

HABP/VABP Patient Outcomes from Previously Conducted Trials

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Outline

- Progress in HABP/VABP trial designs
- Endpoint background and rationale
- Symptoms in non-ventilated HABP
- Signs and symptoms in ventilated HABP/VABP
- Mortality and “Mortality Plus” in HABP/VABP

Progress in HABP/VABP trial designs

- Public discussions and evaluations of data have helped bring new ideas to design of HABP/VABP trials that should improve feasibility:
 - Use of Gram stain and ITT as the primary analysis population, with sensitivity analysis in the microbiological ITT population
 - 24 hours of prior antibacterial therapy should not preclude enrollment, with sensitivity analysis by amount of prior therapy
 - Single HABP/VABP trial with supportive evidence
 - Lower than expected control mortality rates treated as “review issue” not requiring use of odds ratios for the primary analysis
 - Allow unapproved active comparators on a case-by-case basis
- Sample size is n=268 subjects per arm:
 - 90% power, 10% margin, assumed 15% mortality rate

Desired endpoint properties

- Well-defined and reliable:
 - Standardized definition for multicenter trials
- Direct measure of patient benefit:
 - No need for surrogates or biomarkers in an acute disease in which mortality and morbidity are common
- In a non-inferiority trial, evidence for a margin

Rationale for retrospective data analysis

- Learn from previously conducted trials
- Understand from available data what outcomes change, when they change, and by what amount
- Question from FNIH is how a “CABP like” symptom endpoint would perform for non-ventilated HABP
- Limitations:
 - Outcomes retrospectively assessed from previously conducted trials were not meant for primary analyses, so data may have been incomplete or imprecise
 - Margin would be dependent on extrapolation of “no treatment” results from CABP analyses, if scientifically appropriate

Data analysis and masking

- Several HABP/VABP trials combined:
 - Results pooled through meta-analysis
- Subjects pooled across treatment arms
- Percentages are displayed without denominators

Baseline sketch from several trials

	All subjects	Ventilated	Non-ventilated
Age in years			
<50	23%	26%	19%
50-64	24%	25%	24%
≥65	53%	49%	58%
APACHE II score			
<15	41%	27%	60%
15-19	28%	33%	24%
≥20	30%	39%	15%
Ventilation status			
Ventilated	58%		
Non-ventilated	42%		

Symptoms in non-ventilated HABP

- What was measured?
 - Cough, chest pain, dyspnea, sputum production
- How was it measured?
 - Usually absent/mild/moderate/severe or close analog
- When was it measured?
 - Varied between trials
 - Data to be presented for Baseline, approx. Day 3, approx. Day 6
 - Often unclear when later intubation prevented assessment

Baseline symptoms: Non-ventilated HABP

	Absent	Mild	Moderate	Severe
Cough	5%	95%		
Chest pain	82%	7%	9%	3%
Dyspnea	15%	32%	40%	11%
Sputum	4%	31%	45%	21%

- Symptoms were usually present, with the exception of chest pain

Symptom progression: Non-ventilated HABP

- Rows restricted to subjects with the symptom present at baseline

Day 3	Improved	Unchanged	Worsened	Not available
Cough	29%	60%	1%	9%
Chest pain	63%	32%	1%	5%
Dyspnea	50%	37%	4%	10%
Sputum	48%	41%	4%	8%
Day 6	Improved	Unchanged	Worsened	Not available
Cough	44%	39%	1%	18%
Chest pain	73%	11%	0%	16%
Dyspnea	64%	15%	1%	19%
Sputum	60%	20%	1%	18%

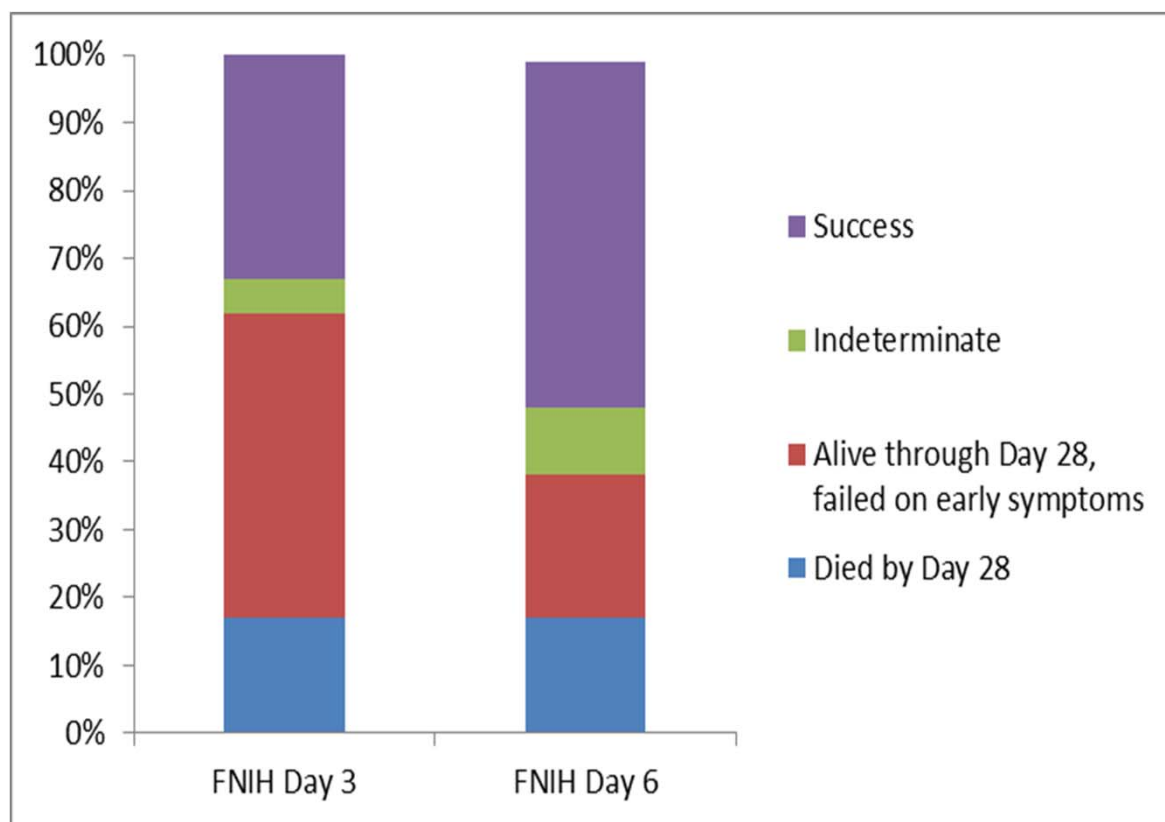
Early symptom endpoint results: Non-ventilated HABP

- FNIH Working Group proposed evaluations:
 - Survival through Day 28
 - Improvement in ≥ 2 symptoms, worsening in no symptoms

	Alive through Day 28, symptom success	Alive through Day 28, symptom failure	Death by Day 28	Cannot be determined
Day 3 FNIH	33%	45%	17%	5%
Day 6 FNIH	51%	21%	17%	10%

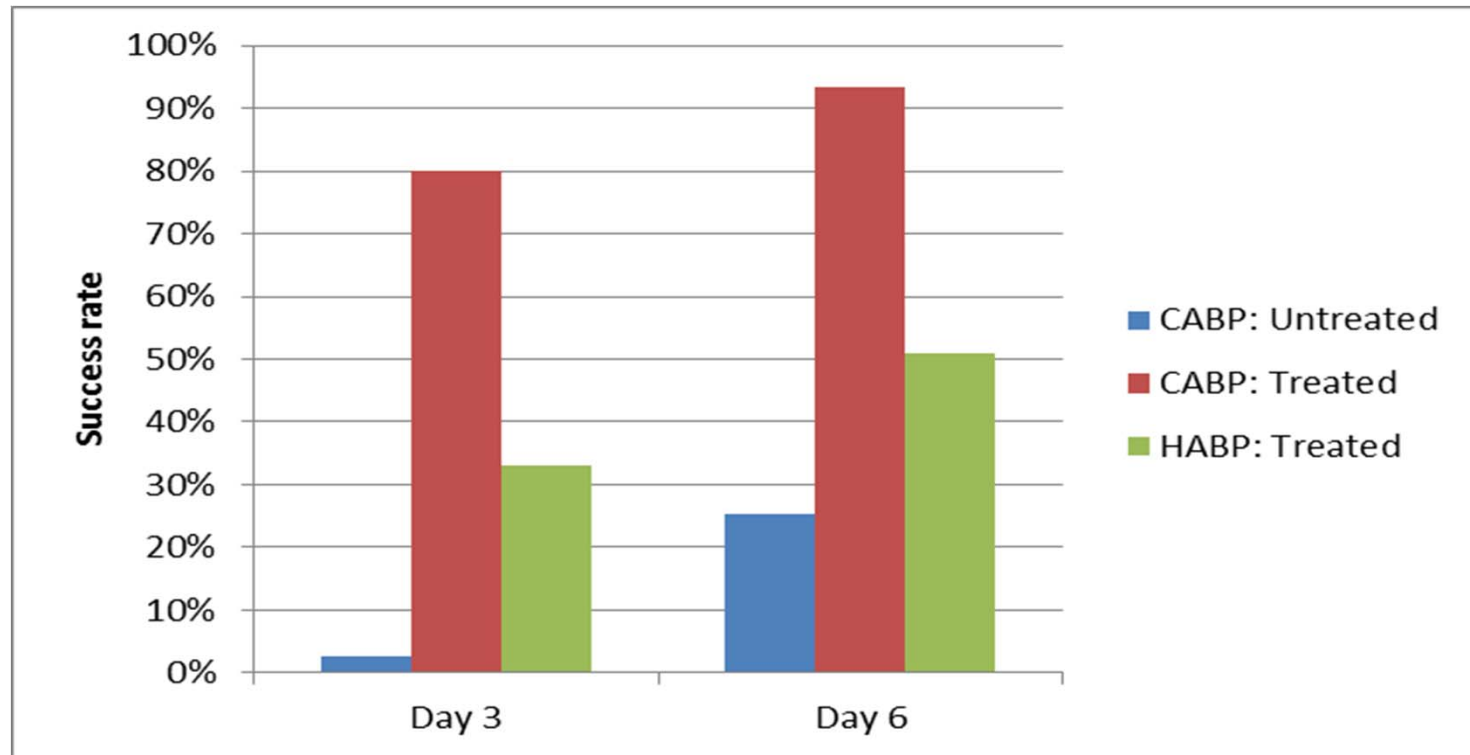
- In contrast, approximately 80% success in CABP for Day 3-5 symptoms⁶

Symptom endpoints at Days 3 and 6: Non-ventilated HABP



- Success = improvement in ≥ 2 symptoms, worsening in none
- Symptom data based on FDA review of selected datasets

Symptom improvement NI margin: Can we extrapolate from CABP to HABP?



- Non-inferiority margin for CABP symptom endpoint based on historical data comparing recovery of treated¹ and untreated² subjects
- Symptom data based on FDA review of selected datasets

Symptom-based endpoints: Non-ventilated HABP

- Some considerations:
 - No longer have a mortality-driven endpoint. The composite is equally driven by components with varying levels of importance (mortality and symptom improvement)
 - Ability to consistently and reliably measure symptoms is unclear. The symptom combination and improvement threshold was proposed by FNIH for interim use in CABP.
- Success rates are much lower in HABP than CABP:
 - Approximately 50% success rates at Day 6
 - Requires increasing the sample size or the non-inferiority margin
- Nontrivial missing symptom data in retrospectively assessed trials

Signs and symptoms: VABP and ventilated HABP

- Sputum production was measured in most trials:
 - Usually as absent, mild, moderate, or severe
- Hypoxia was available in some datasets
- PaO₂/FiO₂ was available in some datasets:
 - May not be a direct measure of patient benefit
 - Not measured post-baseline in ≥20% of initially ventilated subjects
 - Non-measurement may relate to extubation or improvement

Sputum production: VABP and ventilated HABP

	Absent	Mild	Moderate	Severe	Missing
Baseline	2%	14%	52%	31%	1%
Day 3	8%	27%	42%	12%	10%
Day 6	18%	29%	25%	7%	21%

Non-mortality endpoints: VABP and ventilated HABP

- Similar challenges as with non-ventilated HABP
- In addition, a treatment effect on a biomarker-driven endpoint might not reliably predict improvement in patient feeling, function, or survival
- PaO₂/FiO₂ often was not assessed:
 - Protocols were not designed for oxygenation-based endpoints

Mortality and “Mortality Plus”

- Analyzed composite of all-cause mortality or major nonfatal events related to progression or extension of disease³:
 - Acute respiratory distress syndrome
 - Respiratory failure
 - Empyema (rare)
 - Endocarditis (rare)
 - Meningitis (rare)
- Events were taken from treatment-emergent SAE datasets
- In the future, definitions could be standardized
- In the future, events could be added or removed (e.g., kidney failure)

Mortality and “Mortality Plus”

Non-ventilated subjects	Mortality	Mortality Plus
Day 14	10.2%	13.3%
Day 21	12.9%	17.1%
Day 28	17.1%	20.3%
Ventilated subjects	Mortality	Mortality Plus
Day 14	14.3%	18.0%
Day 21	20.0%	23.8%
Day 28	23.6%	27.7%

- In previous trials, mortality has not been a rare event

Mortality Plus

- Major nonfatal events are of definite importance
- The endpoint is driven by mortality events, for which there are clear data for a treatment effect and a non-inferiority margin^{4,5}
- It increases the event rate over all-cause mortality by about 4%, which may address concerns about risk differences versus odds ratios

Endpoints and sample sizes

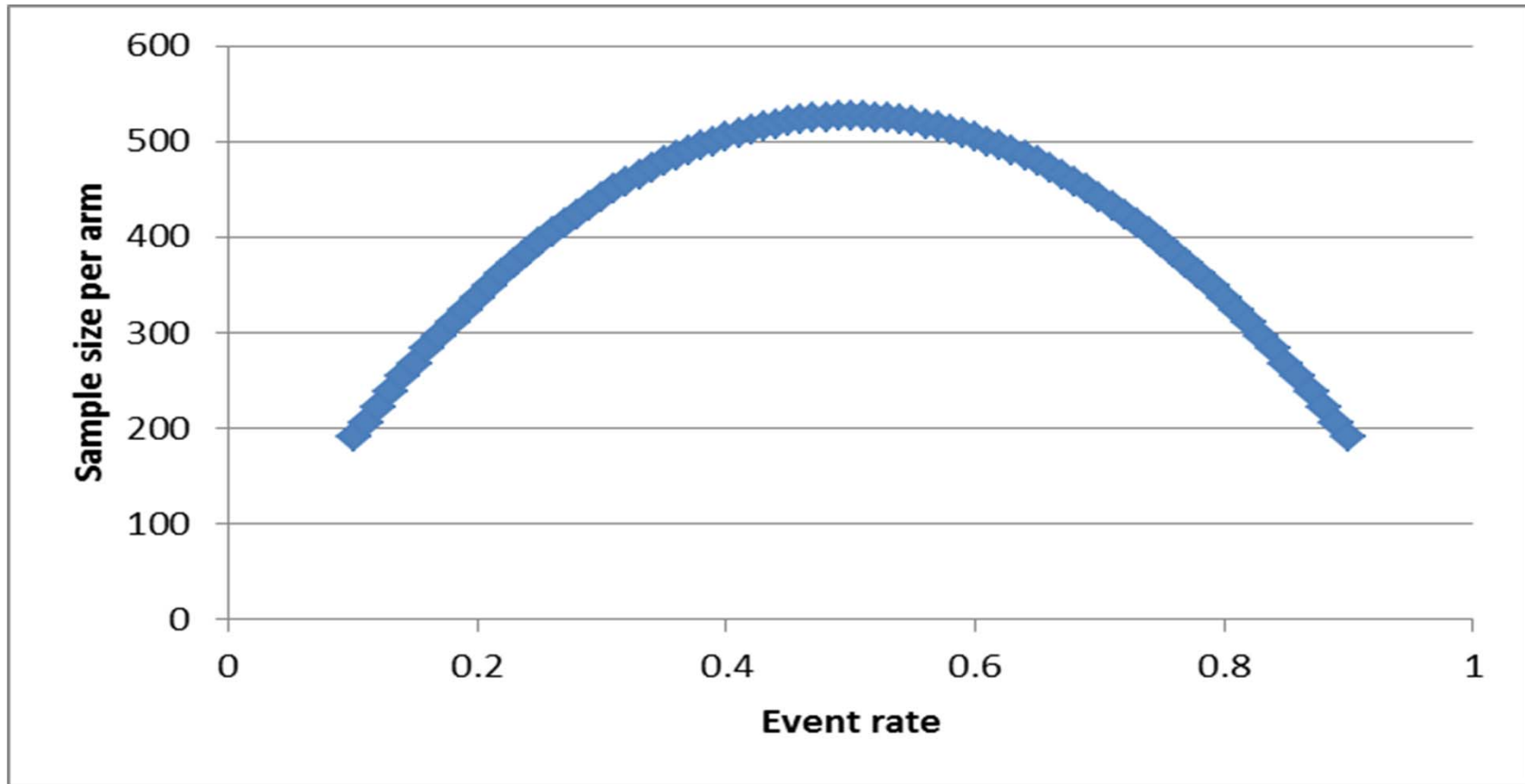
- Adding components to a mortality composite *increases* sample size:
 - Risk difference: sample size increases as event rate approaches 50%
 - Non-inferiority mortality trials are possible with the risk difference because mortality is not a rare event, and there is a large treatment effect on the absolute scale for severe subjects^{4,5}
 - Sample size implications not the same for risk difference, odds ratio

Sample size per arm: 90% power, 10% risk difference margin, $\alpha = 0.05$

Endpoint	Anticipated event rate	Sample size per arm
All-cause mortality	15%	n = 268
“Mortality Plus”	20%	n = 337
Clinical Response	60%	n = 505

Sample size as a function of event rate:

90% power, 10% risk difference margin, $\alpha = 0.05$



Summary

- An endpoint based on early symptoms does not appear to behave similarly between CABP and non-ventilated HABP
- A composite of mortality and major nonfatal events could be refined:
 - How could events be better defined?
 - What events should be added or removed?
- Endpoint selection can have counterintuitive sample size implications:
 - For fixed NI margin and risk difference, sample size increases when moving from mortality → mortality plus → clinical response
- We respectively thank CTTI and FNIH for important work towards:
 - Improving efficiency and quality of HABP/VABP trials
 - Further development of endpoints for HABP/VABP trials

References

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