

**Clinical Trials for NP and VAP :  
Regulatory Approach to  
Non-inferiority (NI) Margin Justification**

**Alfred Sorbello, DO, MPH  
Scott Komo, DrPH**

**Center for Drug Evaluation and Research  
US Food and Drug Administration**

---

# Overview

- Background
- Methodology for NI Margin determination
- Literature search
- NI Margin for valid non-inferiority trials
- Additional perspectives

---

# Background

## Nosocomial Pneumonia and Risk for Mortality

# Factors that are independently associated with Mortality in mechanically ventilated patients in the ICU

- Nosocomial pneumonia
- Nosocomial bacteremia
- Rapidly fatal underlying disease
- Multi-organ dysfunction/failure
- APACHE score

## Comparison of Infections Acquired in the Intensive Care Unit Between Survivors and Non-survivors

Infection	Survivors (n=1436)	Nonsurvivors (n=542)	<i>P</i>	OR (95% CI)
Pneumonia, No. (%)	156 (10.9)	172 (31.7)	<.001	3.84 (3.00-4.91)
Bacteremia, No. (%)	93 (6.5)	129 (23.8)	<.001	4.53 (3.39-6.05)
Urinary tract infection, No. (%)	182 (12.7)	93 (17.2)	.01	1.43 (1.09-1.88)

\*OR indicates odds ratio; CI, confidence interval.

---

# Factors that affect Mortality in patients with Nosocomial Pneumonia

- Age
- Bacterial Pathogen
- Inappropriate initial antibiotic therapy
- APACHE score
- Progressive respiratory failure
- Shock
- Ultimately fatal underlying disease

---

# Inappropriate/inadequate antibiotic therapy: Various definitions in the scientific literature

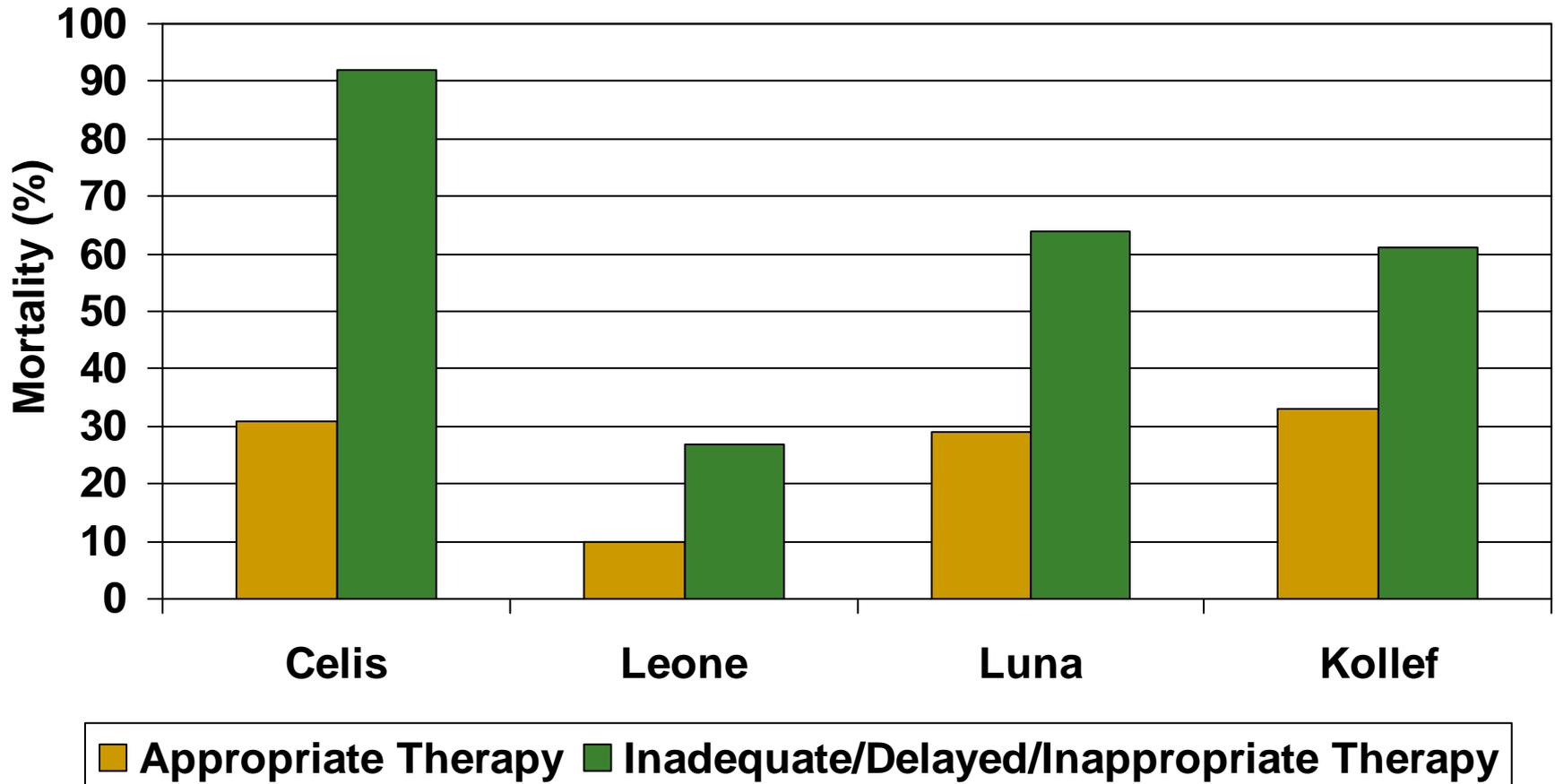
- Isolation of at least one resistant or intermediate-susceptible pathogen
- Lack of coverage for all pathogens isolated
- Presence of a non-bacterial pathogen
- Failure to treat with at least one antibiotic to which all isolates were susceptible *in vitro*; Failure to treat with at least 2 active agents against *Pseudomonas*

---

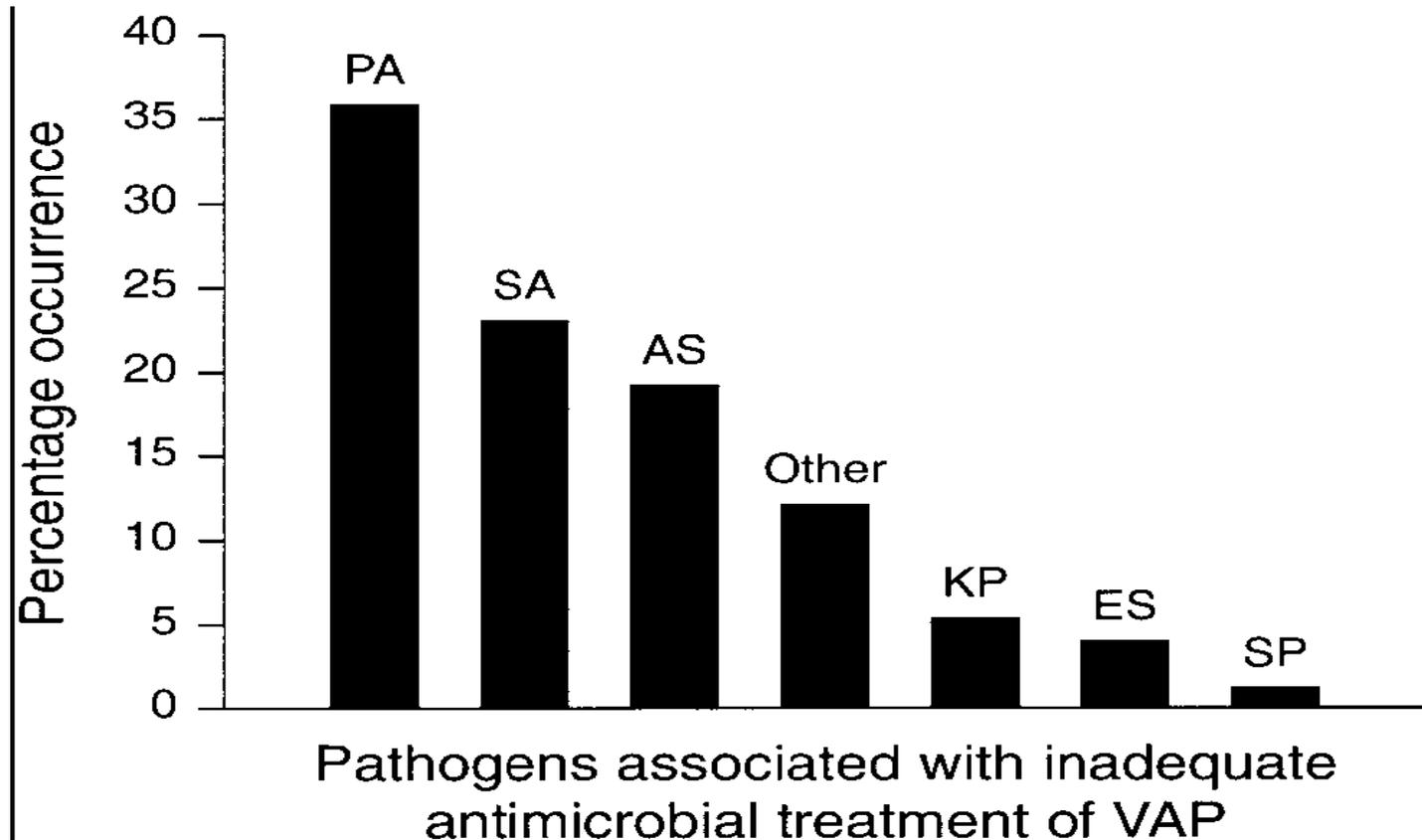
# Delayed initiation of appropriate therapy

- Delayed initiation of appropriate therapy (DIAT): defined as being present if appropriate therapy was given within 24 h of the clinical diagnosis of VAP but also if the patient had a CPIS  $\geq 5$  on the day before the clinical diagnosis was made. DIAT involved a delay in initiating treatment based on clinical diagnosis compared to CPIS score.

# Appropriate initial antibacterial treatment reduces the mortality rate for NP and VAP



# Bacterial Pathogens



Ranking of bacterial pathogens associated with administration of inadequate antimicrobial treatment of ventilator-associated pneumonia (VAP). AS, *Acinetobacter species*; ES, *Enterobacter species*; KP, *Klebsiella species*; PA, *Pseudomonas aeruginosa*; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*; other, *H. influenzae*, *E. coli*, *P. mirabilis*, *S. marcescens*, and *Legionella species*

# Methodology: NI Margin Justification

- Determine the Primary Endpoint
- Determine the treatment effect of active control over placebo
- Determine the non-inferiority margin for valid NI trials

**Literature  
Search  
and Review**

---

# Literature Search

- Original journal articles (1970-2008)
- No placebo-controlled clinical trials
- Placebo effect estimated indirectly:
  - Two observational studies that included mortality data on patients left untreated (pre-1975)
  - Historical studies of patients administered inappropriate, delayed, or inadequate initial treatment (1988-2007)
    - Primary endpoint: All-cause crude mortality
    - Included some attributable mortality data
- Active control agents:
  - Comparative clinical trials
    - Primary endpoint: Clinical response
    - Secondary endpoint: all-cause mortality

---

# Methodology: NI Margin Justification

- Potential Endpoints
  - All-cause mortality
    - FDA perspective: primary endpoint for NI margin
    - Preponderance of data
  - Attributable mortality
    - Limited data; potentially subjective
    - Heterogeneity in matching criteria used
  - Clinical response
    - No placebo data
    - Active control agents: Comparative clinical trials

---

# Methodology: NI Margin Justification

- Determine the treatment effect of active control over placebo
  - Estimate the placebo effect
    - No placebo-controlled studies
    - Placebo effect estimated indirectly
  - Estimate the active control effect
    - Comparative controlled clinical trials

# Mortality Rates: Studies of Inappropriate, Delayed, or Inadequate Initial Treatment

Author	Year Pub	Study Design	All-cause Mortality Rates n/N (%)	
			Appropriate	Inappropriate
Celis	1988	Prospective case finding, case-control study of 120 consecutive episodes of NP involving 118 adults	33/108 (31%)	11/12 (92%)
Kollef	1998	Prospective cohort study of 130 mechanically ventilated adults with suspected VAP	17/51 (33%)	31/51 (61%)
Luna	2006	Prospective, multicenter, cohort study of 76 mechanically ventilated adults with VAP	7/24 (29%)	33/52 (64%)
Leone	2007	Prospective study of 115 patients who developed VAP in ICU	10/100 (10)	4/15 (27%)

# Mortality Rates: Hospitalized Patients left untreated with pneumonia due to *P. aeruginosa*

Author	Year Pub	Study Design	All-cause Mortality Rates n/N (%)	
			Treated	Left untreated
Smith	1970	Retrospective analysis of antibiotic efficacy in treatment of pneumonia due to <i>P. aeruginosa</i> in hospitalized patients: 325 adults with (+) culture; 85 had pneumonia	37/77 (48%)	5/8 (62%)
Stevens	1974	Retrospective study of >700 adults in ICU; 153 patients had 158 episodes of pneumonia; 75 had pneumonia due to <i>Pseudomonas</i>	33/41 (80%)	20/34 (59%)

# Mortality Rates: Comparative clinical efficacy trials involving Piperacillin/tazobactam

Author	Year Pub	Study Design	All-cause Mortality Rates n/N (%)	
			Pip/Taz	Active Comparator
Brun-Buisson	1998	Open-label, multicenter, randomized study in patients with VAP: Pip/taz 4.5 gm q6h + amikacin vs. Ceftazidime 1 gm q6h + amikacin	18/98 (18.4)	22/99 (22.2)
Alvarez-Lerma	2001	Open-label, multicenter, randomized (2:1) study in patients with NP: Pip/taz 4.5 gm q6h + amikacin vs. Ceftazidime 2 gm q8h + amikacin	27/88 (30.7)	8/36 (22.2)
Joshi	2006	Double-blind, multicenter, randomized study in patients with acute NP: Pip/taz 4.5 gm q6h + tobramycin vs. Imipenem 500 mg q6h + tobramycin	23/222 (10.4)	17/215 (7.9)
Schmitt	2006	Double-blind, multicenter, randomized study in patients with NP: Pip/taz 4.5 gm q8h vs. Imipenem 1 gm q8h Aminoglycoside for <i>P. aeruginosa</i> coverage	17/110 (15.5)	11/110 (10.0)

# Mortality Rates: Comparative clinical efficacy trials involving Imipenem

Author	Year Pub	Study Design	All-cause Mortality Rates n/N (%)	
			Imipenem	Active Comparator
Fink	1994	Double-blind, multicenter, randomized study in patients with severe NP: Imipenem 1 gm q8h vs. Ciprofloxacin 400 mg q8h	38/200 (19.0)	43/202 (21.3)
West	2003	Open-label, multicenter, randomized study in adult patients with NP: Imipenem 500 mg q6-8 h followed by oral Ciprofloxacin vs. Levofloxacin 750 mg qDay followed by oral Levofloxacin; For <i>P. aeruginosa</i> : add amikacin for imipenem group or ceftazidime for levofloxacin group	32/218 (14.7)	38/220 (17.3)

---

# Limitations associated with the published observational and randomized studies of NP and VAP

- No placebo-controlled trials
  - Placebo effect estimated indirectly using all-cause mortality data
  - No clinical response data
- Marked variability and heterogeneity across studies
  - Methodological differences: study design, blinding, study population size
  - Advances in diagnosis and treatment; technologic developments
  - Confounding: Age distribution, co-morbid conditions, severity of illness
  - Generalizability: Single vs multi-center studies

---

# Methodology: NI Margin Justification

- Determination of the non-inferiority margin for valid NI trials

---

# Objectives in a Non-inferiority Trial

Noninferiority trials are designed to:

- Determine whether the effect of a new treatment is not too inferior to an already approved treatment (decision based on an acceptable clinical margin)

AND

- Determine whether the new treatment would be superior to “placebo” if a placebo were included in the study;
- Determine whether the effect of the active control relative to placebo is well-characterized, reliable, clinically meaningful and consistent from trial to trial.

---

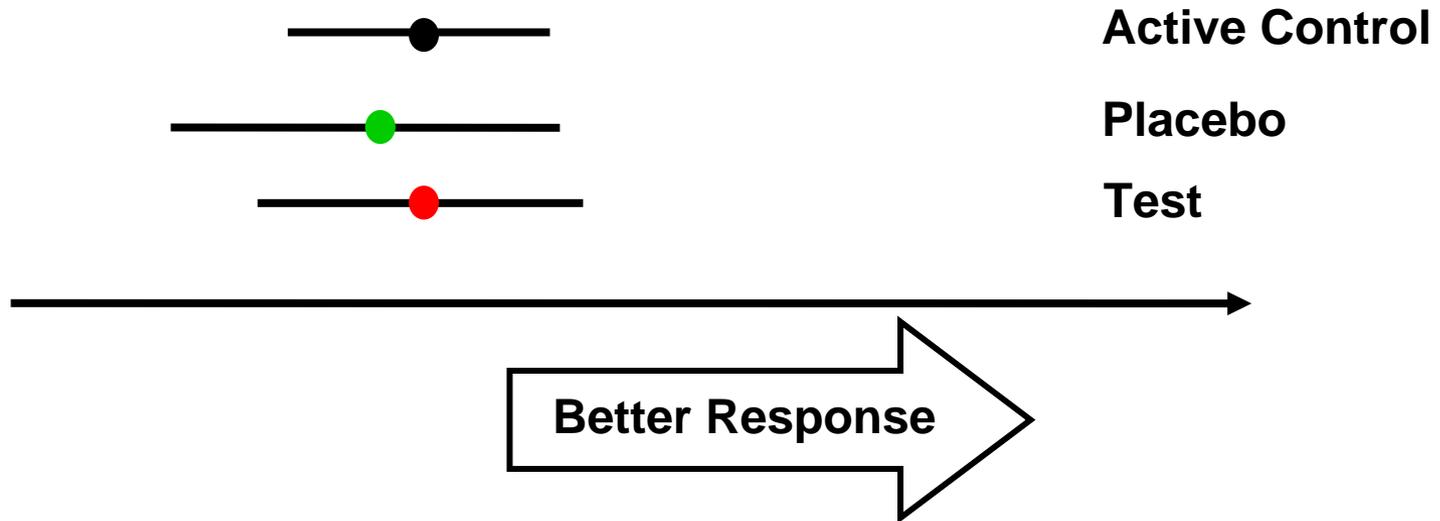
# Critical steps in designing a NI trial

- Determine whether historical evidence of sensitivity to drug effect (HESDE) exists.
- Determine the design features of the historical placebo-controlled trials from which HESDE has been determined.
- Determine a scientifically justifiable non-inferiority margin.
- Assure the quality of the non-inferiority trial and its conduct.
  - Subjectivity or imprecision can be rewarded in a non-inferiority trial by artificially making treatments look similar, when, in fact, they are not similar.

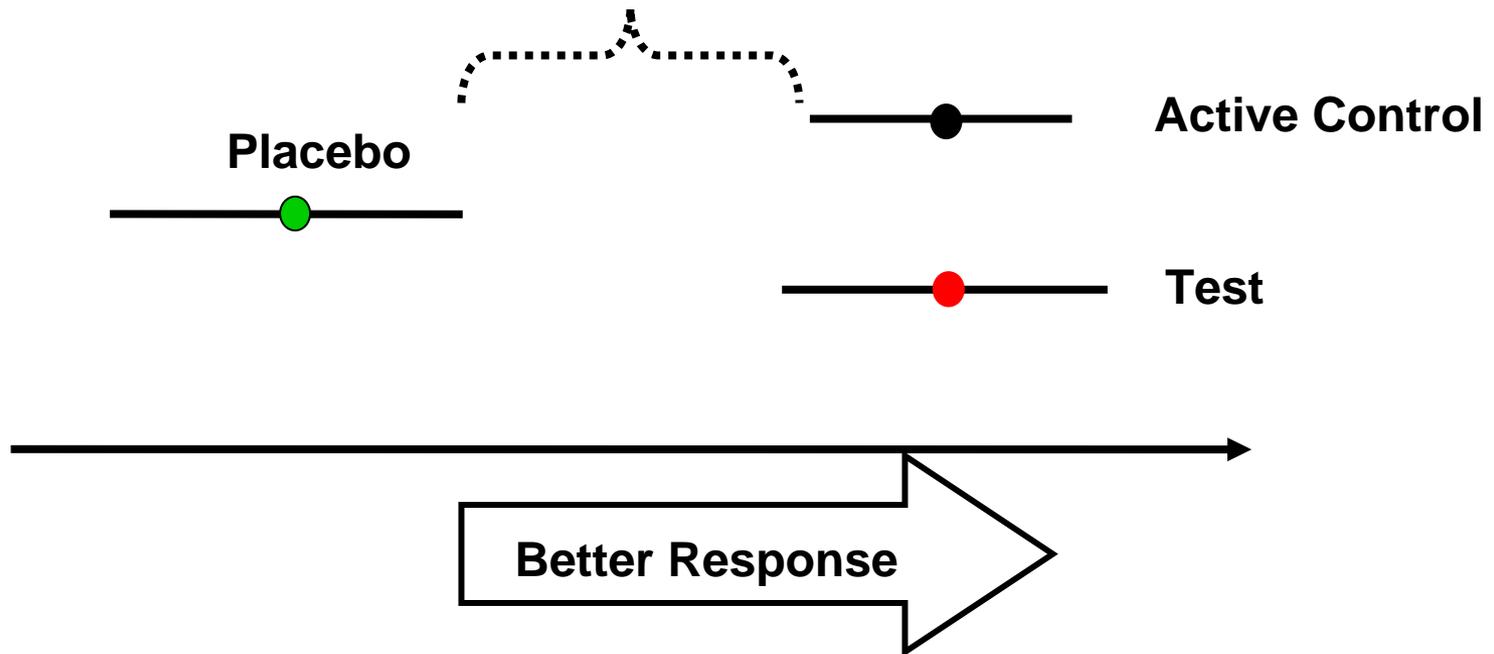
# Characteristics of Adequate and Well-Controlled Studies (21 CFR 314.126)

- (b)(1): A clear statement of objectives and a summary of proposed methods of analysis
- (b)(2): Study design permits a valid comparison with a control to provide a quantitative assessment of drug effect
  - (b)(2)(iv): Active treatment concurrent control: If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective.
- (b)(3): Method of selection of subjects provides adequate assurance that they have the disease or condition being studied
- (b)(4): Method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables (age, gender, etc)
- (b)(5): Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.
- (b)(6): Methods of assessment of subjects' responses are well-defined and reliable.
- (b)(7): There is an analysis of the results of the study adequate to assess the effects of the drug.

# Unclear Treatment Effect



# Large Treatment Effect of Active Control and Test Drug



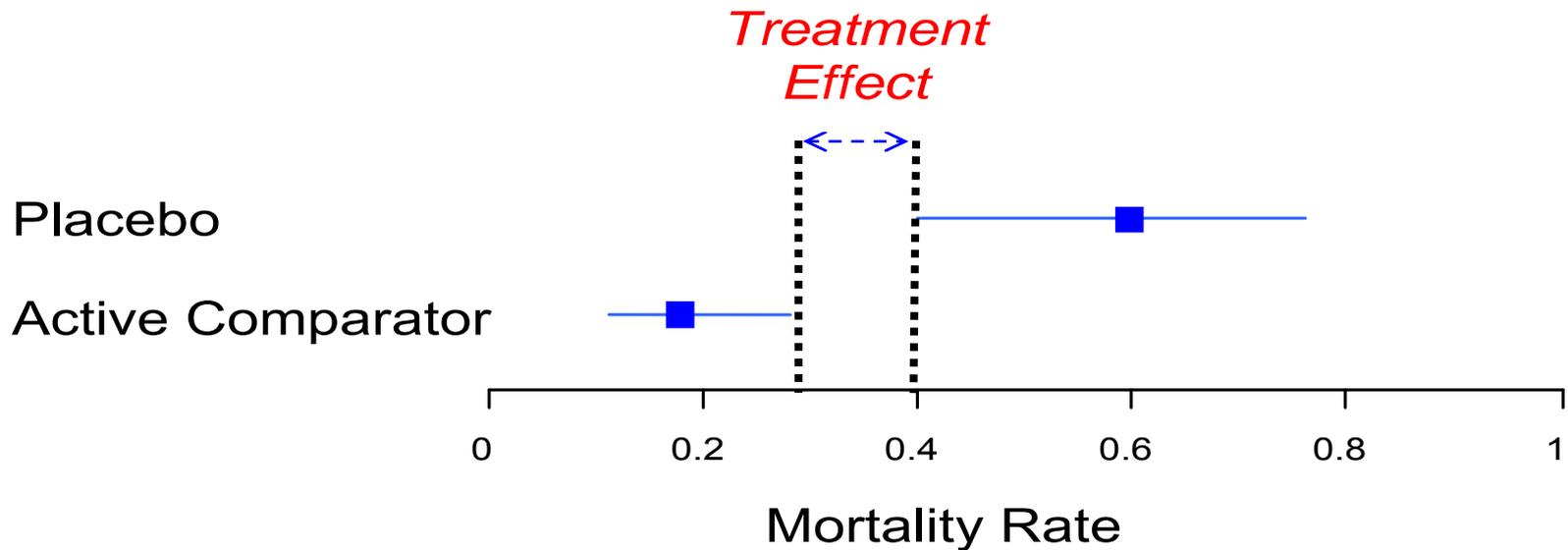
---

# Agency Approach to Justify the Noninferiority Margin

## Fixed Margin Approach

1. Estimate the active comparator treatment effect (M1)
2. Select NI margin that preserves fraction of M1 such that potential loss in efficacy is clinically acceptable

# Estimating the Treatment Effect



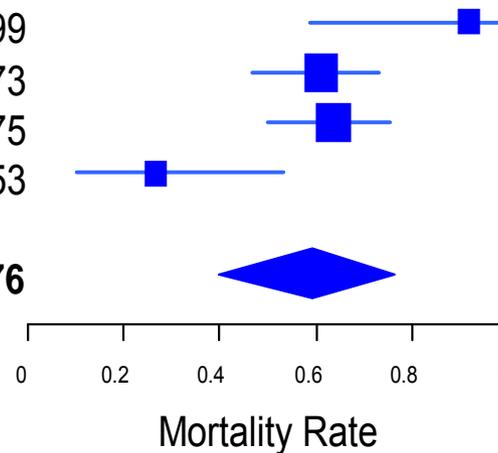
---

# Estimation of the Placebo Mortality Rate

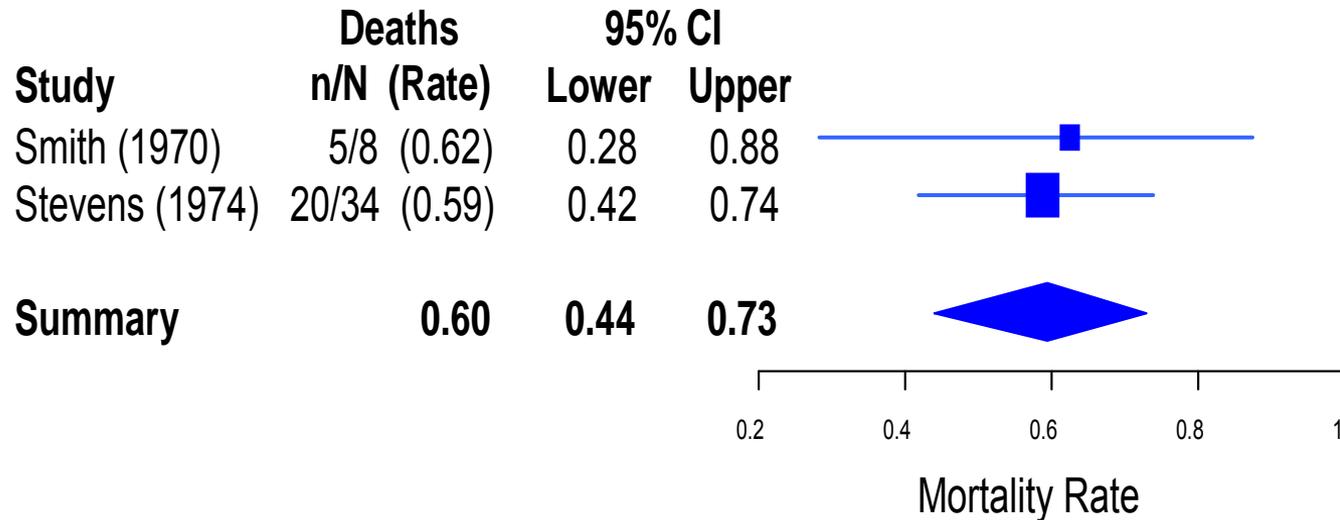
- No placebo controlled studies, so placebo rate cannot be directly estimated.
- Placebo estimate based on mortality rate of patients who received inadequate, inappropriate, or delayed initial therapy.
- Substantiate the placebo mortality rate based on untreated hospitalized NP patients with *P. aeruginosa*.

# Mortality in NP Patients Treated with Inadequate, Inappropriate, or Delayed Initial Therapy

Study	Deaths	95% CI	
	n/N (Rate)	Lower	Upper
Cellis (1988)	11/12 (0.92)	0.59	0.99
Koleff (1998)	31/51 (0.61)	0.47	0.73
Luna (2006)	33/52 (0.64)	0.50	0.75
Leone (2007)	4/15 (0.27)	0.10	0.53
<b>Summary</b>	<b>0.59</b>	<b>0.40</b>	<b>0.76</b>



# Mortality in Untreated Hospitalized NP Patients with *P. aeruginosa*



---

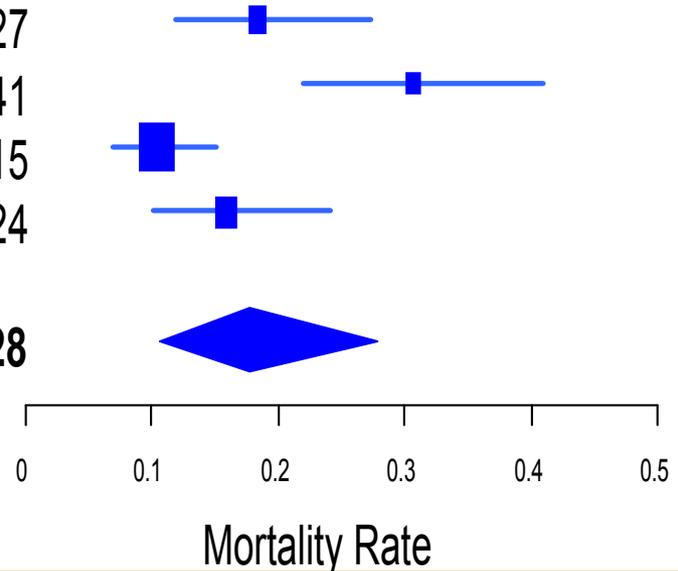
# Placebo Mortality Rate

## Estimated Placebo Mortality Rate

- Meta-analysis of patients who received inappropriate, inadequate, or delayed initial therapy: estimate of placebo mortality (ITT) was 59% with a 95% CI of (**40%**, 76%).
- Thus, estimated placebo mortality rate is likely no lower than 40%, based on the lower bound of 95% CI.
- This estimate was supported by the meta-analysis of untreated hospitalized NP patients with *P. aeruginosa*: mortality estimate (ITT) was 60% with a 95% CI of (**44%**, 73%).

# Mortality in Clinical Trials Studying Piperacillin/Tazobactam

Study	Deaths	95% CI	
	n/N (Rate)	Lower	Upper
Brun-Buisson (1988)	18/98 (0.18)	0.12	0.27
Alvarez-Lerma (2001)	27/88 (0.31)	0.22	0.41
Joshi (2006)	23/222 (0.10)	0.07	0.15
Schmitt (2006)	17/110 (0.16)	0.10	0.24
<b>Summary</b>	<b>0.18</b>	<b>0.11</b>	<b>0.28</b>

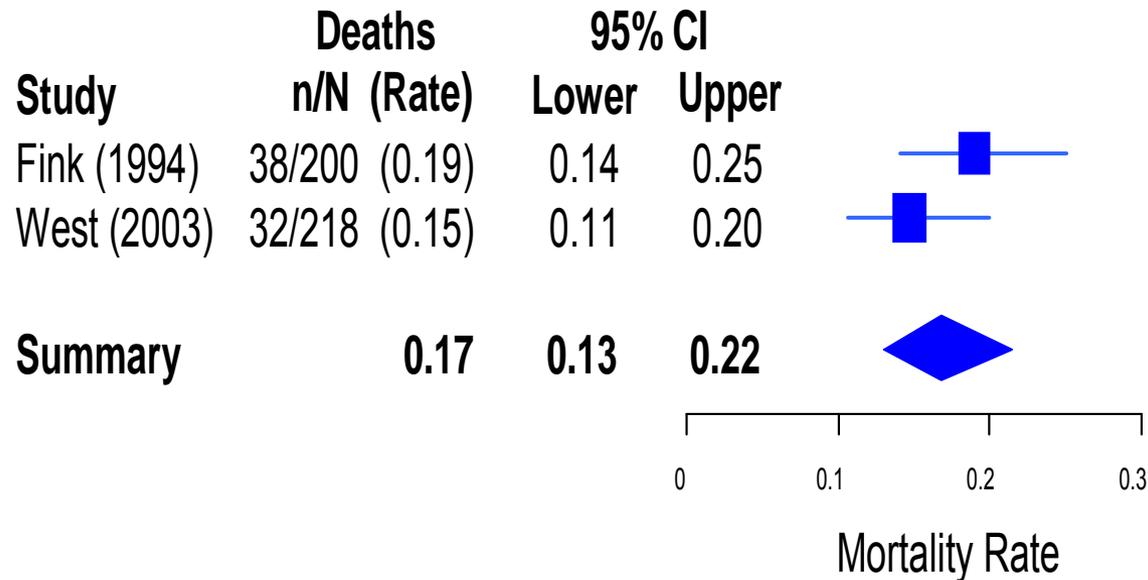


---

# Piperacillin/Tazobactam Mortality Rate

- Meta-analysis of piperacillin/tazobactam clinical studies: mortality estimate (ITT) was 18% with a 95% CI of (11%, **28%**).
- Thus, estimated piperacillin/tazobactam mortality rate is likely no higher than 28% based on the upper 95% confidence bound.

# Mortality in Clinical Trials Studying Imipenem

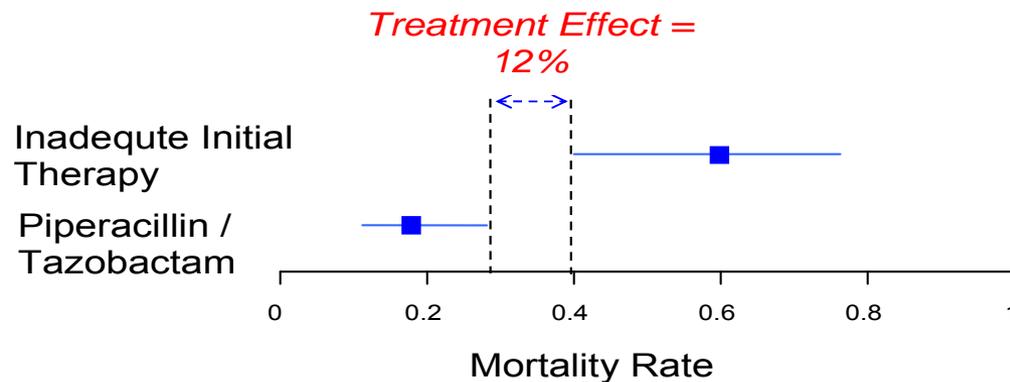


---

# Imipenem Mortality Rate

- Meta-analysis of imipenem clinical studies: mortality estimate (ITT) was 17% with a 95% CI of (13%, **22%**).
- Thus, estimated imipenem mortality rate is likely no higher than 22% based on the upper 95% confidence bound.

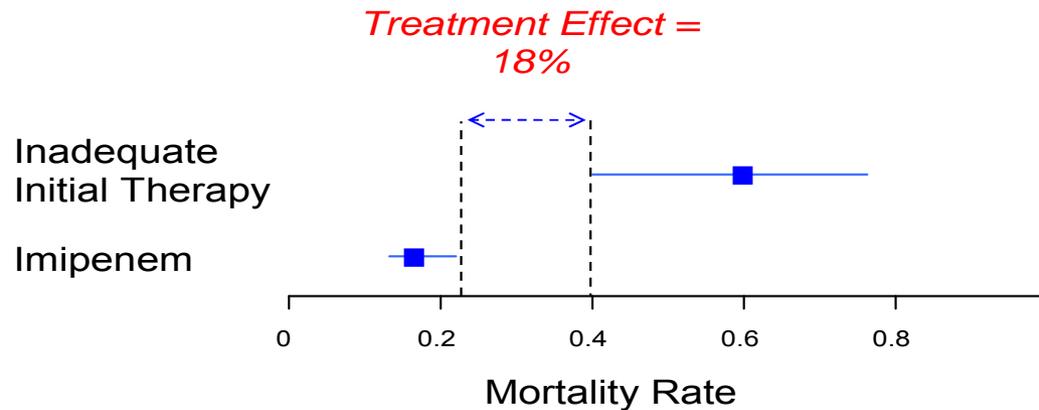
# Estimate of the piperacillin/tazobactam treatment effect (M1)



= Estimated placebo - piperacillin/tazobactam mortality rate  
= 40% - 28%  
= 12%

Thus, estimated piperacillin/tazobactam treatment effect is 12%

# Estimate of the Treatment effect (M1) for Imipenem



= Estimated placebo - imipenem mortality rate

= 40% – 22%

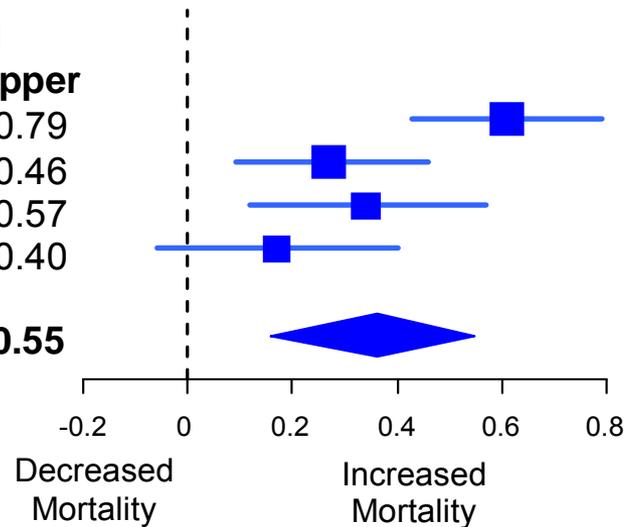
= 18%

Thus, estimated imipenem treatment effect is 18%

# Mortality Risk Difference Between Appropriate and Inappropriate, Inadequate, or Delayed Initial Therapy

Mortality Difference (Inappropriate – Appropriate)

Study	Mortality Difference	95% CI	
		Lower	Upper
Cellis (1988)	0.61	0.43	0.79
Koleff (1998)	0.27	0.09	0.46
Luna (2006)	0.34	0.12	0.57
Leone (2007)	0.17	-0.06	0.40
<b>Summary</b>	<b>0.36</b>	<b>0.16</b>	<b>0.55</b>



---

# Estimation of the Active Control Treatment Effect (M1)

- Mortality treatment effect for the antibacterial agents ranged from 12% to 18%
- Choose 12% as the conservative estimate of the treatment effect to allow for the uncertainties in the cross-study comparisons

# NI Margin for All-Cause Mortality

- Mortality treatment effect (M1) = 12%
- NI margin = fraction of M1 preserved x M1  
e.g., an NI margin of 6% preserves 50% of the treatment effect
- Need to preserve significant fraction of M1 because the NI margin is the amount of increased mortality one is willing to accept and still consider a new drug noninferior to active comparator
- **Question:** What fraction of the mortality treatment effect should be preserved?

---

# Limitations of the Observational Studies of NP and VAP

- No placebo-controlled trials
  - Placebo surrogates provided all-cause mortality data
  - No clinical response data
- Marked variability and heterogeneity across studies
  - Methodological differences: study design, blinding, study population size
  - Advances in diagnosis and treatment; technologic developments
  - Confounding: Age distribution, co-morbid conditions, severity of illness
  - Generalizability: Single vs. multi-center studies

---

# Additional Limitations with the Approach

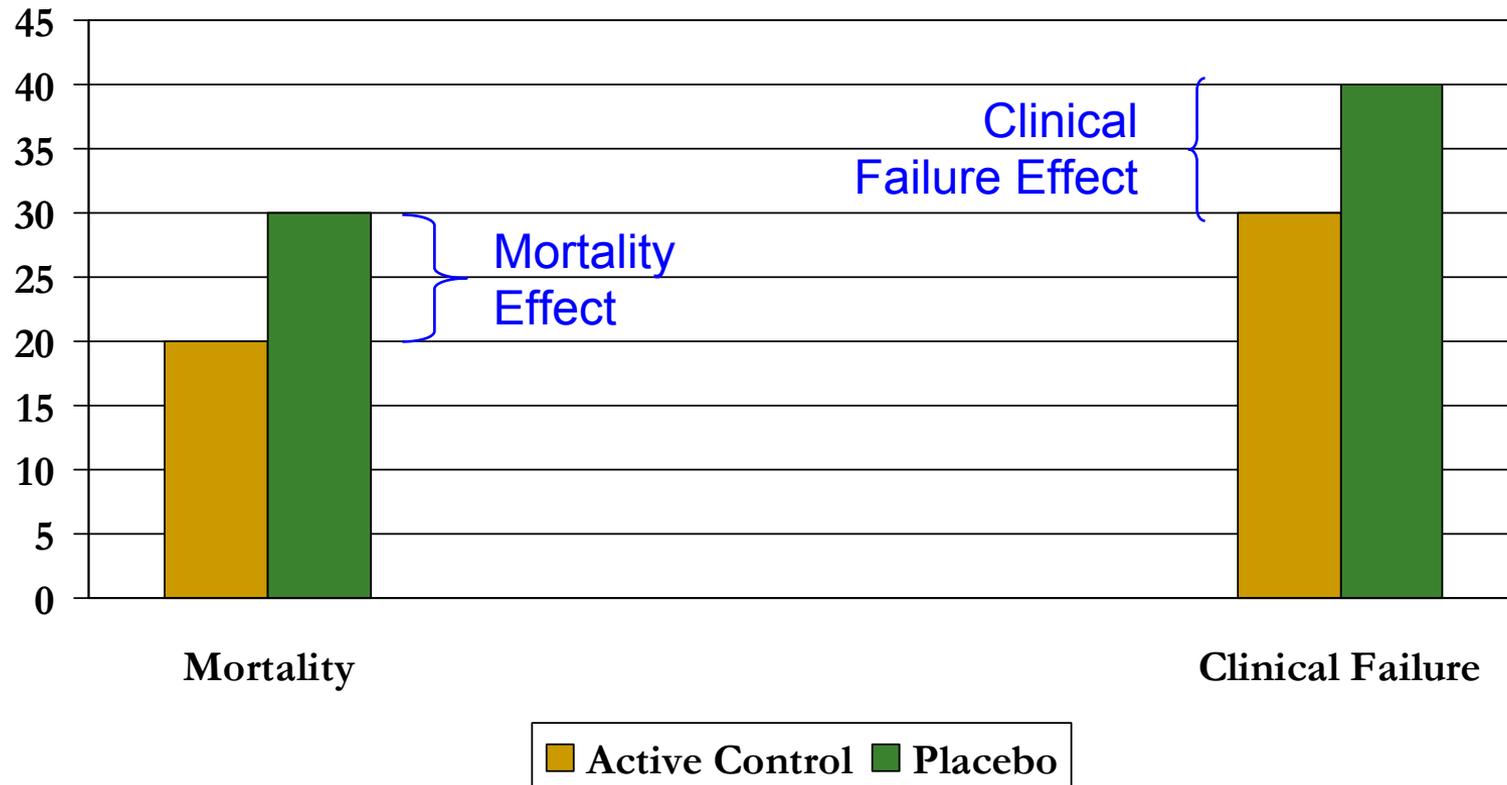
- Observational studies of inappropriate, inadequate, or delayed initial therapy studies were used to estimate the placebo rate.
- These studies had substantial heterogeneity in mortality rates.
- Mortality rates for placebo and active comparator were estimated from different studies – concerns of comparability of subjects

# Clinical Response as an Alternative Endpoint

Clinical response where all deaths are considered clinical failures

- Pros
  - Clinically relevant
  - Effect of rescue medication given to patients who do poorly will not affect outcome, i.e. already a clinical failure.
  - Likely higher event rate than mortality may permit a smaller sample size
- Cons
  - No placebo data – unable to estimate treatment effect of antibacterial agents
  - More subjective endpoint than mortality – possible issue in noninferiority studies
  - Composite endpoint – need to ensure that mortality and clinical failure are in same direction

# Mortality vs. Clinical Failure Treatment Effect



---

# NI Margin for Clinical Response

If some patients receive effective rescue medication that prevents death then

- it may be plausible to extrapolate the mortality treatment effect to clinical response by assuming that treatment effect for clinical response is at least as large as that for mortality.
- making above assumption, it may be possible to choose a larger NI margin (preserve smaller fraction of treatment effect).

# NI Margin for Clinical Response

- NI margin cannot be larger than 12%
  - The assumed clinical response treatment effect should not be larger than the mortality treatment effect it was extrapolated from
- NI margin should preserve a fraction of the treatment effect
- It may be possible to choose a larger NI margin (preserve smaller fraction of treatment effect) based on administration of effective rescue medication
- **Question:** Is it possible to extrapolate treatment effect from mortality to clinical response? If so, what NI margin should be used in clinical studies?

---

# Summary

- Valid NI trials can be done in NP and VAP
  - with an all-cause mortality endpoint using an NI margin that preserves a substantial fraction of the 12% treatment effect
  - with a clinical response endpoint where all deaths are considered clinical failures, if the extrapolation of the benefit in mortality to clinical response can be scientifically justified