Article Title: Improving Conduct and Feasibility of Clinical Trials to Evaluate Antibacterial Drugs to Treat Hospital Acquired Bacterial Pneumonia (HABP) and Ventilator Associated Bacterial Pneumonia (VABP): Recommendations of the CTTI Antibacterial Drug Development (ABDD) Project Team

Authors

Charles Knirsch[1], Demissie Alemayehu[1], Radu Botgros[2], Sabrina Comic-Savic[3], David Friedland[4], Thomas Holland[5], Kunal Merchant[6], Gary J. Noel[7], Eric Pelfrene[2], Christina Reith[8], Jonas Santiago[9], Rosemary Tiernan[9], Pamela Tenearts[10], Jennifer C. Goldsack[10], Vance G. Fowler[5]

Affiliations

[1] Pfizer, Inc., New York, NY, USA; [2] Office of Anti-infectives and Vaccines, European Medicines Agency, London, UK; [3] The Medicines Company, Parsippany, NJ, USA; [4] Wockhardt USA, Parsippany, NJ, USA; [5] Duke University, Durham, NC, USA; [6] RRD International, LLC, Rockville, MD, USA; [7] Johnson & Johnson, Raritan, NJ, USA; [8] University of Oxford, Oxford, UK; [9] Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [10] Clinical Trials Transformation Initiative, Durham, NC, USA

Corresponding Author Information:

Vance G. Fowler, Jr., MD, MHS,
PO BOX 102359, Room 153 Hanes Building,
Duke University Medical Center,
Durham, NC 27710
Tel: (919) 613 5678
vance.fowler@duke.edu

Running Head

Streamlining Protocol Elements for HABP/VABP Trials

ABSTRACT

Background: The etiology of hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) is often multidrug-resistant infections, and the evaluation of new antibacterial drugs for efficacy in this population is important, as many antibacterial drugs have demonstrated limitations when studied in this population. HABP/VABP trials are expensive and challenging to conduct due to protocol complexity and low patient enrollment among other factors. The Clinical Trials Transformation Initiative (CTTI) seeks to advance antibacterial drug development by streamlining HABP/VABP clinical trials to improve efficiency and feasibility while maintaining ethical rigor, patient safety, information value, and scientific validity.

Methods: In 2013, CTTI engaged a multidisciplinary group of experts to discuss challenges impeding the conduct of HABP/VABP trials. Separate work streams identified challenges associated with HABP/VABP protocol complexity. The Project Team developed potential solutions to streamline HABP/VABP trials using a Quality by Design (QbD) approach.

Results/Discussion: CTTI recommendations focus on four key areas to improve HABP/VABP trials: informed consent processes/practices, protocol design, choice of an institutional review board (IRB), and trial outcomes. Informed consent processes should include legally authorized representatives. Protocol design decisions should focus on eligibility criteria, pre-study antibacterial therapy considerations, use of new diagnostics, and sample size. CTTI recommends that sponsors use a central IRB and discuss trial endpoints with regulators, including defining a clinical failure and evaluating the impact of concomitant antibacterial drugs.

Conclusion: Streamlining HABP/VABP trials by addressing key protocol elements can improve trial startup and patient recruitment/retention, reduce trial complexity and costs, and ensure patient safety while advancing antibacterial drug development.

Key words: *hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, protocol development, clinical trials, CTTI*

Main Text

Introduction

Infections caused by multidrug-resistant (MDR) bacteria have emerged as an important health threat worldwide. In the US alone, each year at least 2 million people acquire serious infections with bacteria that are resistant to one or more of the available antibacterial therapies designed to treat them [1]. Some of the most common hospital-acquired infections (HAI) are caused by MDR pathogens, including hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), which have a high mortality rate [2, 3]. Recognizing that bacteria continually develop resistance to antibacterial drugs, there is an urgent need to develop a pipeline of new therapies to treat HABP/VABP now and in the future.

Several initiatives, such as "New Drugs for Bad Bugs" [4], "Detect and Protect Against Antibiotic Resistance" [5], and the "10 x '20 Initiative" [6], are underway to address the many challenges posed by MDR bacteria. One recent advancement intended to stimulate antibacterial drug development is the Generating Antibiotics Incentives Now provision (GAIN), which was signed into law in the United States (US) in 2012. Under GAIN, products with the designation of Qualified Infectious Disease Product (QIDP) receive the following: a priority review, a fast-track designation upon request, and an additional 5 years of market exclusivity in the US [7]. While the passage of GAIN is a positive step, considerable challenges still exist in developing a new antibacterial drug.

It is important to evaluate the efficacy of a drug for the treatment of patients with HABP/VABP as this patient population is seriously ill and has several comorbidities. Additionally, a number of antibacterial drugs with demonstrable efficacy in the treatment of other serious bacterial infections have shown limitations when studied as a treatment for HABP/VABP. Because this observation indicates a potential hazard in drawing conclusions about efficacy and safety of new therapies for patients with HABP/VABP based on studies in other patient groups, clinical trials specifically focused on HABP/VABP patients are needed to fully address the unmet medical need as many MDR bacteria can cause these bacterial pneumonias. However, clinical trials to evaluate the efficacy and safety of new antibacterial drugs for HABP/VABP are challenging for several reasons, including low patient enrollment (averaging as little as 0.12 patients per site per month in some cases [8]), protocol complexities, and high costs (in part due to high patient trial screening failure rates [9]). Because HABP/VABP trials are especially expensive to conduct, they are considered to have a relatively poor return on investment (ROI), and few drug developers are willing to invest in conducting them.

The Clinical Trials Transformation Initiative (CTTI) is a collaborative organization that seeks to improve the quality and efficiency of clinical trials. An Antibacterial Drug Development (ABDD) Project Team was formed to identify challenges in and advance the science of antibacterial drug trial conduct. Streamlining the conduct of scientifically valid, feasible, and clinically meaningful HABP/VABP trials is one of three main projects currently defined in the CTTI ABDD program [10-12]. CTTI undertook its HABP/VABP project in order to identify the inefficiencies and challenges faced when conducting a HABP/VABP trial. In general, these challenges are predominantly related to trial enrollment, protocol complexities, and trial conduct. In this manuscript, we describe the current progress of the HABP/VABP ABDD Project Team in advancing the science of clinical trials to study new drugs for treating patients with HABP/VABP.

Methods

An expert team of various stakeholders across the clinical research enterprise; including academic scientists, clinicians, regulators, trial monitors and coordinators, and patient and industry representatives; convened on multiple occasions through a variety of means (including teleconferences, webinars, conference presentations [13], and face-to-face meetings) to develop various sections of the project (Figure 1), discuss the current challenges associated with HABP/VABP trials, and pose novel solutions.

The ABDD Project Team identified the challenge of protocol complexity and developed "protocol elements" to address specific areas of clinical trial design and conduct. Experts discussed potential solutions to streamline HABP/VABP trials using a Quality by Design (QbD) approach [14, 15]. Several subgroups were convened to address specific topics and refine the ideas stemming from these discussions. These efforts resulted in ABDD Project Team recommendations based on consensus statements.

Results and Discussion

The CTTI ABDD Project Team recommendations to improve HABP/VABP protocol design elements identified four key areas to streamline the design and conduct of HABP/VABP trials: (1) informed consent, (2) protocol design, (3) central institutional review board (IRB) use, and (4) trial outcomes and efficacy endpoints (Table 1).

Informed Consent

The ABDD Project Team has identified overcoming enrollment challenges as critical to conducting HABP/VABP trials successfully. The provision of voluntary informed consent (IC) to participate in a clinical trial is the foundation upon which all ethical research is conducted in addition to being a

regulatory requirement. One major factor that influences the success and speed of patient enrollment into trials is the current process for obtaining IC. In general, this process has become encumbered by a number of barriers (e.g., extremely lengthy and complex IC documents, lack of staff training in helping patients understand the most salient points of IC, and how to best convey these points to patients). These specific issues are not addressed here; a separate CTTI project is devoted to improving the IC process for participants in any clinical trial [16].

Considerations relevant to the HABP/VABP population, beyond those inherent to the standard IC process are addressed here. In its deliberations, the ABDD Project Team recognized that individuals obtaining IC from patients with HABP/VABP need to consider that many of these patients can be unconscious or mentally disoriented, either due to the severity of their infection or secondary to sedation, and are therefore not capable of making decisions on their own behalf. This presents ethical and legal challenges and requires a heightened degree of understanding of the pertinent issues. When patients are determined to lack capacity, alternative means through which IC can be feasibly and ethically obtained need to be developed and may include use of a legally authorized representative (LAR).

Fostering staff training and understanding, as described in Lentz et al. (in review) [17], is one strategy to streamline IC. Specifically, for HABP/VABP trials, research and hospital staff should be trained on the challenges typically faced with obtaining consent from the HABP/VABP patient population, with an emphasis on best practices for obtaining consent from these seriously ill, often incapacitated patients and their LARs. A LAR is defined as an individual or judicial body authorized under applicable law to provide consent on behalf of a prospective research participant; many times, the LAR may also be a patient's family member [18-20]. While family members or the LAR may be aware of a patient's wishes regarding treatment and resuscitation status, they may remain largely unsure of the individual's wishes/opinions regarding research trial participation if the patient becomes incapacitated. The ABDD Project Team felt that substantial benefits could be derived from a physician broaching the subject of trial participation early with patients and their LARs and encouraged further research on this possibility. This strategy of early discussion could also facilitate enrollment.

Approaches to early recording of potential trial participant's consent may be general or targeted. With a general approach, patients at increased risk to develop HABP/VABP may be engaged while they are not critically ill and are of sound mind to discuss and record their views on trial participation. A targeted approach may also be explored. Patients who may be at particularly high risk for developing HABP/VABP may be inpatients (i.e., immunocompromised patients, patients admitted to the intensive care unit [ICU]) or outpatients (i.e., individuals with chronic diseases who are frequently hospitalized).

These patients can be informed and educated specifically about HABP/VABP trials at a time when they are not incapacitated and can have a more extensive discussion regarding the benefits and risks of trial participation. Additionally, the discussion should address the possibility of the physician obtaining consent through a patient's LAR, should they become eligible for the HABP/VABP trial but unable to consent themselves. For the benefit of both the physician and the patient, it is recommended that the LARs be involved in these early conversations.

CTTI recommendations for best practices with obtaining IC from HABP/VABP trial participants

- The IC process should be streamlined as much as possible, and trial/research staff should be thoroughly educated on best practices [21] for obtaining consent from these seriously ill, often incapacitated patients.
- Whenever possible, patients at risk of developing HABP/VABP should be approached early, when they are not critically ill and are of sound mind, to discuss and record their views on participating in research. Legally authorized representatives are encouraged to be involved in this process should the patient subsequently become decisionally impaired.

Protocol Design

Before initiating a HABP/VABP trial, several protocol design elements should be considered (Table 1). CTTI has previously issued QbD recommendations [15] to guide sponsors on best practices during clinical trial design. These principles are intended to help sponsors focus on the trial activities essential to the safety of trial participants and to the reliability of trial results. Operational issues specific to HABP/VABP trials should be considered only after these trial recommendations have been implemented.

One specific operational concern in HABP/VABP trials on which CTTI has focused is data collection and recording. Specific strategies for streamlining HABP/VABP trial data collection are also available through the CTTI website [11].

Eligibility criteria

HABP, ventilated HABP, and VABP share common clinical signs and symptoms, as defined in the Food and Drug Administration (FDA) guidances and European Medicines Agency (EMA) guidelines [22-24]. When considering HABP/VABP patients for trial participation, the entry criteria should be restricted to those that are essential to address the scientific objectives of the trial and safety of the trial population. This can facilitate trial recruitment while also maximizing the applicability of the trial results to the broadest possible population. Because HABP/VABP trials are often difficult to enroll, with as little as

10% or less of the screened patients meeting the eligibility criteria in some cases [8], relaxing the exclusion criteria to include immunosuppressed patients or patients with additional comorbidities may increase the proportion of screened patients that are enrolled in the trial and also allows for data to be generated for these critical patients. During the ABDD Project Team meeting, it was questioned whether relaxing the exclusion criteria, and therefore possibly enrolling a more heterogeneous patient population, may lead to the treatment arms being imbalanced with respect to certain confounders (e.g., number of immunosuppressed patients in each treatment group); however, given the sample size expectations of current-day HABP/VABP trials and with use of robust randomization techniques, imbalance between treatment groups is unlikely to be an issue [25, 26].

Pre-trial antibacterial therapy criterion

Typically, inclusion criteria specify that patients should not receive certain therapies prior to trial conduct, especially those therapies that overlap with the spectrum of activity of the antibacterial drug being tested. However, due to the seriousness of HABP/VABP and the established relationship with delay in appropriate therapy having a substantial effect on morbidity and mortality (also supporting the important role of initial therapy), it is widely considered unethical to withhold from or delay initiation of antibacterial drug therapy for a patient with HABP/VABP. At the November 2011 FDA Anti-Infective Drugs Advisory Committee Meeting, the allowance of up to 24 hours of pre-trial antibacterial therapy was discussed [27, 28]. As part of this meeting, the Infectious Disease Society of America (IDSA) provided comments on the issue of prior antibacterial therapy [29]. It has not yet been determined whether the effect of prior antibacterial therapy may potentially obscure the ability to detect reduced efficacy of the investigational antibacterial drug in HABP/VABP; as a matter of practicality, the Committee discussions supported an allowance for a limited period of prior therapy.

The 22-23 April 2013 CTTI Multistakeholder Expert Meeting also discussed this issue, and many agreed with the practical need for allowance of some prior effective antibacterial drug therapy despite that its effect on obscuring the assessment of efficacy has not been established. This allowance for prior antibacterial therapy is also in accordance with the EMA addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (effective May 2014) [22]. Trials in patients who have pneumonia have allowed the enrollment of patients who received pre-trial effective antibacterial drug therapy [30, 31]. A subgroup analysis from one trial showed that pre-trial effective antibacterial drug therapy can obscure a deficit in efficacy for an antibacterial drug [30].

In general, participant recruitment is a challenge in HABP/VABP trials due in part to the reality that many potential subjects have already received more than 24 hours of effective antibiotics by the time they are

identified and approached for enrollment. Concern has been raised that the frequency of prior therapy as a cause for screening failure in HABP/VABP trials will continue to be a major obstacle in identifying trial patients. Although extending the allowance to 48 hours may help increase patient recruitment, it may also obscure the ability to evaluate the efficacy of the investigational drug. The ABDD Project Team advised prospective collection of data to assess how many patients received 0, 24, 36, and 48 hours of prior effective antibacterial drug therapy at the time of identification for enrollment. As results from Pertel et al. illustrates the risks of using prior effective therapy [30], an approach that extends the pre-study antibacterial therapy window may adversely impact the ability to assess drug efficacy.

Available diagnostics and biomarkers

Respiratory specimens should be obtained from patients enrolled in HABP/VABP trials as soon as possible and within 24 hours of randomization. To help define the bacterial etiology for HABP/VABP, respiratory specimens (i.e., sputum, bronchoalveolar lavage, protected brush, and tracheal aspirate) are submitted for Gram stain and culture [32]. Rapid diagnostic tests may contribute to screening and enriching the population for a pathogen of interest. The ABDD Project Team agreed that simultaneous testing of new diagnostics and biomarkers with the investigational antibacterial drug(s) in an individual registrational trial could be beneficial for both the successful testing of the drug as well as the diagnostic. In the recent past, there has been little economic incentive for developing antibacterial therapies and new diagnostics [33, 34] despite the growing need. The critical importance of this need was underscored in September 2014 when the Obama administration announced a 20 million dollar diagnostics prize [35] that could hopefully be used to encourage the development of diagnostics.

Low Sample Size

HABP/VABP trials have been difficult to enroll largely due to the paucity of eligible patients, which is driven by avoiding inclusion of subjects in whom there is a concern that comorbid conditions could result in progression of illness independent of an antibacterial drug's effect. Further complicating the challenge of identifying eligible trial patients, recent advances in medical practice may be reducing the frequency of HABP/VABP. Therefore, enrollment of future trials will only continue to be complicated by the difficulty in finding eligible trial patients. For this reason, sponsors should consult with regulators about using a single, large, adequately powered HABP/VABP trial for registration purposes for multiple regulatory authorities worldwide [36]. Although there are some variations in requirements and guidance across authorities, commonalities in the EU and US guidelines exist for many major points [22-24]. One protocol design consideration that both guidelines address is defining the analysis population of a trial: both guidelines permit studying HABP and VABP in a single trial [22-24].

Taken together, these protocol design considerations can promote efficiency while maintaining data quality, increase enrollment in HABP/VABP trials, help limit trial complexity, and incentivize new diagnostics.

CTTI recommendations for optimizing protocol design for HABP/VABP trials

- Inclusion/exclusion should incorporate only elements that are critical to trial objectives and patient safety.
- Further research on the effect of pre-trial antibacterial therapy is encouraged.
- Sponsors should consider simultaneously testing new diagnostics in conjunction with the investigational antibacterial therapy when possible.
- In a drug development program, depending on the investigational drug, a single HABP/VABP trial conducted by a sponsor may be used for registration purposes for more than one regulatory authority worldwide. The recommended primary HABP/VABP trial endpoints for the FDA and EMA may differ, but information relevant to these endpoints (mortality, complications of HABP/VABP, failure to respond to therapy and need to initiate rescue therapy) should generally be collected in all trials regardless of whether the endpoints are primary or secondary. Global drug development programs accordingly design their primary and secondary endpoints to satisfy the respective regulatory agency(ies), based on different statistical analysis plans of the same studies.

Central Institutional Review Board

Experience in conducting HABP/VABP trials supporting a regulatory approval clearly indicates that these trials will almost always involve multiple (often over 100) sites and require over a year or two to complete [8]. Given the resources required to have each site process applications for IRB approval individually, the efficiency of using a central institutional review board should be considered. A central institutional review board (IRB) is defined as a single IRB of record to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of IC. Using a central IRB in HABP/VABP trials may also have the benefit of reducing differences in site decisions/processes (e.g., practices for obtaining IC and adjudicating decisional capacity of patients) and delays with trial startup [37, 38]. While some barriers to using a central IRB still exist (e.g., concerns about regulatory and legal liability), several publications and tools have been developed to inform and assist sponsors in delineating responsibilities of institutions and a central IRB [39-42].

CTTI recommendations for choice of an IRB in HABP/VABP trials

- To accelerate trial startup and reduce complexity, use of a central IRB in HABP/VABP trials is strongly recommended.

Trial Outcomes and Efficacy Endpoints

Definition of the Primary Endpoint

The 2014 FDA guidance provides 2 options for evaluating success of antibacterial therapies in the HABP/VABP population: 1) all-cause mortality or 2) survival without complications [24]; however, the EMA indicates that as their primary endpoint, clinical response should be assessed at a protocol-defined time point [22]. Clinical response has generally been a physician's appraisal of whether the patient has responded to treatment; patients who die or experience complications of HABP/VABP are considered clinical failures. Given existing regulatory guidelines, the choice of a primary endpoint in HABP/VABP trials may be influenced by the regulatory authorities from whom approval is being sought. Sponsors may also wish to discuss with EMA and FDA how they may use different statistical analysis plans from the same trial to use the trial to support a regulatory application in the US and Europe. Additionally, sponsors are encouraged to discuss with regulators which specific events (in addition to mortality) will qualify as a treatment failure prior to finalization of the trial protocol. Any combination of a mortality endpoint and significant clinical events should be clearly defined (e.g., "mortality plus") and pre-specified in the protocol as the co-primary endpoint when seeking US FDA approval. Examples of a "mortality plus" endpoint could include acute respiratory distress syndrome, respiratory failure, endocarditis, meningitis, or empyema [24, 43].

FDA guidance already indicates that certain conditions (e.g., empyema) may be included as part of the primary endpoint [24]; however, sponsors can include additional relevant conditions provided that they are clearly outlined in the protocol. Events that constitute a clinical failure should be evaluated between randomization and a pre-specified follow-up time (e.g., day 28 post-randomization) [23, 24].

The greatest concern with evaluating a clinical response early is claiming a successful outcome before adequate time has passed in order to make an accurate assessment. A specific patient can be designated as a clinical failure at any point throughout the treatment and post-treatment course, but a clinical success should only be determined after a sufficient period of time.

Use of Concomitant Antibacterial Therapy

Concomitant antibacterial therapy in a HABP/VABP trial includes an antibacterial drug given at the same time with the investigational antibacterial drug. The greatest concern with ancillary antibacterial drug therapies is the possibility of overlapping antibacterial spectrums, making it difficult to evaluate the contribution of the investigational drug in treating HABP/VABP. The concomitant use of an antibacterial drug with the investigational antibacterial drug for HABP/VABP during the trial may be necessary.

An investigational antibacterial drug may not fully encompass the broad spectrum of bacterial pathogens implicated in HABP/VABP. Investigational drugs with more limited antibacterial activity can be targeted for development for the treatment of HABP/VABP, but in this case, most patients would need initial concomitant antibacterial drug therapy to treat the broad spectrum of bacterial pathogens before culture results are available. Another consideration for HABP/VABP trial design and review is that different patterns of bacterial etiologies may be responsible for HABP/VABP at each clinical trial site. Because concomitant antibacterial drugs can confound the interpretation of the treatment effect in a non-inferiority trial, the protocol design should specify any use of concomitant antibacterial drugs that may be permitted for the initial treatment of patients with HABP/VABP. To the extent possible, the concomitant antibacterial drug should not have antibacterial activity similar to the spectrum of activity of the investigational drug. After culture and *in vitro* susceptibility testing results are available, if there is a defined level of clinical improvement, sponsors should consider de-escalation of concomitant therapy [44]. Whenever possible, treatment should be completed as monotherapy, with the investigational drug administered to patients randomized to the investigational drug group, enhancing the possibility of drawing stronger conclusions about an investigational drug's overall treatment effect.

<u>CTTI recommendations for choice of trial outcome measurements and efficacy endpoints in HABP/VABP trials</u>

- Following consultation of the current guidelines, if sponsors wish to use a "mortality plus" endpoint that includes specific events in addition to mortality that determine a treatment failure, the proposal should be discussed with regulators and pre-specified in the protocol.
- Clinical failure should be based on clinical events that occur at any time between randomization and a pre-specified follow-up time; clinical success should only be determined after a sufficient period of time.
- The use of concomitant antibacterial drugs should be described in the protocol to the greatest possible extent. Ideally, recommended concomitant therapy options should minimize the degree to which the concomitant therapy overlaps with the spectrum of activity of the investigational antibacterial drug.

Potential Limitations and Outstanding Issues

The ABDD Project Team focused their efforts on broadly addressing key protocol elements of HABP/VABP trials in need of reform. Challenges related to a specific drug, drug class, or therapy, are not discussed here; therefore, this manuscript by no means contains an exhaustive list of the important decisions that sponsors face. Typically, HABP/VABP trials, like other ABDD trials, are non-inferiority trials because it would be unethical to include a control arm that offers a potentially ineffective or less effective treatment for patients with these infections. Significant progress has been made in the understanding and design of non-inferiority clinical trial design over the last decade [25, 45, 46]. The FDA has convened workshops and Advisory Committee meetings and worked closely with other organizations, such as the Foundation for the National Institutes of Health and IDSA to discuss issues related to determining the non-inferiority margin and development of guidance to assist sponsors with clinical trial conduct, design, and statistical evaluations [47]. The recommendations issued by CTTI on streamlining HABP/VABP trials are intended to complement such efforts in conjunction with existing regulatory and ICH guidelines and new diagnostics as they emerge.

The ABDD Project Team recommends the use of central IRBs for HABP/VABP trials when possible. While use of a central IRB has demonstrated increased efficiency in certain trials [38], the inclusion of a central IRB in multi-national trials may not provide the same efficiencies because requirements vary locally. Additionally, for HABP/VABP trials, site selection may be primarily based on infection clusters, and this may require the inclusion of institutions that may not be able to participate in a central IRB, thus reducing the efficiency gained in this manner.

Conclusions

The lack of new antibacterial drugs to treat MDR pathogens is a global health threat. New ideas to improve the feasibility and conduct of HABP/VABP trials for ABDD have been discussed with a goal toward maintaining trial feasibility and scientific rigor while facilitating the development of new antibacterial drugs. Streamlining HABP/VABP trial design and conduct by addressing key protocol elements will accelerate trial startup, increase patient recruitment and retention, reduce trial complexity and costs, and ensure patient safety while advancing the development of new antibacterial agents.

NOTES

Disclaimer: The views expressed herein represent those of the authors and not necessarily the views or practices of the authors' employer or any other party.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Author Contributions: All authors contributed extensively to the work presented in this paper.

Acknowledgments: The authors wish to acknowledge the contributions of the CTTI Streamlining HABP/VABP Trials Project Team and those experts who participated in the expert meetings and discussions. Medical writing assistance was provided by Kelly Kilibarda, PhD, in affiliation with Whitsell Innovations, Inc.

Funding: Funding for this manuscript was made possible, in part, by the Food and Drug Administration through grant R18FD005292 and cooperative agreement U19FD003800. Views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. Partial funding was also provided by pooled membership fees from CTTI's member organizations.

Supplement Sponsorship: This article appeared as part of the supplement "Facilitating Antibacterial Drug Development in a Time of Great Need" sponsored by the Clinical Trials Transformation Initiative (CTTI).

Conflict of Interest Information for All Authors:

C. Knirsch works for and holds stocks of a pharmaceutical company, Pfizer Inc.

D. Alemayehu works for and holds stocks of a pharmaceutical company, Pfizer Inc.

T. Holland reports paid consulting for The Medicines Company and royalties from UpToDate.

V. G. Fowler reports the following potential conflicts of interest: Chair of the Scientific Advisory Board for Merck V710; paid consultant for Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea, Affinergy; Grants pending from MedImmune, Actavis/Forest/Cerexa, Pfizer,

Merck/Cubist, Advanced Liquid Logics, Theravance, and Novartis; royalties from (UpTo- Date), personal fees for development or presentation of educational presentations (Green Cross, Cubist, Cerexa, Durata, Theravance), outside the submitted work; and patent pending related to sepsis diagnostics.

All other authors: no reported conflicts.

REFERENCES

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, GA, USA: Centers for Disease Control and Prevention, , **2013** 2013.
2. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America **2013**; 34(1): 1-14.
3. Rosenthal VD, Maki DG, Jamulitrat S, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009. American journal of infection control **2010**; 38(2): 95-104 e2.
4. Innovative Medicines Initiative. New Drugs for Bad Bugs. Available at: http://www.imi.europa.eu/content/nd4bb.
5. Centers for Disease Control and Prevention. Detect and Protect Against Antibiotic Resistance. Available at: http://www.cdc.gov/drugresistance/detect-and-protect/.
6. Infectious Diseases Society of America. Antibiotic Development: The 10 x '20 Initiative. Available at: http://www.idsociety.org/10x20/.
7. Woodcock J. Three encouraging steps towards new antibiotics. Available at: http://blogs.fda.gov/fdavoice/index.php/tag/gain-act/. Accessed December 17.
8. Barriere SL. Challenges in the design and conduct of clinical trials for hospital-acquired pneumonia and ventilator-associated pneumonia: an industry perspective. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2010**; 51 Suppl 1: S4-9.

9. Stergiopoulos S, Tenaerts P, Getz K. Cost Drivers of a Hospital Acquired Bacterial Pneumonia and Ventilator Acquired Bacterial Pneumonia (HABP/VABP) Phase Three Clinical Trials. ID Week. San Diego, CA, **2015**.

10. Clinical Trials Transformation Initiative. Streamlining HABP/VABP Trials: Project Summary. Available at: http://www.ctti-clinicaltrials.org/what-we-do/ctti-projects/habpvabp-trials. Accessed December 1, 2015.

11. Clinical Trials Transformation Initiative. AB Drug Development. Available at: http://www.ctti-clinicaltrials.org/what-we-do/ctti-project-categories/ab-drug-development. Accessed December 1, 2015.

12. Knirsch C, Alemayehu D, Botgros R, et al. Streamlining Safety Data Collection in Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Trials: Recommendations of the CTTI Antibacterial Drug Development (ABDD) Project Team. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2016**; TBD.

13. Clinical Trials Transformation Initiative ABDD HABP/VABP Working Group:, Behm M, Comic-Savic S, et al. A Collaboration to Facilitate the Development of Antibacterial Agents for Unmet Need: Streamlining Clinical Trial Protocols. DIA's 50th Annual Meeting. San Diego, CA, **2014**.

14. Clinical Trials Transformation Initiative. QbD: Project Summary. Available at: http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm. Accessed December 1, 2015.

15. Clinical Trials Transformation Initiative. CTTI Recommendations: Quality by Design. Available at: http://www.ctti-clinicaltrials.org/files/QbD_toolkit/CTTI%20Quality%20by%20Design%20Recommendations_FINAL_1JUN15.pdf. Accessed December 1, 2015.

16. Clinical Trials Transformation Initiative. Informed Consent: Project Summary. Available at: http://www.ctti-clinicaltrials.org/what-we-do/study-start-up/informed-consent. Accessed December 1, 2015.

17. Lentz J, Kennett M, Perlmutter J, Forrest A. Paving the Way to a More Effective Informed Consent Process: Recommendations from the Clinical Trials Transformation Initiative. **(in review)**.

18. U.S. Department of Health and Human Services. Frequently Asked Questions: Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject? Available at: http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html. Accessed December 1, 2015.

19. Food and Drug Administration. General requirements for informed consent. In: Food and Drug Administration Vol. 45 CFR §46.116.

20. Food and Drug Administration. Definitions. Vol. 45 CRF §46.102(c).

21. Clinical Trials Transformation Initiative. CTTI Recommendations: Informed Consent. Available at: http://www.ctti-clinicaltrials.org/files/Informed_Consent/CTTI-InformedConsent-Recs.pdf. Accessed February 8, 2016.

22. European Medicines Agency. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. London, UK, **2013** 24 October 2013.

23. European Medicines Agency CfHMPC. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. London, UK, **2011** 15 December 2011.

24. Food and Drug Administration. Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment (Draft Guidance, Revision 2). Rockville, MD, USA, **2014** May 2014.

25. Spellberg B, Talbot G. Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.

Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2010**; 51 Suppl 1: S150-70.

26. European Medicines Agency CfHMPC. Guideline on adjustment for baseline covariates in clinical trials. London, UK, **2015** February 26, 2015.

27. Craven D. Ventilator-Associated Pneumonia (VAP) Hospital-Acquired Pneumonia (HAP) Definitions, Diagnostics & Outcomes. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM281977.pdf. Accessed February 3, 2016.

28. Food and Drug Administration. November 4, 2011 Anti-Infective Drugs Advisory Committee Meeting Announcement. Available at: http://www.fda.gov/AdvisoryCommittees/Calendar/ucm273363.htm. Accessed February 3, 2016.

29. Infectious Diseases Society of America. Re: Comments on Docket #FDA-2010-D-0589; Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP): Developing Drugs for Treatment; 75 Federal Register 73107; Novemeber 29, 2010. Available at: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Position_Papers/IDSA%20Comments%20on%20HABP%20and%20VABP.pdf. Accessed December 28.

30. Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2008**; 46(8): 1142-51.

31. Rubinstein E, Cammarata S, Oliphant T, Wunderink R, Linezolid Nosocomial Pneumonia Study G. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clinical infectious

diseases : an official publication of the Infectious Diseases Society of America **2001**; 32(3): 402-12.

32. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2013**; 57(4): e22-e121.
33. Projan SJ. Why is big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol **2003**; 6(5): 427-30.
34. Spellberg B. The future of antibiotics. Crit Care **2014**; 18(3): 228.
35. Office of the Press Secretary. FACT SHEET: Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria. Available at: https://www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistan. Accessed October 6, 2015.
36. European Medicines Agency. Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study. London, UK, **2001**.
37. Menikoff J. The paradoxical problem with multiple-IRB review. The New England journal of medicine **2010**; 363(17): 1591-3.
38. Wagner TH, Murray C, Goldberg J, Adler JM, Abrams J. Costs and benefits of the national cancer institute central institutional review board. J Clin Oncol **2010**; 28(4): 662-6.
39. Check DK, Weinfurt KP, Dombeck CB, Kramer JM, Flynn KE. Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature. Clin Trials **2013**; 10(4): 560-7.
40. Clinical Trials Transformation Initiative. Considerations to Support Communication between Institutions and Outside IRBs When Responsibilities are Being Assigned for Multi-center Clinical Trial Protocols. Available at: http://www.ctti-

clinicaltrials.org/files/Central_IRB/Considerations%20Document%20-%20Use%20of%20Central%20IRBs%20for%20Multicenter%20Clinical%20Trials%20NB2web.pdf. Accessed December 1, 2015.

41. Flynn KE, Hahn CL, Kramer JM, et al. Using central IRBs for multicenter clinical trials in the United States. PLoS One **2013**; 8(1): e54999.

42. Food and Drug Administration. Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials. Rockville, MD, **2006**.

43. Clinical Trials Transformation Initiative. Antibacterial Drug Development Program Update: Summary of Working Group Webinar held 29 August 2013, **2013**.

44. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **2005**; 171(4): 388-416.

45. Food and Drug Administration. Guidance for Industry: Non-Inferiority Clinical Trials Draft Guidance. Silver Spring, MD, **2010**.

46. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9, **1998** February 5, 1998.

47. Toerner JG, Burke L, Komo S, Papadopoulos E. A collaborative model for endpoint development for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2012**; 55(8): 1122-3.

Figure Legends

Figure 1: CTTI Work Streams for HABP/VABP Trials Project.

Within the CTTI ABDD Program, a multistakeholder group was formed to identify challenges in current HABP/VABP trials and pose solutions. Following expert meetings and discussion, separate projects and workstreams within each project were formed to tackle specific issues that currently hinder the conduct of HABP/VABP trials. The "Protocol Elements" Project Team (also termed "ABDD Project Team") is part of the "Streamlining HABP/VABP Trials" project. Recommendations from this group were refined by experts after initial solutions were proposed and discussed at length.

Tables

Table 1 Protocol Design Elements to Consider in HABP/VABP Trials

Consideration	Challenge(s)	Consequence(s)	Recommendation(s)
Informed consent	Incapacitated patients are unable to give IC	Failure or delayed enrollment	1. Educate research staff on best practices. 2. Earlier identification and engagement of patients at increased risk for HABP/VABP and document patient's views on trial participation 3. Include the LAR in conversations about trial participation.
Protocol design	Restrictive eligibility criteria	Low patient enrollment, Lack of generalizability of trial results	Reduce criteria to essential elements only
	Adherence to < 24-hour pre-trial antibacterial therapy criterion	Screen failures, If >24 hours pre-trial antibacterial therapy, possible interference with interpreting efficacy effects	Use existing guidelines, Further research on increased interval for pre-trial antibacterial therapy, depending on the type of organism

	Available diagnostics and biomarkers	Impedes ability to quickly and precisely define etiology of infection	Test new diagnostics concurrently with investigational antibacterial drugs
	Low sample size	Difficulties in conducting trials that are statistically powered	Use a single adequately sized HABP/VABP trial for registration purposes
Choice of IRB	IRB variability with multicenter trials	Delayed startup, Increased confusion/complexity	Use a central IRB
Trial outcomes and efficacy endpoints	Define the type of primary endpoint (all-cause mortality or a clinical response endpoint) while still	Impacts trial sample size and may impact how some data elements collected	1. Consult existing regulatory guidance 2. Consider combining mortality with specific events that would qualify as a treatment failure 3. Collect relevant information on endpoints (mortality, complications, response to therapy) regardless whether they are primary or secondary
	Use of a concomitant antibacterial therapy when combination therapy is considered the standard of care	May confound efficacy interpretation	The use of concomitant antibacterial drugs should be addressed in the protocol and investigator training. Consider the effects of concomitant antibacterial therapy on interpretability of trial results.