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Cost Drivers of a Hospital Acquired Bacterial Pneumonia and Ventilator Acquired Bacterial Pneumonia (HABP/VABP) Phase Three Clinical Trials

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INTRODUCTION

Hospital Acquired Bacterial Pneumonia (HABP) and Ventilator Acquired Bacterial Pneumonia (VABP) are acute infections that occur in hospitalized patients. A hospital stay of 48 hours or more will expose patients to potential infections with a variety of gram-positive and gram-negative bacteria.

HABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, cough, or chest pains accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital. VABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever, hypothermia, chills, rigors, purulent respiratory secretions and increased oxygen requirements accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient receiving mechanical ventilation such as an endotracheal tube for a minimum of 48 hours.[1]

Studies indicate that the prevalence rate of hospital acquired and ventilator associated bacterial pneumonia (HABP/VABP) -- conditions that are very challenging and expensive to manage -- has been rising.[2] There are many challenges associated with clinical trials targeting this disease area due to the variety of pathogens. HABP/VABP clinical trials are very costly to conduct given protocol complexities and difficulty recruiting and retaining patients. A new study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) and the Clinical Trials Transformation Initiative at Duke University (CTTI) evaluates the drivers of HABP/VABP direct and indirect clinical trial costs and identifies opportunities to lower these costs.

METHODS

Tufts CSDD, in collaboration with CTTI developed a comprehensive, detailed mapping of direct and indirect cost elements. Primary cost elements include per-patient direct procedure costs, per-trial and per-site costs:

Direct Costs (per-patient)
- Patient Costs

Direct Costs (per-trial)
- Personnel Costs (Pharmaceutical Company and Investigative Site)
- Site and Clinical Supply Costs; Trial Insurance
- Printing / Paper / Data Costs

Indirect Costs (per-trial)
- Upper Management Time
- Overhead Costs
- Misc. Costs

Figure 1. The Primary Cost Elements

Tufts CSDD gathered benchmark data to create a model calculating a fully-loaded (direct and indirect) cost profile of a typical phase three HABP/VABP clinical trial. Costs for phase III oncology trials and endocrine trials were also calculated for comparison. Data were gathered from the following:

- Internal databases provided site and subject (patient) data
- Medidata Solutions provided protocol and site cost data
- Oracle Clinical benchmarking costs for HABP/VABP
- ePharma Solutions provided country-site distribution data
- PMG, and CenterWatch provided site cost estimates (e.g. IRB fees, case report form fees; etc.)
- FDA, Centerphase Solutions and Mckane et al [3] provided patient screen-failure rates and randomization rates.
- Data involving printing costs, translation costs, and server costs for electronic data capture (EDC), and clinical trial insurance costs were gathered from companies provided these services and solutions.

All cost data were inflation adjusted to reflect 2014 USD. Assumptions provided on study duration were derived from industry experts. This study was conducted from November, 2014 to May 2015.

METHODS (Continued)

PER-PATIENT COST ELEMENTS

- Patient Recruitment
- Patient Retention (i.e. compensation)
- Informed Consent
- Clinical Trial Insurance
- Screen Fails
- Procedures
- Lab tests
- Query Resolution
- Data Entry

PER-TRIAL AND PER-SITE COST ELEMENTS

Personnel Costs	Site and Clinical Supply Costs	Printing / Paper / Data Costs

• Sponsor Personnel
  • Clinical Pharmacology
  • CRO/Site Contract Management
  • Document Manager
  • Clinical Research Associate
  • Physician
  • Statistical Programmer
  • Study Manager
  • Pharmaceutical Technician
  • Product Development
• Site Personnel
  • Principal Investigator
  • Co-Investigator
  • Research Nurse / Study Coordinator
  • Technician
  • Other Administration
  • Recruitment Specialist
  • Microbiologist
  • Regulatory Affairs
  • Pharmacist / Pharmacy tech
	•IRB Fees (Local)
	•Amendment Fees
	•Record Keeping and Storage
	•Site Recruitment Costs (marketing)
	•PI Training / Travel Costs
	•Meeting costs for clinical travel team (venue, food, travel)
	•Clinical Supply Costs (for this model is fixed)
	  •Manufacturing
	  •Comparator
	  •Trial Insurance Costs
		• Investigator Brochure
		  • Printing
		  • Translation
		• Study Protocol
		  • Printing
		  • Translation
		• Informed Consent
		  • Printing
		  • Translation
		• Case Report Form
		  • Printing
		  • Translation
		• Data Costs
		  • Server charges for EDC
		  • IT Charges for EDC
		  • Storage Costs
		  • Data Entry Costs

Figure 2. List of Per-Trial and Per Site Cost Elements.

INDIRECT COST ELEMENTS

Upper Management Time	Overhead Costs	Other Costs
• Vice President • Executive (Medical) Director • Associate Director • Biostatistics Manager	• Travel and Meetings • Depreciation (equipment) • Depreciation (buildings) • Other infrastructure costs • Material and office supplies • IT costs	• Administration Costs • Training and Professional Development • Employee Benefits

Figure 3. List of Indirect Cost Elements

STUDY ASSUMPTIONS

Variable	HABP/VABP	Oncology	Endocrine
Total Sites (all locations)	200 sites	279 sites	123 sites
Total Subjects (all locations)	1,000 subjects	448 subjects	582 subjects
Total Number of Countries	32 countries	32 countries	32 countries
Randomization Rate	1 patients randomized per 100 screened	25 patients randomized per 100 screened	45 patients randomized per 100 screened

Figure 4. Study Assumptions.
Site and patient (subject) assumptions based on internal Tufts CSDD databases.

SITE DISTRIBUTION ASSUMPTIONS

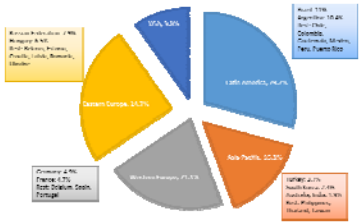

Figure 5. Graph of Site Distribution
Data provided by ePharmaSolutions. Clinical Trial country index from IMS. It was assumed that Oncology and Endocrine trials have the same site distribution.

RESULTS

AVERAGE COST PER PATIENT FOR ENDOCRINE, ONCOLOGY, AND HABP/VABP PHASE III CLINICAL TRIALS

Therapeutic Area	Total Cost Per Patient ($000)
Endocrine	$44
Oncology	$69
HABP/VABP*	$78

Figure 6. Average cost-per-patient for a Phase III Endocrine, HABP/VABP, and Oncology trial.
•HABP/VABP trials may run to a maximum of $165,000 per patient under the same assumptions (1,000 patients; 200 sites; 32 countries). Maximum provided by Oracle Clinical.

HABP/VABP COST-PER-PATIENT BY PRIMARY COST ELEMENT

Primary Cost Element	HABP-VABP Total Cost Per Patient ($000)
Per-Patient	$20
Per-Trial and Per-Site	$55
Indirect	$3
Total Cost	**$78**

Figure 7. Average cost-per-patient for a Phase III HABP/VABP trial by primary cost element.

RESULTS (Continued)

COST DRIVERS

Scope Variables	Process Variables
•Number of Sites	• Screen Failure Rates
•Number of Patients	• Cost of Screen Fails
•Procedure Costs	• Cost of Recruitment

Figure 8. Main Cost Drivers for HABP/VABP Phase III Clinical Trials

IMPACT OF CHANGING ONE COST DRIVER AT A TIME FOR HABP/VABP CLINICAL TRIALS

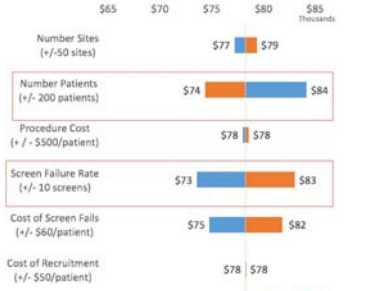

Figure 9. Cost Drivers: Changing One Driver
Using current assumptions: cost is $78,000 per patient. Assuming geographic distribution of patients is equal to the geographic distribution of sites (10% of patients in the US). Increasing the number of patients decreases costs as the number of patients outside of the US (in less expensive regions) increases.

IMPACT OF CHANGING MULTIPLE COST DRIVERS AT A TIME FOR HABP/VABP CLINICAL TRIALS

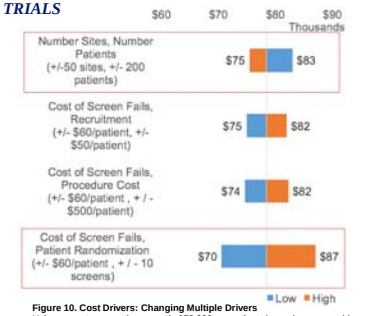

Figure 10. Cost Drivers: Changing Multiple Drivers
Using current assumptions: cost is $78,000 per patient. Assuming geographic distribution of patients is equal to the geographic distribution of sites (10% of patients in the US).

SUMMARY

- Tufts CSDD determined the fully-loaded cost of a HABP/VABP phase III clinical trial with 1,000 patients and 200 global sites to be, on average, $78,000 per patient.
- Phase III HABP/VABP clinical trials are $9,000 per-patient more expensive than phase III oncology clinical trials, and $34,000 per-patient more expensive than endocrine studies.
- Key variables affecting the cost of a typical phase three HABP/VABP trial can be stratified are the number of patients, the number of sites, procedure costs, screen failure rates, the cost of screen fails, and the cost of patient recruitment.

LIMITATIONS

- Assessment of certain variables for sensitivity assessment is limited (e.g. procedure costs)
- Some cost elements are average costs across all therapeutic areas
- Assuming that proportion of sites by country is the same as proportion of patients by country
- Assuming that site-patient percentage is the same for HABP/VABP, oncology and endocrine trials
- Assuming internal work effort is the same for HABP/VABP, oncology and endocrine trials

CONCLUSIONS

- Opportunities to lower the high costs of HABP/VABP clinical trials exist.
- The cost of screen fails, as well as screen failure rates are the main drivers of cost for a phase III HABP/VABP trial.
- Future studies are looking to asses best practices for protocol design in order to decrease costs while maintaining scientific rigor.

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2. Jones RN. Microbial Etiologies of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia. Clin Infect Dis. 2010 Aug 1; 51 Suppl 1: S81-7. DOI: 10.1086/653053.
3. Mckane A. et al. Determinants of Patient Screen Failure in Phase 1 Clinical Trials. Invest New Drugs. 2013 June: 31(3):774-9.

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