CLINICAL TRIALS TRANSFORMATION INITIATIVE

A Collaboration to Facilitate the Development of Antibacterial Agents for Unmet Need: Streamlining Clinical Trial Protocols

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ABSTRACT

Abstract Objective:

This multidisciplinary effort aims to identify challenges in clinical trial conduct of antibacterial agents for the treatment of hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), and propose alternate approaches to design more efficient trials.

Method:

This collaboration includes the participation of a multi-disciplinary working group led by the Clinical Trials Transformation Initiative (CTTI). Several meetings and workshops were held to gain a wider understanding of issues, and several solutions using a Quality-by-Design approach were proposed.

Results:

A working group consisting of multidisciplinary partners from academia, industry, patient groups, and government, including the FDA/CDER's Antibacterial Drug Development Task Force, was formed. The working group identified and focused on critical protocol elements where efficiencies leading to high-quality, more feasible trials that can complete enrollment in a timely manner could be introduced. The protocol elements of primary focus were: 1) patient population, 2) study design and endpoints, 3) safety considerations, and 4) operational issues. Recommendations of the working group, including alternate approaches to design efficient and clinically meaningful trials to establish the safety and efficacy of new antibacterial agents for the treatment of HABP/VABP, will be presented.

Conclusion:

This endeavor to improve protocol design and introduce operational efficiencies may help overcome obstacles for the conduct and regulatory review of HABP/VABP trials, hence addressing a critical unmet medical need.

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INTRODUCTION

- There are an estimated 648,000 patients with 721,800 health care–associated infections (HAIs) in U.S. acute care hospitals based on a survey* conducted in 2011.
- Hospital-acquired pneumonia was reported to be the most common HAI (21.8%) per this survey.
- Increasing resistance among etiological pathogens of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) has compounded the problem, underscoring the urgent need for new therapies to treat these infections.
- However, HABP/VABP trials are complex; they are typically conducted globally, are operationally difficult, take a long time to enroll, and are therefore expensive and challenging to conduct.
- Varying regulatory standards for these global trials have further increased their complexity.
- Due to the cost and complex requirements of conducting these trials, research and development of new antibacterial drugs to treat HABP/VABP has slowed.
- Therefore, innovative approaches are needed to address this important issue.

The goal of this project is to develop alternate approaches for designing HABP/VABP trials that preserve their scientific integrity while increasing their operational efficiency, so as to maximize the information gained for the investment made.

* Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care–associated infections. N Engl J Med 2014;370:1198-208.

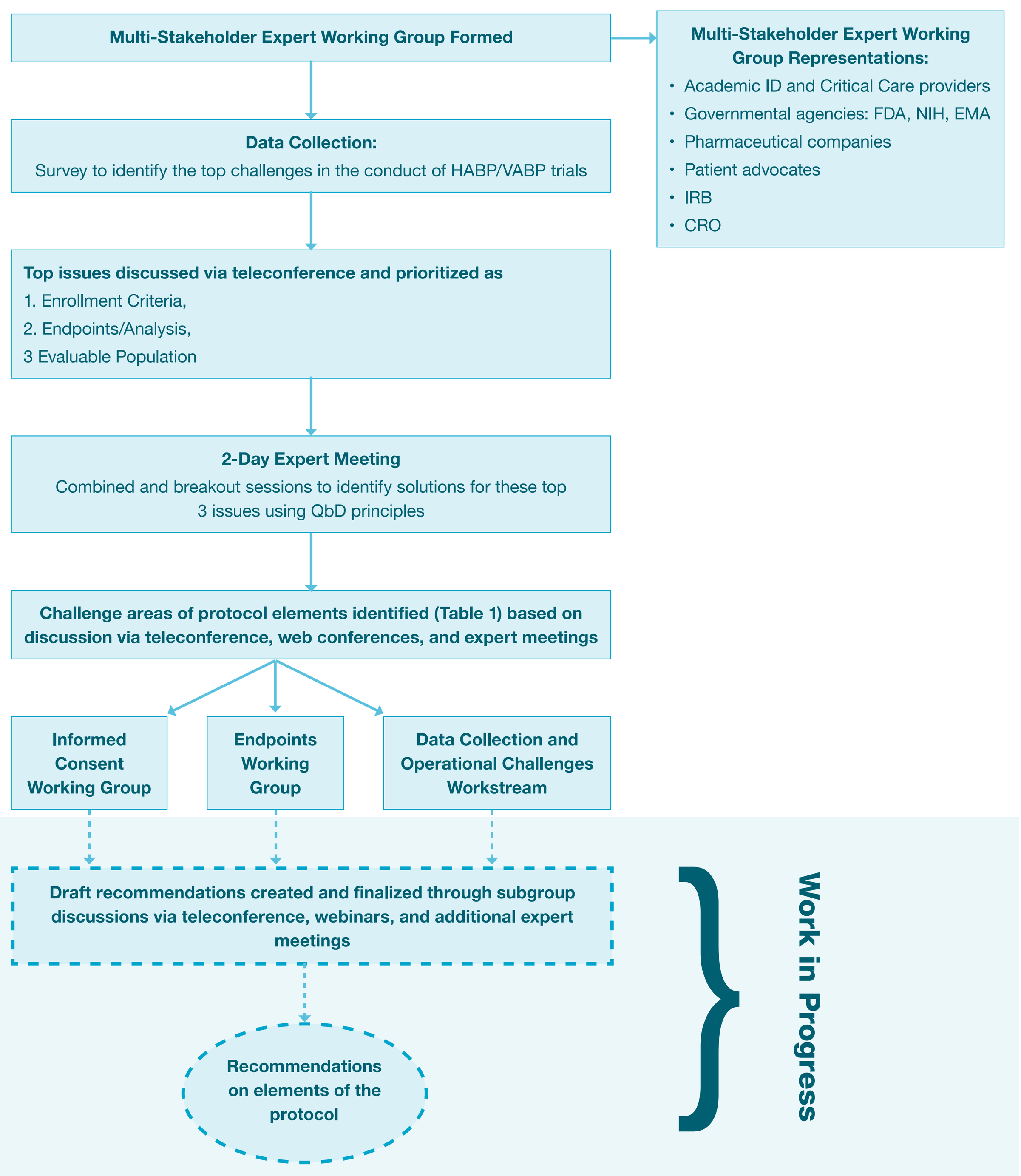
METHODS

The CTTI ABDD HABP/VABP Working Group was convened to include key stakeholders whose remit was to:

- Identify the burdens and inefficiencies of current processes in antibacterial trial conduct;
- Explore novel ideas and issue recommendations on designing scientifically valid, feasible, and clinically meaningful trials to establish the efficacy of antibacterial drugs for the treatment of HABP/VABP;
- Build a pilot network of sites globally with a capability of conducting HABP/VABP studies.

The working group used a Quality-by-Design (QbD) approach to identify critical elements of trial design and propose a path forward. Figure 1 describes the methods and project progress.

Figure 1



RESULTS

- Together with a wider group of experts, the working group has identified several key topics for which it is seeking consensus solutions (see Table 1).
- A global network of about 30 sites with proficiency and interest in HABP/VABP trials and accessibility to the HABP/VABP patient population is under development.
- Next steps include developing recommendations to streamline the study design and elements of the protocol, to introduce efficiencies in the operational processes.

Table 1: Challenge Areas and Critical Protocol Elements Where Efficiencies May Be Introduced

HABP/VABP Trial Protocol Challenges			
Patients	**Trial Design**	**Safety Considerations**	**Operational Issues**
Inclusion/ Exclusion Criteria a. Definition of HABP/VABP b. Pre-study antibacterial therapy c. Severity-of-illness parameters d. Combining HABP and VABP patients in one trial	**Key Design Elements** a. Randomization and stratification b. Choice of active comparator therapy c. Choice of concomitant adjunctive therapy d. Use of rescue therapy e. Noncompliance with study therapy and per-protocol population analysis	**Safety Data Collection** a. Excessive AE data collection b. Excessive safety lab collection c. Regulatory requirements and expedited reporting of unexpected events d. Data and safety monitoring boards	**Protocol Complexities** a. Conducting trials in hospitalized patients b. Availability of rapid diagnostics c. Number of inclusion/exclusion criteria d. Complex case report form
Informed Consent a. Barriers to obtaining consent from critically ill patients b. Caregiver role in consent and advanced directives c. Regional regulations and policy differences d. Transparency regarding non-inferiority study design for study participants and caregivers	**Study Outcomes** a. Analysis Populations definition • Patients with confirmed pathogens • Patients who received pre-study antibacterial therapy b. Primary endpoint rationale • Mortality • Clinical response		**Multicenter Trials** a. Inflexibility in protocol to support recruitment and retention of sites/ patients b. Changing regulatory requirements in each country c. Monitoring data quality • Consistent implementation globally • Clear metrics for benchmarking progress

CONCLUSIONS

This endeavor involves a multi-stakeholder team and uses a QbD approach that has explored issues from a wide variety of perspectives on why HABP/VABP clinical trials are so difficult to plan and execute. Future work may serve to transform the way HABP/VABP trials are designed and conducted in the future.

DISCLOSURES

Author(s) of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Mark Behm: Employee and stock shareholder — AstraZeneca Industries

Sabrina Comic-Savic: Employee — Medicines Company

Vance Fowler: Consultant — Pfizer, Novartis, Galderma, Novadigm, Durata, Achaogen, Affinium, Medicines Co., Cerexa, Trius, MedImmune, Bayer, Theravance, Cubist; Grants/Grants Pending — NIH, MedImmune, Forest/Cerexa, Pfizer, Merck, Advanced Liquid Logics, Theravance, Novartis; Royalties — UptoDate

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Rosemary Tiernan: Nothing to disclose