Summary of unmet need guidance and statistical challenges

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Disclaimer

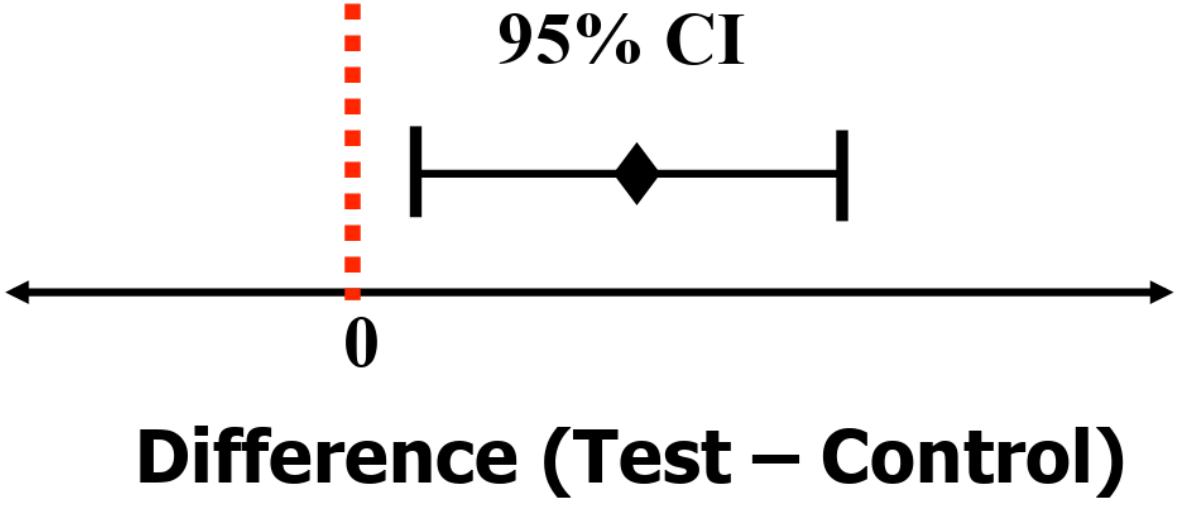
- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- **Superiority design**
- Non-inferiority design
- External controls
- Lessons from combination trials

Superiority design

- Evaluate whether a new treatment leads to better clinical outcomes than a control regimen



Superiority design

- Utility:
  - Answers the most relevant question
  - Provides the most statistically reliable answer

- Possible inducements:
  - Pooling of infections at different body sites
  - Less stringent statistical significance level

Superiority design

- Challenges:
  - Must hypothesize large effect size over best current therapy
  - Resistance must be prevalent

Control failure rate	Treatment failure rate	Sample size per arm
50%	30%	N = 91
50%	35%	N = 167
50%	40%	N = 385
50%	45%	N = 1562

Assumes one-sided $\alpha = 0.025$ significance level, 80% power

Outline

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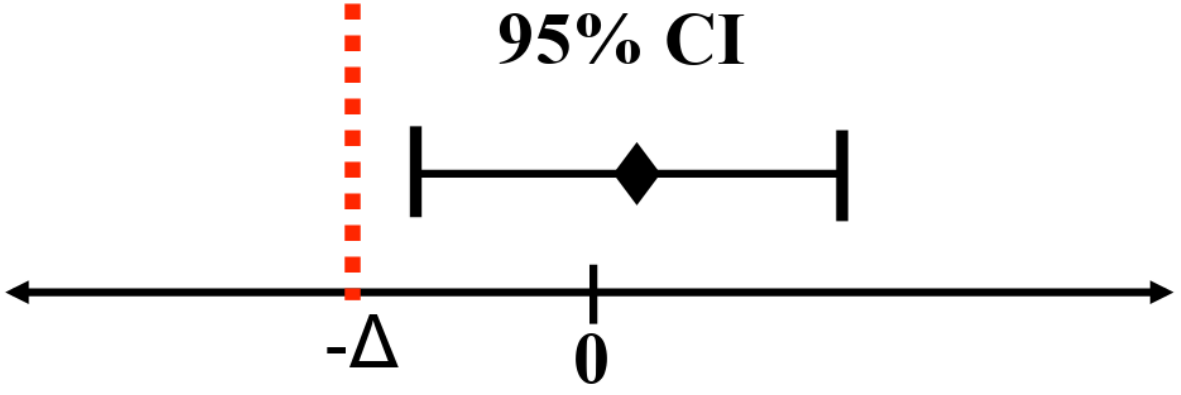
Non-inferiority design

- Must determine whether the test drug is unacceptably worse than the active control, according to margin Δ



Non-inferiority design

- Utility:
  - Traditional method for developing an antibiotic is to conduct a non-inferiority trial in patients with infections at a specific body site

- Challenges in design and analysis:
  - Historical evidence of sensitivity to drug effects
  - Constancy assumption
  - Assay sensitivity
  - Preservation of active control effect

Non-inferiority design

- Guidance discussion:
  - Conduct trial in patients with acceptable current options
  - Wider than normal non-inferiority margin
  - Extrapolate efficacy to group with unmet need

- Challenge of extrapolation:
  - Patient factors differ between those with susceptible pathogens and those with resistant pathogens
  - Patient factors are prognostic of outcomes and can modify treatment effects

Non-inferiority design

Table 1. Demographics and Outcomes of Sensitive vs Resistant ICU-Acquired Infections

Demographics and outcomes	Sensitive	Resistant	p Value
n	1,669	739	—
Age, y, mean ± SEM	52.8 ± 0.4	53.7 ± 0.5	0.16
Male sex, %	61.5	61.5	1.00
Body mass index, kg/m^2, mean ± SEM	30.4 ± 0.2	31.4 ± 0.3	0.007
APACHE II score, mean ± SEM	19.2 ± 0.1	20.2 ± 0.2	<0.001
WBC, maximum, mean ± SEM	15.7 ± 0.2	15.0 ± 0.3	0.06
Trauma, %	49.4	35.9	<0.001
Transplant recipient, %	12.3	21.9	<0.001
Transfused, %	82.8	93.2	<0.001
Hemodialysis, %	17.1	28.1	<0.001
Ventilator dependence, %	68.8	73.2	0.01

Source: Rosenberger et al. (2012)

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- Superiority designs
- Non-inferiority designs
- **External controls**
- Lessons from combination trials

External controls

- Conduct a randomized controlled trial, but augment the control group with external data on subjects treated with the control regimen

- Utility:
  - Increased statistical power when patients are scarce
  - Avoids single arm case series with descriptive statistics

External controls

- Challenges encountered putting idea into practice:
  - Selection of the control group (Chart review? Literature?)
  - Ensuring patient comparability with matching or adjustment
  - Minimizing bias in the analysis with pre-specification

- Challenges specific to antibacterial setting:
  - Patients do not uniformly die or fail to recover
  - Heterogeneous outcomes across studies
  - Underlying co-morbidities predictive of outcomes

External controls

- Selected summary of literature reports of pandrug-resistant (i.e., resistant to all antibiotics) Gram-negative infections

First author	Year published	Sample size	Recovery/survival rate
Falagas	2005	n = 7	5/7 (71.4%)
Beno	2006	n = 10	3/10 (30.0%)
Mentzelopoulos	2007	n = 5	4/5 (80.0%)
Falagas	2008	n = 24	14/24 (58.3%)
Elemam	2009	n = 2	1/2 (50.0%)
Tsioutis	2010	n = 21	16/21 (76.2%)
Giamarellou	2013	n = 3	3/3 (100%)
Oliva	2014	n = 3	2/3 (66.7%)
Total		n = 75	48/75 (64.0%)

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- **Lessons from combination trials**

Lessons from combination trials

- Three recent randomized, pathogen-specific trials comparing colistin monotherapy to combinations for cabapenem-resistant *A. baumannii* infections

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 + IV Fosfomycin

Lessons from combination trials (pooling body sites)

Infection	Durante-Mangoni	Aydmir	Sirijatuphat
Pneumonia	77.5%	100%	76.6%
Bacteremia	20.1%	0%	5.4%
Intra-abdominal	2.4%	0%	6.4%
Urinary tract	0%	0%	5.4%
Other	0%	0%	6.4%

Lessons from combination trials (mortality results)

Trial	Mortality in randomized groups		
Durante-Mangoni	Colistin	Colistin + Rifampicin	
	45/105 (42.9%)	45/104 (43.2%)	
Aydemir	Colistin	Colistin + Rifampicin	
	16/22 (72.7%)	13/21 (61.9%)	
Sirijatuphat	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%)

Lessons from combination trials

- Bias:
  - It could be misleading to make non-randomized cross-study comparisons, as mortality rates significantly varied over trials
- Variance:
  - No evidence of mortality benefit for combinations over monotherapy, but benefit cannot be excluded. Absent dramatic treatment effects, large numbers of subjects can be needed for definitive answers.
- Enrollment:
  - It has been possible to enroll a moderate number of subjects in settings of resistance, unmet need, and pathogen-specific trials

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