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%

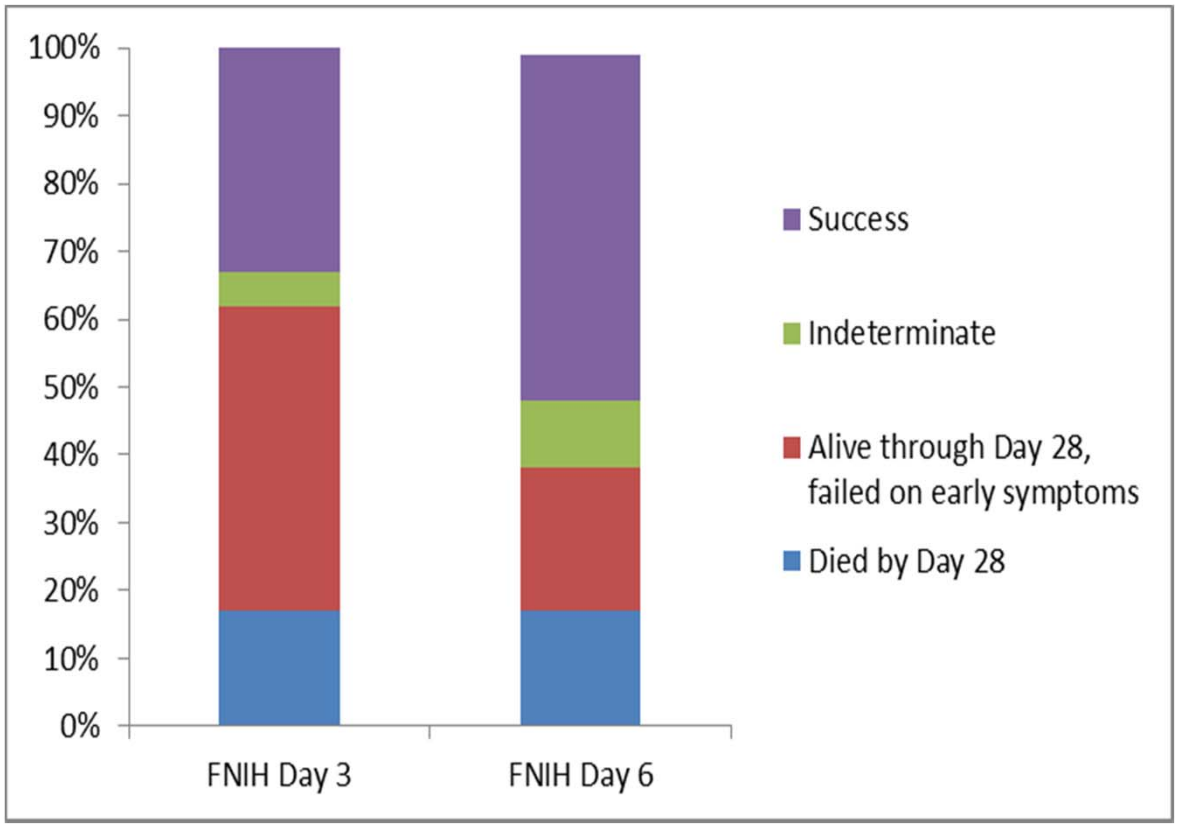
Early symptom endpoint results:
Non-ventilated HABP

- 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%

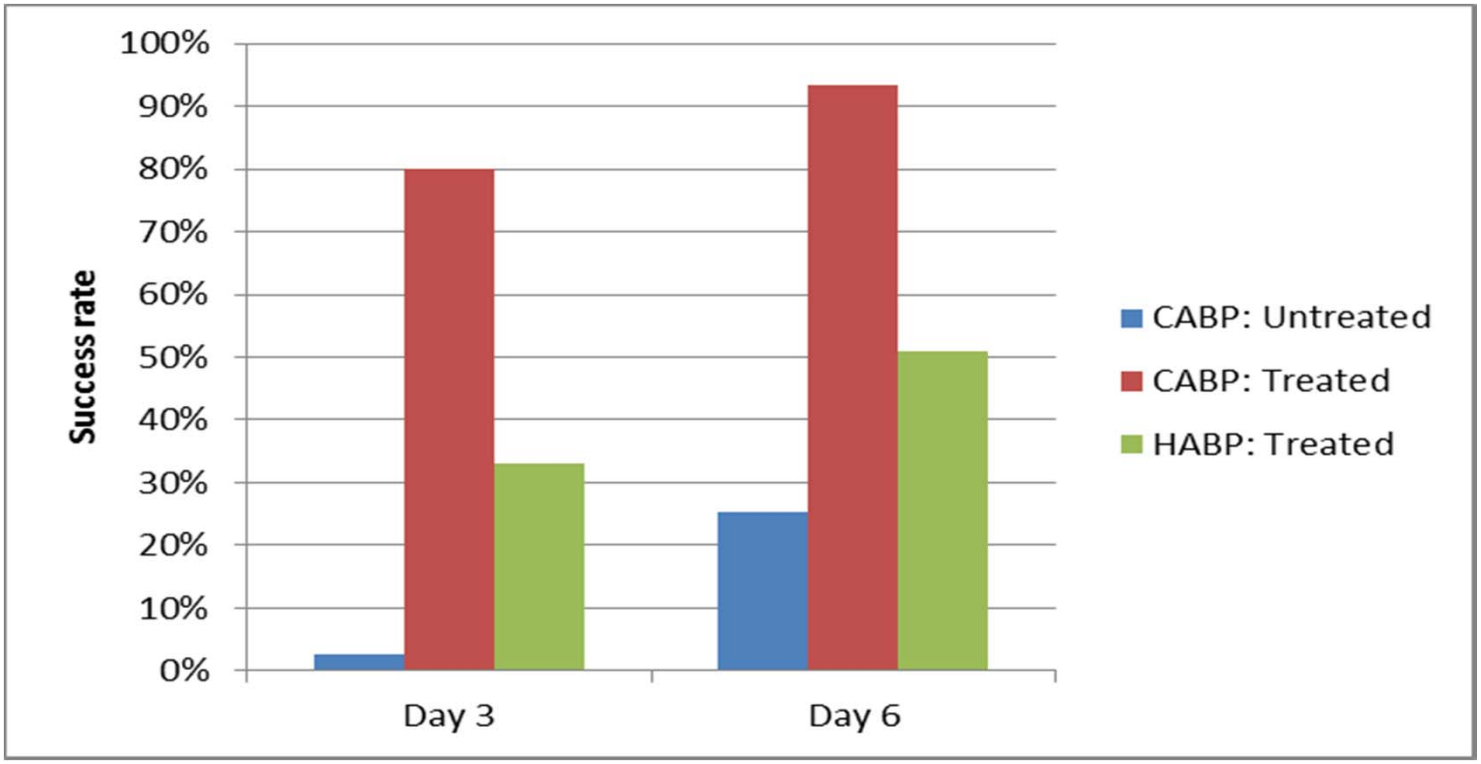
- In contrast, approximately 80% success in CABP for Day 3-5 symptoms[6]

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 treated[1] and untreated[2] 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
- PaO_2/FiO_2 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

- PaO_2/FiO_2 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 disease[3]:
  - 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

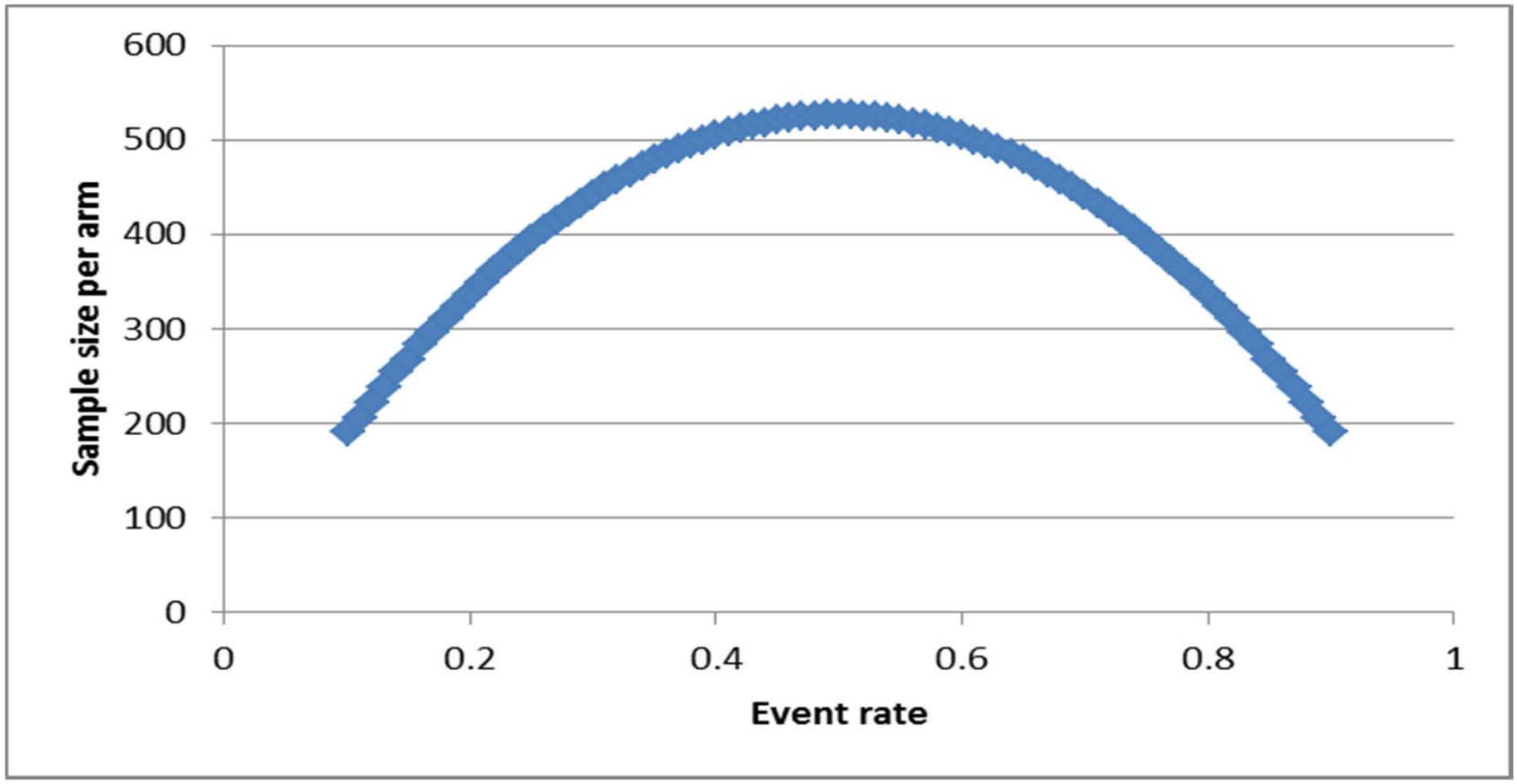
- Adding components to a mortality composite *increases* sample size:
  - Risk difference: sample size increases as event rate approaches 50%
  - Non-inferiority mortality trials are possible with the risk difference because mortality is not a rare event, and there is a large treatment effect on the 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, α = 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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