogen setting

Trial location	Mortality in randomized groups		
Italy	Colistin	Colistin + Rifampicin	
	45/105 (42.9%)	45/104 (43.2%)	
Turkey	Colistin	Colistin + Rifampicin	
	16/22 (72.7%)	13/21 (61.9%)	
Thailand	Colistin	Colistin + Fosfomycin	
	27/47 (57.4%)	22/47 (46.8%)	
Pooled trials	Colistin	Colistin + Add-on	Difference (95% CI)
	88/174 (50.6%)	80/172 (46.5%)	4.1% (-6.4% to 14.5%)

Randomized trials in the resistant pathogen setting

- Fully powered randomized trials would provide the most statistically reliable answers to the most important questions.
- For complicated patients with many co-morbidities, randomization ensures that treatment effect estimation is not confounded.
- The most natural questions are superiority questions:
  - Patients with effective therapeutic options could be folded into more traditional non-inferiority trials.
- However, it must be possible to enroll a relatively large number of subjects with infections due to multidrug resistant pathogens:
  - Are there strategies to enroll sufficient numbers (e.g., cluster randomization, better diagnostics for pathogen identification)?
  - How should we proceed if enrollment is not possible?

Platform trials

- A platform trial using a common master protocol could potentially allow for a study of multiple antibacterial drugs, studies of multiple indications, or a study using a shared control group.

- Potential gains from sharing a control group:
  - If two sponsors run separate trials of Drug A versus control and Drug B versus control with 100 subjects per arm, the sponsors together must enroll a total for 400 subjects and compete for study sites.
  - If instead there is a 3 arm trial with Drug A, Drug B, and control with 100 subjects per arm, the trial only enrolls a total of 300 subjects. Separate statistical comparisons could be made for Drug A versus control and Drug B versus control.

*Also see LaVange (2014)

Platform trials

- Straightforward platform trial design:
  - Drugs enter or exit the study in a staggered manner
  - Attempt to answer multiple questions of interest
  - Advantages in shared clinical trial infrastructure, study sites, IRBs
  - Prospectively plan for how comparisons change if the standard of care regimen must be updated due to the ongoing trial results
  - The comparisons of interest would be between subjects concurrently randomized to test and control drugs

*Also see LaVange (2014)

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Platform trials

- Many statistical design features could be part of a platform trial but are separate issues that need to be considered independently of whether to evaluate antibacterial drugs using a common protocol:
  - Response-adaptive randomization
  - Bayesian adaptation for efficacy and futility stopping criteria
  - Use of statistical modeling with non-randomized comparisons, such as comparisons between subjects in the trial assigned to Drug A or Drug B who were not concurrently randomized

Combining body sites of infection

- Centers for Disease Control and Prevention on carbapenem-resistant Enterobacteriaceae (CRE):
  - "Patients whose care requires devices like ventilators, urinary catheters, or intravenous catheters, and patients who are taking long courses of certain antibiotics are most at risk for CRE infections. Some CRE bacteria have become resistant to most available antibiotics."
- Should we conduct a single trial
  - combining subjects with
    - nosocomial pneumonia, bloodstream infections, and complicated urinary tract infections
  - despite
    - Possible differences in endpoints, comparators, treatment durations, and patient characteristics
    - recent examples of antibacterial drugs that may have had discordant efficacy results across body sites?

Combining body sites of infection

- In principle, we can use body site-specific endpoints or responder definitions, comparators, and treatment durations.

- Statistical methods using smoothing/shrinkage can be used to form more accurate body site-specific estimates of treatment effects by borrowing information across subgroups.

- Whether to do this is less a statistical heterogeneity issue than a clinical decision regarding whether patients with infections at different body sites constitute a reasonable target population:
  - We may have low statistical power to detect heterogeneous treatment effects across different body sites.
  - With small sample sizes, statistical methods cannot guarantee accurate estimation for every body site subgroup.

Trials of combination therapies for life-threatening carbapenem-resistant *Acinetobacter baumannii* infections

Trial author	Percentage of trial subjects with infections at different body sites					
	Pneumonia	Bacteremia	Intra-abdominal	Urinary tract	Other	Total
Durante-Mangoni	77.5%	20.1%	2.4%	0%	0%	100%
Aydmir	100%	0%	0%	0%	0%	100%
Sirijatuphat	76.6%	5.4%	6.4%	5.4%	6.4%	100%

What if randomized trials cannot enroll enough subjects with resistant pathogens?

- To statistically demonstrate superiority with a reasonable number of subjects, the new antibacterial drug would need to provide relatively large benefits compared to current standards of care:

Treatment failure rate	Control failure rate	Sample size per arm
30%	50%	N = 91
35%	50%	N = 167
40%	50%	N = 385

Assumes two-sided $\alpha = 0.05$ significance level, 1:1 randomization, 80% power

Inferential and descriptive statistics

- FDA has traditionally interpreted trials that use inferential statistics and formal tests of hypotheses as providing reliable evidence.
- A descriptive analysis of a clinical trial would present success rates for Drug A and Drug B but would not formally test a hypothesis.
- Examples of descriptive statistical analyses of antibacterial drugs:
  - Many Phase 2 studies, pediatric studies, and safety studies.
    - Phase 2 studies factoring into FDA approval of ceftazidime-avibactam in 2015
  - FDA approvals of antibacterial drugs in earlier decades.
  - Clinical data used to set susceptibility breakpoints.
- Can trials pre-specify decision criteria other than $p<0.05$ that give reasonable operating characteristics in the unmet need setting?

Frequentist inferential statistics

- Frequentist methods such as p-values and confidence intervals have been the default paradigm for clinical trials.
- Type I error rate control:
  - With two-sided $\alpha=0.05$ level tests, approximately only 1 out of 40 clinical trials of ineffective treatments will falsely conclude efficacy
- Coverage guarantees:
  - In approximately 95 out of every 100 clinical trials, the confidence interval for the treatment effect will contain the true effect
- Statistical theory provides Type I error rate control and coverage guarantees under minimal conditions (e.g., randomization, low missing data) without modeling assumptions or external data.

Bayesian inferential statistics

- Bayesian methods can integrate trial data with prior evidence from other sources.
- For antibacterial drugs the prior evidence may come from:
  - Previous randomized or observational studies of the new drug, comparator, or related antibacterial drugs
  - Previous studies at different body sites of infection
  - Pharmacokinetic/pharmacodynamic data
  - Animal data
  - *In vitro* data
  - Expert elicitation
- Advantage: Bayesian methods attempt to incorporate all available information into the analysis and formalize sources of uncertainty.
- Disadvantage: Can lead to erroneous answers if prior beliefs are incorrect.

Frequentist example

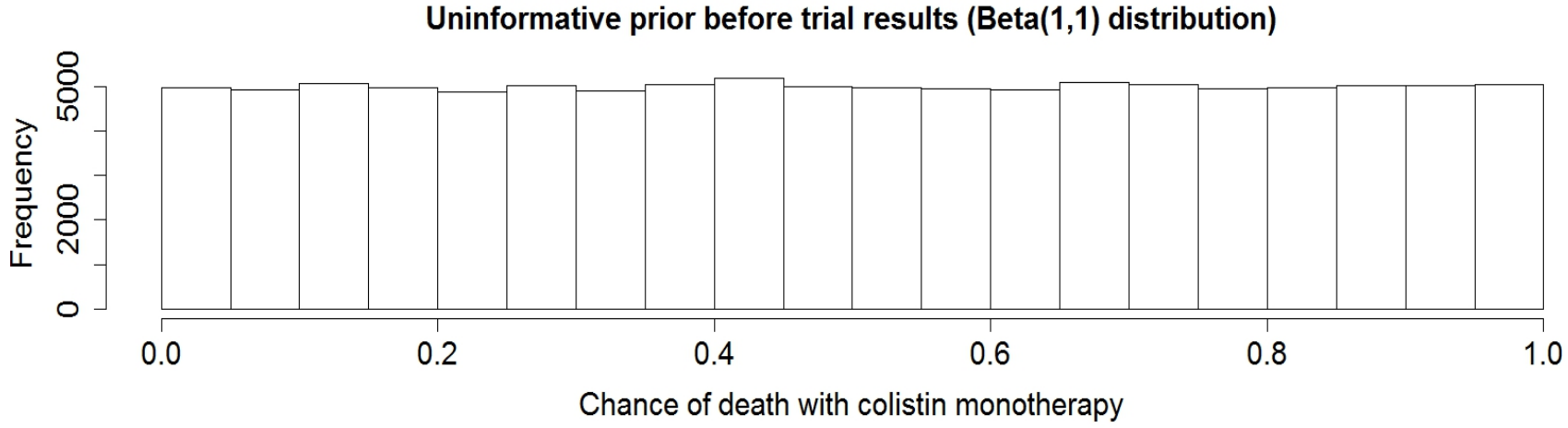
- *We saw earlier that in pooled randomized trials there were mortality rates of 88/174 (51%) for colistin monotherapy and 80/172 (47%) for combination therapy to treat carbapenem-resistant A. baumannii.*

- Frequentist analysis (ignoring pooling of studies): Estimate (monotherapy – combination therapy) difference in mortality rates to be 4%, with a confidence interval from -6% to 15%.

- Interpretation: The confidence interval is too wide to tell us whether combination therapy improves survival.

Bayesian example

- *We saw earlier that in pooled randomized trials there were mortality rates of 88/174 (51%) for colistin monotherapy and 80/172 (47%) for combination therapy to treat carbapenem-resistant A. baumannii.*
- Bayesian analysis can depend on prior information:
  - Uninformative prior:
    - Prob(combination mortality < monotherapy mortality) = 0.50.
    - If we handle the treatment and control as neutrally as possible, Bayesian and frequentist decisions will be similar.
  - Informative prior: Suppose before the trials we modeled from available evidence that there was an 80% chance the mortality rate for colistin monotherapy was between 0.60 and 0.70. After the trials, find from a beta-binomial model that
    - Prob(combination mortality < monotherapy mortality) = 0.99.
    - Interpretation: Combination therapy improves survival.


Uninformative prior before trial results (Beta(1,1) distribution)
Frequency
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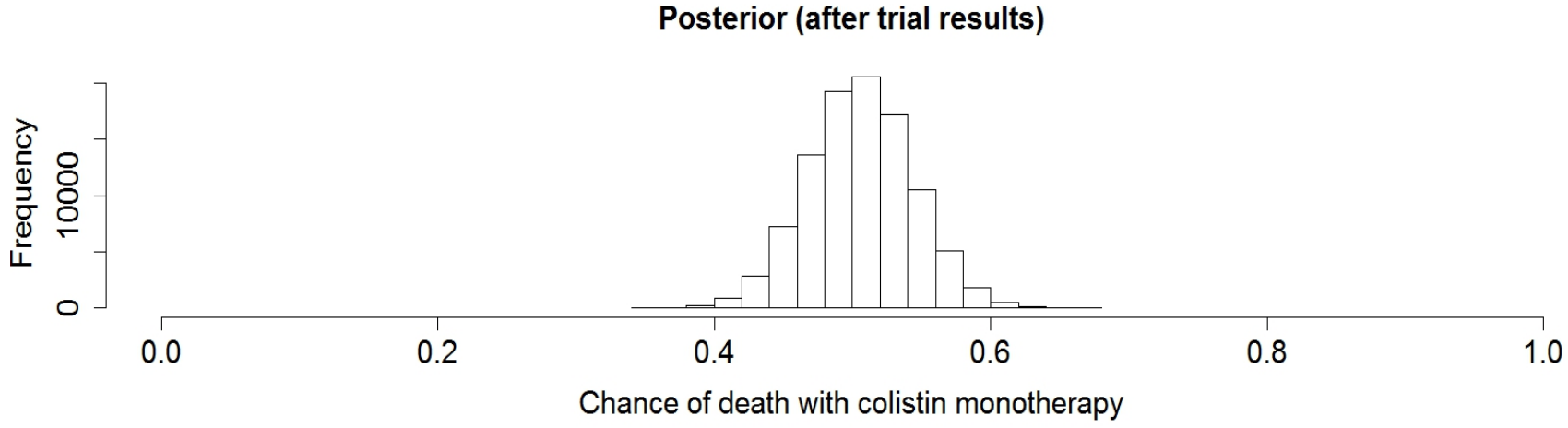
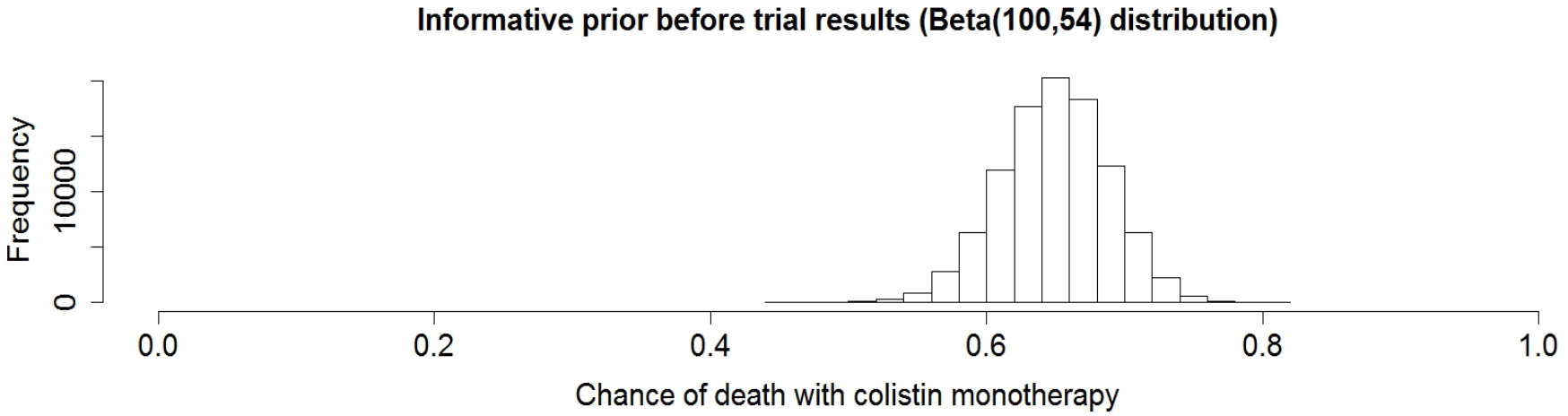
2000
5000
0.0
0.2
0.4
0.6
0.8
1.0
Chance of death with colistin monotherapy


Posterior (after trial results)
Frequency
0
10000
0.0
0.2
0.4
0.6
0.8
1.0
Chance of death with colistin monotherapy


Informative prior before trial results (Beta(100,54) distribution)
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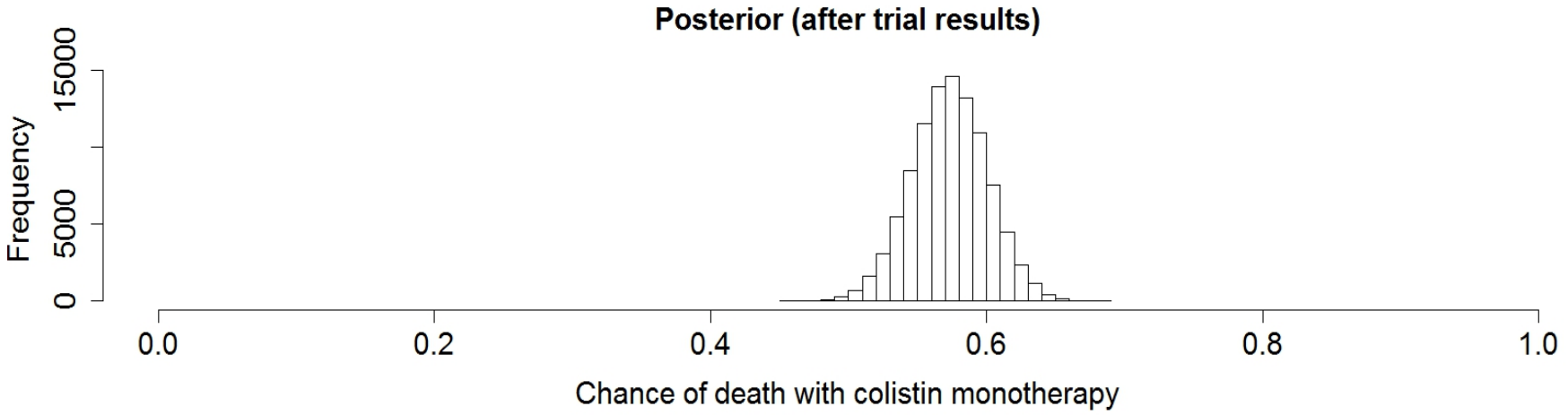
0.4
0.6
0.8
1.0
Chance of death with colistin monotherapy


Posterior (after trial results)
Frequency
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5000
15000
0.0
0.2
0.4
0.6
0.8
1.0
Chance of death with colistin monotherapy

Summary

- There are opportunities for conducting randomized trials in the resistant pathogen setting using platform trials.
- A trial combining subjects with different body site infections can be statistically analyzed, but how should heterogeneity be addressed?
- Conducting powered superiority trials in the unmet need setting requires large treatment effects or sample sizes. What pre-specified decision criteria are reasonable beyond descriptive analysis?
- Bayesian and frequentist methods are both valid statistical tools. In the anti-infective setting, the most important consideration is how much weight to give modeling of non-randomized evidence.

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