The use of limited data to achieve regulatory drug approval: Options for Antibiotic Drug Development

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Ideas in this talk:
Options when only smaller RCTs are possible

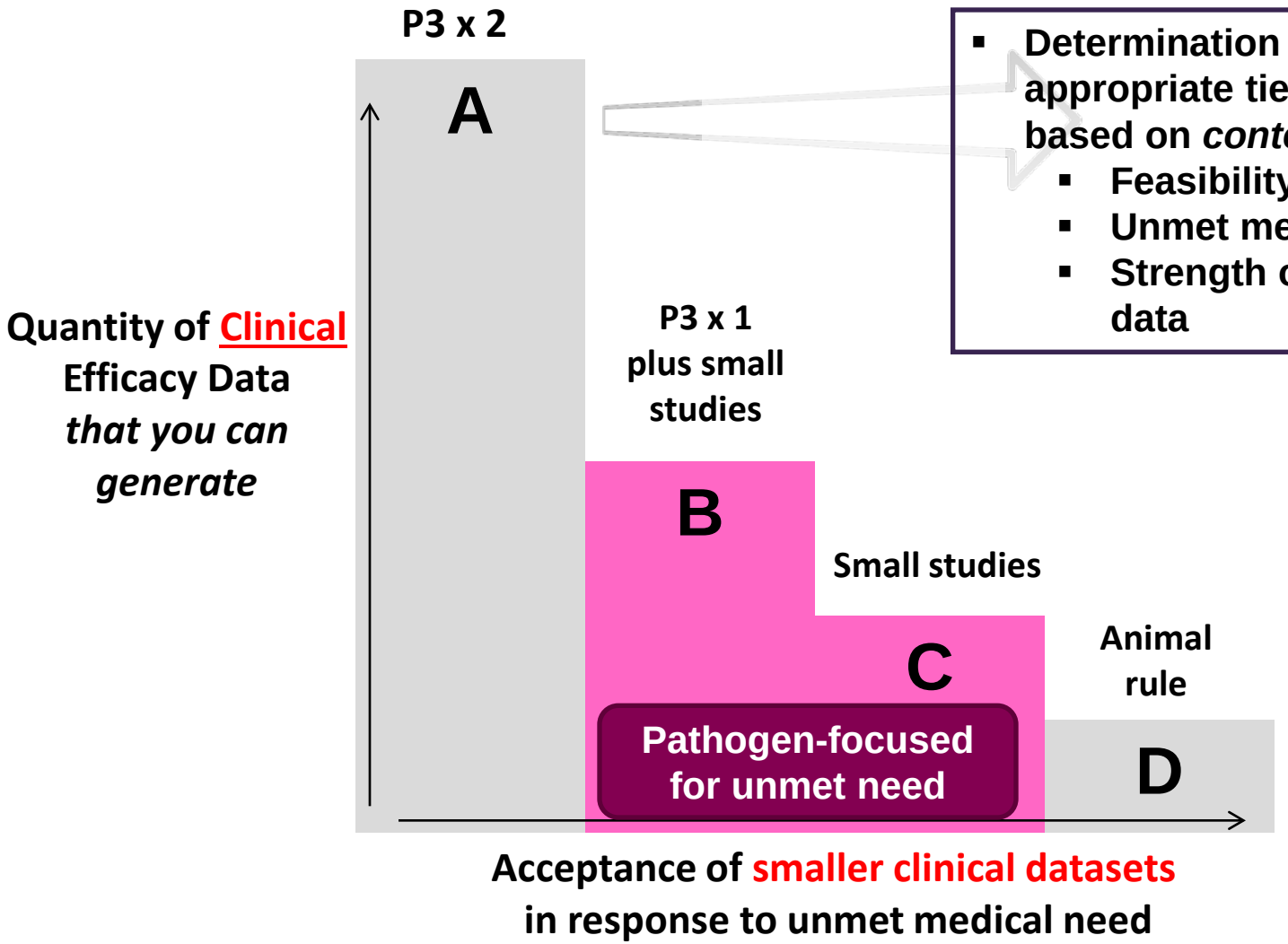
- What is the issue and how could we approach it?
  - A tiered regulatory approach
- Alternate statistical criteria
- ***Bayesian approaches***
- Other areas of ongoing research
- Interpretation of data on small numbers of resistant pathogens

Background

- Antibacterial drug resistance is increasing, with concerns antibiotics will no longer be effective
- We need to run trials when resistance is rare to have treatments available for an emerging unmet need
- Pre-clinical PK/PD data relates well to clinical data, as both assess activity against key pathogens
- Given the challenges, a number of ideas have been explored by Regulatory, Industry and Academic statisticians

Development Options as Tiers

Trial programs balancing unmet need with uncertainty



- Determination of the appropriate tier should be based on *context*:
  - Feasibility
  - Unmet medical need
  - Strength of the preclinical data

Rex et al, Lancet Infectious Diseases, Volume 13, Issue 3, Pages 269 - 275, March 2013

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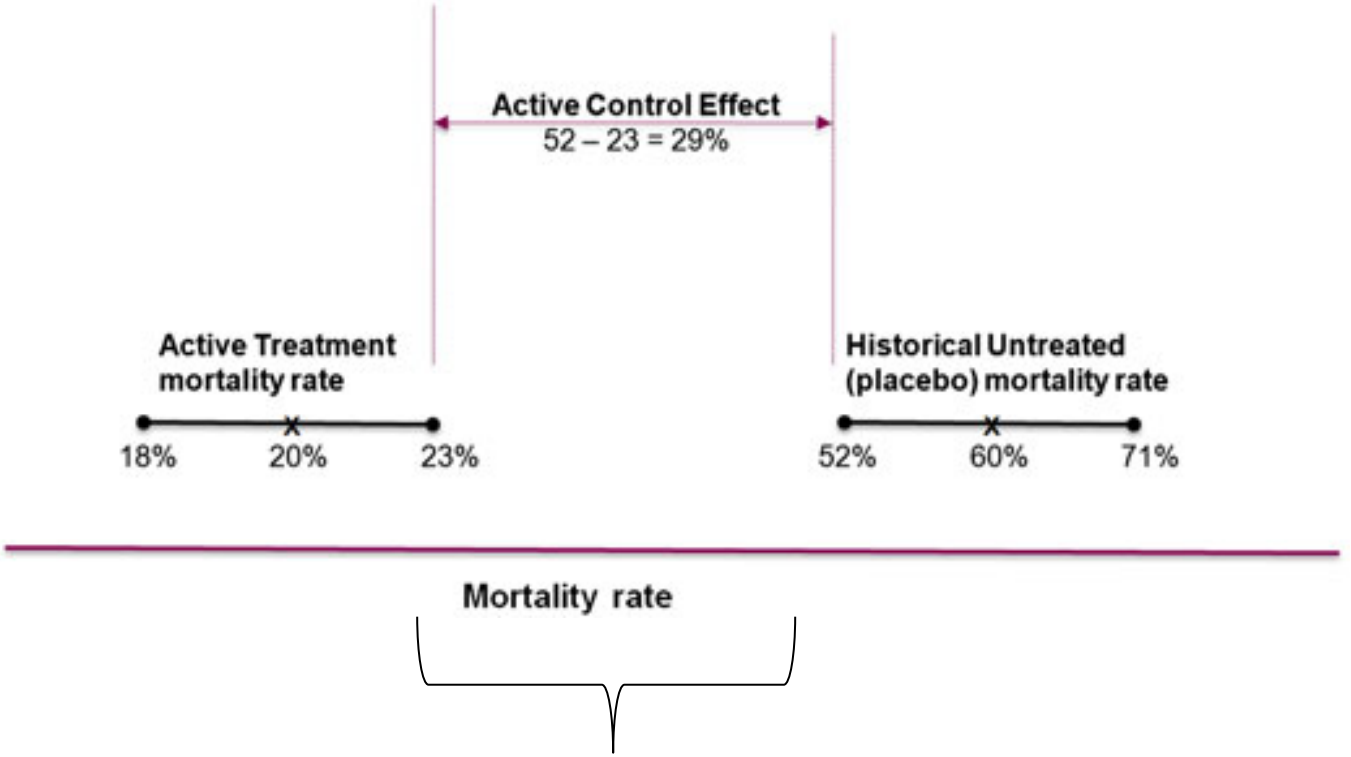
The Current Situation

Conservative NI margin setting for antibiotics

Nosocomial Pneumonia example



Estimated Active Control Effect = 29%
Discount for historical data → 20%
50% Discount for clinical relevance → 10%

Final NI margin = 10%

Different statistical criteria to improve feasibility

- For high unmet need, greater uncertainty may be reasonable

Options:

- Wider NI margin with less discounting

- Alternative α-level, meaning a different regulatory risk

Evaluable patients needed/arm

1-sided alpha	NI margin		
	-10%	-15%	-20%
0.025	337/arm	150/arm	85/arm
0.05	275/arm	122/arm	69/arm
0.10	211/arm	94/arm	53/arm

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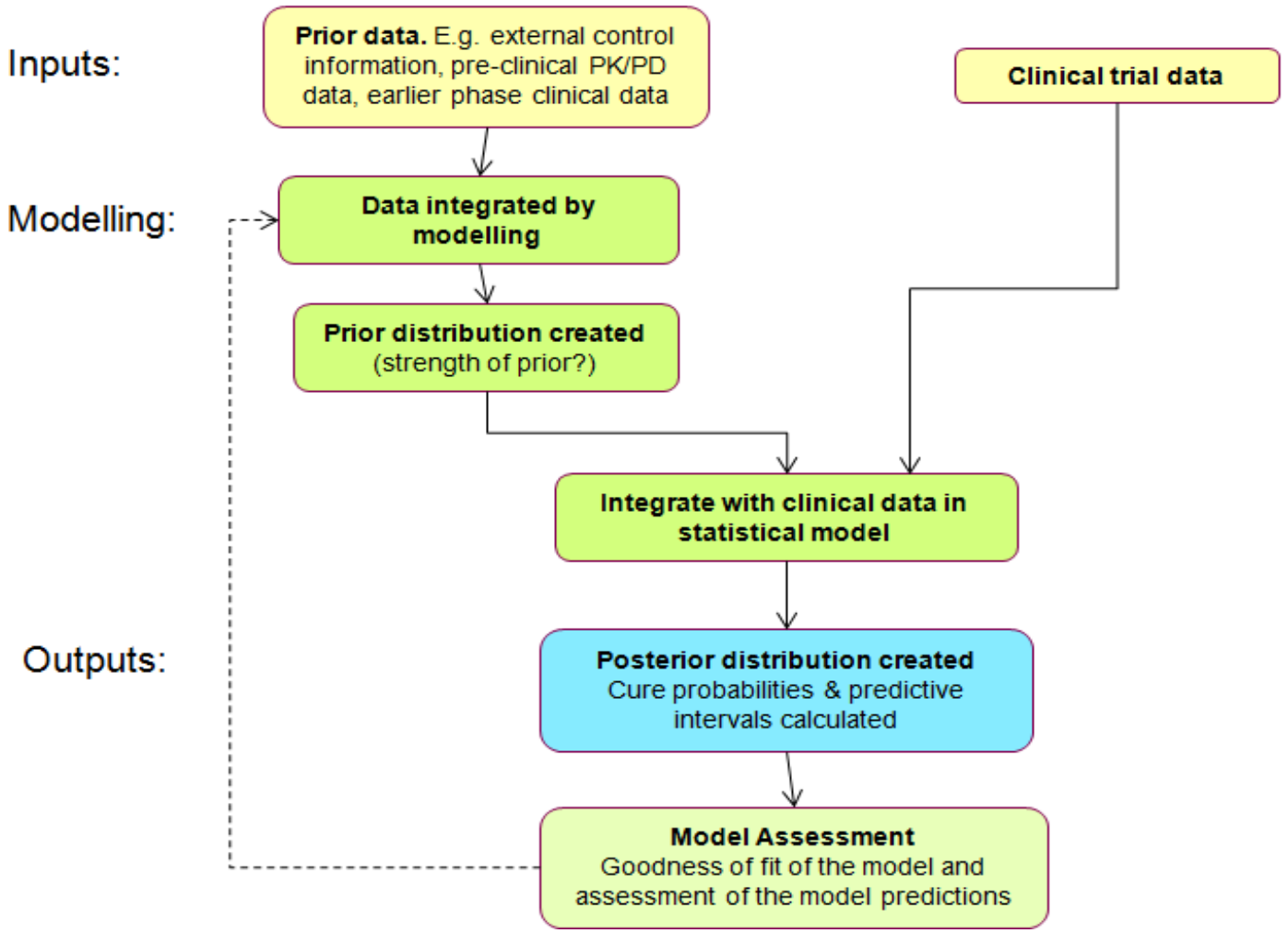
Bayesian Approaches

Role of prior distributions



Bayesian Approaches

(1) Bayesian-augmented Control Designs

- Aim to control type 1 error and power while maximizing sample size savings by borrowing from historical data
- With dynamic borrowing
  - Amount of borrowing depends on precision among control trials and similarity of historical data to concurrent control
  - Need to consider precision of control rate estimate in current trial; with small N it may be difficult to assess similarity to historical data
- If true control rate very different from true historical rate
  - Inflated type I error if true control above observed historical rate
  - Decreased power if true control substantially below historical rate
  - Due to the growing resistance may expect downward drift of control
- Therefore, a similar clinical setting and patient population is needed along with strong belief in similar response rates

(1) Bayesian-augmented Controls

Example – Bayesian approach can reduce patient numbers

- **Traditional (fixed) Design, N=750**
  - Operating Characteristics
    - Active control cure rate = 83%
    - 10% NI margin
    - 90% power and 5% two-sided significance
    - 20% dropout; 1:1 randomization
  - 375 patients per treatment (n = 750 total)

- **Bayesian approach, N=600**
  - N=600 with 2:1 randomization and borrowing
    - 400 subjects on treatment
  - Assumes historical control of 83%
  - Working hypothesis
    - NI concluded if 1-sided 97.5% CI for trt effect $\geq$ -10%
    - Type I error: conclude NI when test trt >10% worse
    - Power: ability to correctly conclude NI

We need to control type I error at <0.025 and retain reasonable levels of power (~90%)

True Control Group Rate	Type I error		Power	
	Traditional	Bayesian	Traditional	Bayesian
78.0%	0.024	0.006	84.2%	70.2%
80.5%	0.026	0.007	87.4%	86.1%
83.0%	0.026	0.017	91.0%	94.2%
85.5%	0.028	0.045	92.9%	96.6%
88.0%	0.030	0.100	95.4%	97.6%

Viele et al (2013) ***Adaptive design for a Phase 3 trial of cUTI that utilizes historical control data*****, manuscript in final draft**

(2) Bayesian Approaches using PK/PD

Use of PK/PD data to construct prior distributions

- Various data sources provide link between PK & MIC*
  - PD target from pre-clinical experiments; human PK from early trials
  - Simulate from PKPD model to get estimates of target attainment.
- Identify relationship between PKPD and clinical endpoint
  - Use data linking PKPD to clinical findings for approved products
  - Use this to provide confidence we can expect efficacy
- Using this relationship assess cure probability (& uncertainty)
  - Construct prior distribution to represent this estimate.
  - Degree of uncertainty in prior depends on confidence in translation
- Risks
  - No relationship between micro effect (PKPD) and clinical endpoint
  - PKPD model does not apply for the new product

MIC = concentration required to inhibit growth of pathogen
Target attainment = % times patient expected to achieve exposure needed to meet PD target

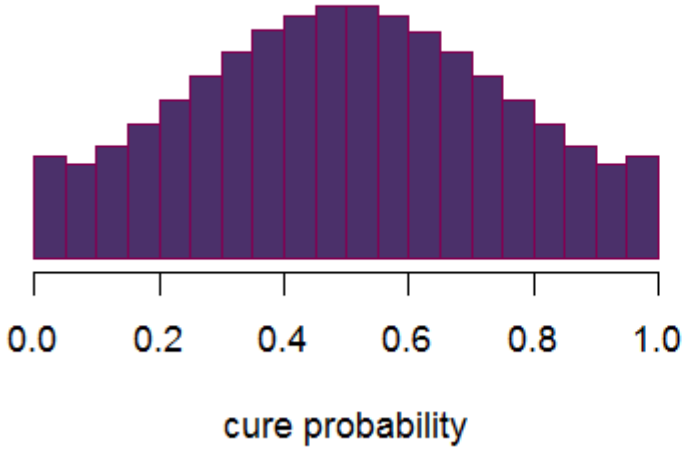
(2) Bayesian Approaches using PK/PD

Use of PK/PD data to construct prior distributions

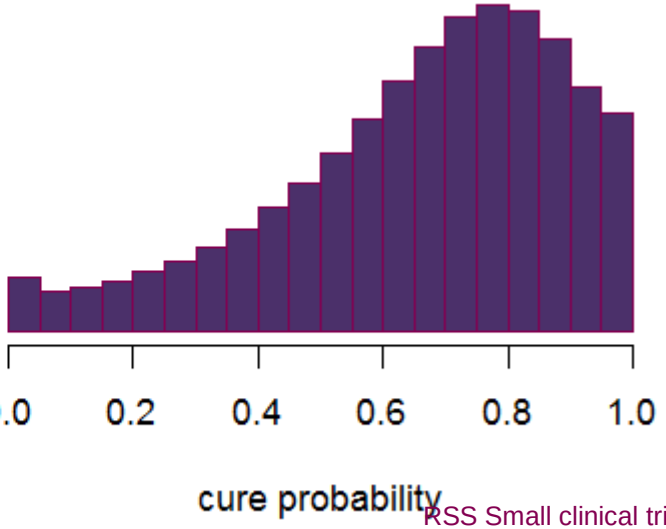
Worked Example

- 240 patients randomised overall
  - 2:1 ratio; 160 experimental v 80 control)
  - 24 patients on experimental and 12 on control with known positive MDR status
- Cure probabilities
  - 78% experimental v 76% control for non-MDR pathogens
  - 66% v 64% for MDR pathogens
- Prior distribution applied to both treatment arms

Broad Prior – centred around 50% response



Stronger Prior – centred around 75% response



(2) Bayesian Approaches using PK/PD

Use of PK/PD data can reduce confidence intervals

80% confidence/predictive intervals for cure probabilities

	Method	80% interval for cure probabilities		80% interval for difference in cure probability
		Experimental	Control	
Overall population (n=160 exp vs. 80 cont)	Frequentist	(0.67, 0.77)	(0.62, 0.77)	(-0.06, 0.11)
	Bayes (broad prior)	(0.66, 0.75)	(0.61, 0.74)	(-0.05, 0.11)
	Bayes (stronger prior)	(0.68, 0.76)	(0.65, 0.76)	(-0.05, 0.09)
MDR-positive patients (n=24 exp vs. 12 cont)	Frequentist	(0.47, 0.76)	(0.33, 0.67)	(-0.16, 0.41)
	Bayes (broad prior)	(0.52, 0.76)	(0.40, 0.68)	(-0.11, 0.23)
	Bayes (stronger prior)	(0.57, 0.79)	(0.48, 0.75)	(-0.13, 0.20)

Exp = experimental; Cont = Control

Possibility of some reduction in credible intervals compared to traditional approaches

(3) Platform Trials using Bayesian approaches

- Mechanism to collect data in a difficult to recruit population
  - Accumulate data on reference group treated with Best Available Therapy
  - Infrastructure that allows sponsors to efficiently generate comparative data
  - Can serve as primary or supportive evidence for registration
- Evaluation of multiple drugs at multiple sites of infection
  - Bayesian Hierarchical model to “borrow” information across body sites
- Trial open on a rolling basis
  - Compounds enter trial after sufficient Ph1/2 data available
  - “Graduate” or “terminate” compounds when there is sufficient evidence
  - Adaptive treatment allocation possible based upon probability of response
- Approach being piloted to understand assumptions and levels of (un)certainty provided
  - Key is whether can achieve level of evidence needed to support registration

Bayesian methods

Bayesian approaches help quantify available data, but the influence of prior distribution must be considered carefully

Points to consider:

- Goodness of fit from any Bayesian predictions or models
- Strength of prior & how influential this is *vs.* observed data
- External data prior
  - Confidence in similarity of design, patient population, anticipated effects
- PK/PD prior: concentration levels not randomly assigned
  - Concentrations may differ by other factors impacting response (age, severity, co-morbidities)

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FDA are actively exploring various approaches

- Network meta analysis
  - Use of additional information to supplement RCT
  - Uses historical data alongside NI trial to use all information available
- Infection site pooling
  - Relies on assumption of exchangeability between infection sites
  - Need evidence of effect in all body sites and clinical justification for pooling
- Bayesian approach to interim analysis
  - Use posterior likelihood at multiple interims, but needs huge effect to be compelling at interim
- Nested superiority design
  - Dual aim of showing NI in susceptible pop^{n}, then superiority in resistant pop^{n}
  - Demonstrated this does not inflate Type I error
  - But does not reduce burden of study or improve feasibility

Endpoints incorporating more patient-level data

Response Adjusted for Duration of Antibiotic Risk (RADAR)
Scott Evans, Harvard

- Ordered categorical scale incorporates benefits and risks
  - 3 point: Benefit/no tox; benefit with tox; death
  - 5 point: Benefit no tox; Benefit with tox; No benefit no tox; No benefit with tox; Death
- This could improve the sensitivity of analyses performed
  - Key is to meaningfully define categories for each disease area
- **University of Frieburg** also exploring use of additional data through use of cure and death data in the same model

Further work needed for both approaches to identify benefits of the approach in terms of regulatory and clinical decision making

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When only limited data are possible…

- When studying a small population with a resistant pathogen there seem to be two options
  - A *very* small RCT (so small inferential testing not possible)
  - *Open-label* data (single arm trial)

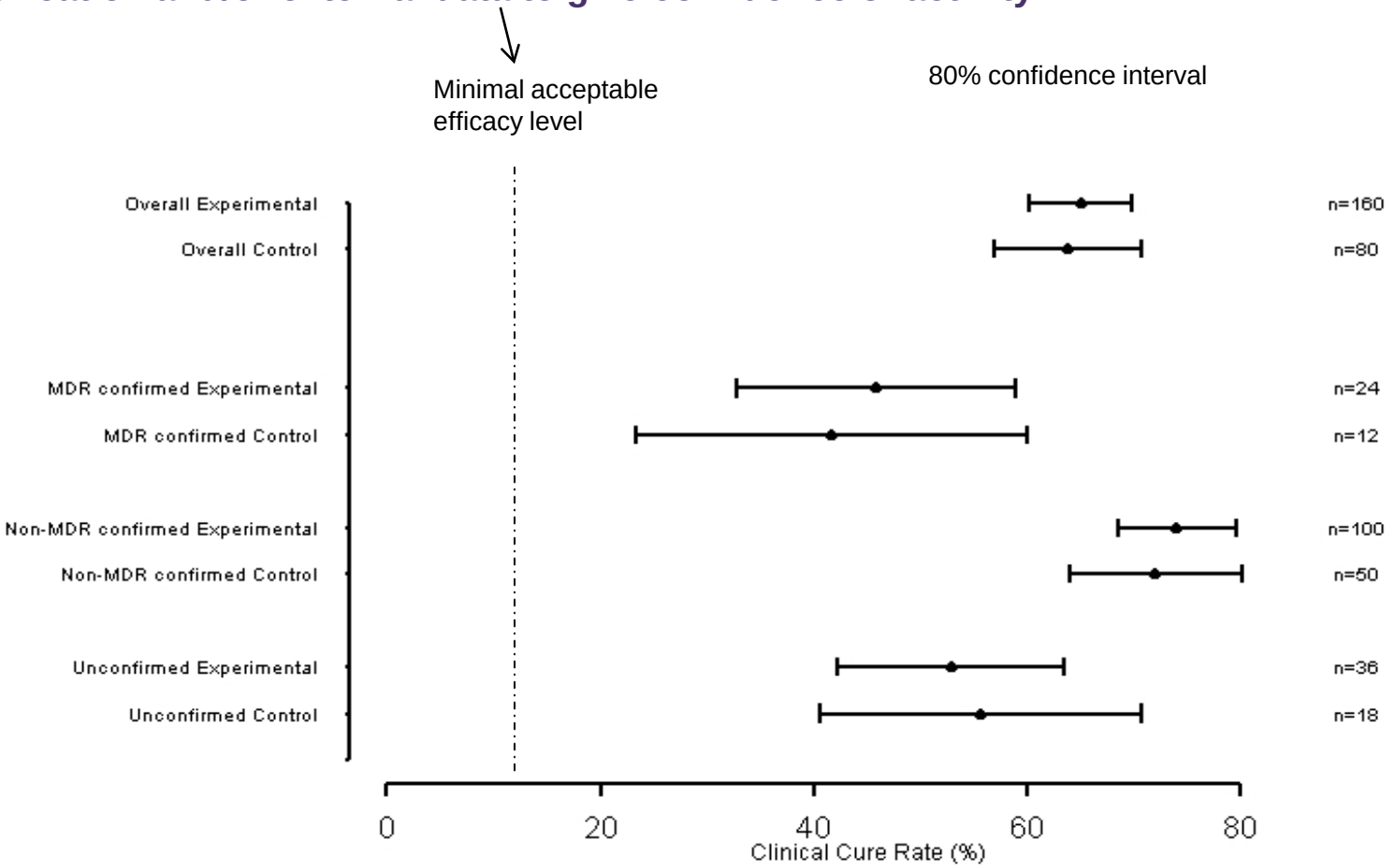
- Balancing these options
  - Small RCT gives randomisation, but heterogeneity may give problems comparing treatment groups
  - Non randomised study means comparing with externally generated data

- For both approaches, external data can help set minimal efficacy levels
  - Optimal route depends on quality & nature of external data available

Data Presentation From Smaller RCT datasets

Use Comparator data to provide context for the disease setting in question

Where possible, include a reference to a minimal level of efficacy based on a clinical justification and/or external data to give confidence of activity



External Controls – key issues to consider

- Key question: Are data available in appropriate population?
- Contemporary controls most useful because resistance patterns, supportive care and other factors are changing
- But: does it really make development more feasible?
  - Historical controls may improve feasibility, but are data appropriate?
  - Prospective data allow designs similar to RCTs, but has similar issue of patient availability as RCT
  - Prospective data generation on SOC during earlier phases of development may help

External data should be considered, but needs to be feasible and relevant

Conclusion

- Traditional statistical inference not possible in some settings
  - Agree nature of unmet need with regulators and define approach accordingly
- A number of different approaches are being explored which may change the way we approach antibiotic development
- External data can help, but should be used with care
- Ultimately a balance of uncertainty & feasibility
  - How much uncertainty are we will to accept for areas of unmet need?
  - Change in uncertainty must be distinguished from approaches which bias interpretation.

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