CTTI HABP/VABP Pilot:
Proposed Study Designs

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Objective of Pilot Study

- Conduct a study that will lead to improved HABP/VABP clinical trial feasibility

- Test the principles and recommendations from:
  - CTTI Antibacterial Drug Development (ABDD) Program
  - Other CTTI projects
Potential Streamlining Elements

- Utilizing HABP/VABP site network (30-50 sites)
- Targeted (reduced) AE collection
- Streamlined data collection (clinical labs, vital signs, etc.)
- Expanding eligibility criteria
- Central IRB (single IRB of record for study)
- Quality by design approach
- Novel secondary endpoint such as early clinical response
- Novel analytic approach
Pilot Study Ideas

- **Design A:** Streamlined Multicenter RCT of Intervention X vs. Intervention Y

- **Design B:** RCT comparing trial enrollment and efficiencies in “traditional” vs. “streamlined” protocols

- **Design C:** Factorial design – randomized to both Drug X vs. Drug Y and streamlined vs. traditional protocol

- **Design D:** Substudy, with expanded access and streamlining, added to existing HABP/VABP clinical trial

- Potential add-on: test of early clinical response as a predictor of 14 or 28 day mortality
Design A: X vs. Y with operational streamlining

- Multicenter RCT of Intervention X vs. Intervention Y
  - two approved drug regimens
- Operational streamlining in both arms
- Endpoints:
  - Cost, enrollment rate/time to completion, etc.
  - Compared to benchmarks of prior/current HABP/VABP trials
Design A: X vs. Y with operational streamlining

Pros:

- Could answer relevant drug X vs. drug Y question
- Would allow novel analytic approach, e.g. RADAR
  - Could investigate superiority of X vs. Y
- Assumed faster/cheaper to complete than design B (with "traditional" arm)

Cons:

- Does not answer streamlining question directly
  - comparison to historical controls
Design B: traditional vs. streamlined protocol

RCT comparing trial enrollment and efficiencies in “traditional” vs. “improved” protocol for HABP/VABP

Antibiotic treatment will be identical in both study arms
- consistent with guidelines/Guidance

Study endpoints will include:
- # of patients enrolled/# screen failures per arm
- # of pages of Adverse event (AE) and Serious Adverse Event (SAE) reporting generated
- time from study initiation to reaching enrollment goal in each study arm
Design B: traditional vs. streamlined protocol

Pros:

- Directly compares trial streamlining approach to traditional approach
- Utility of novel endpoints (e.g. usefulness of early clinical response as a predictor of 14 or 28 day mortality)
Design B: traditional vs. streamlined protocol

Cons:

- Requires running a traditional trial for half the subjects
  - Weighted randomization may be possible
- Only some of the streamlining elements feasible (e.g. allowing >24h pre-study antibiotics, reduced AE monitoring/reporting) but not others (e.g. novel analytic approach, centralized IRB)
- Observational data on treatment regimen
- May need to randomize prior to screening/may need a two step informed consent process
Design C: Factorial Design

Hybrid of Designs A and B - patients are randomized to both
- Drug X versus Drug Y, and
- Streamlined versus traditional protocol

Pros:
- Answers relevant drug question and streamlining question

Cons:
- Complex design
Design D: HABP/VABP Trial Substudy

Randomization visit

Blinded Treatment (7-21 days)

End of Therapy EOT Visit

Follow Up (7-14 days after all antibiotics stopped)

30 day Mortality Assessment

Patients who meet trial criteria are randomized

Trial drug OR Comparator

• Cure
• Indeterminate
• Failure

TOC and Safety Evaluation

Safety Evaluation Only

Mortality Assessment

Main Sponsor trial

Screening

Patients who fail the main trial criteria but meet the criteria for sub-study

Trial drug OR Comparator (TDB if randomized or single arm)

• Cure
• Indeterminate
• Failure

TOC and Safety Evaluation

Safety Evaluation Only

Mortality Assessment

Sub study at few centers
Design D: HABP/VABP Substudy

Pros:
- Cost savings from utilizing existing study infrastructure
- Likely quicker time to startup/enrollment
- Direct comparison of costs of streamlined protocol vs. those in parent study
- Direct assessment of how many patients could be added to a HABP/VABP trial with expanded eligibility
Design D: HABP/VABP Substudy

Cons:

- Challenge of locating parent study
- Buy-in from investigator/sponsor may be difficult due to directly comparing their existing trial to expanded trial
- Competing enrollment / able to enroll only a subset of HABP/VABP patients, which may not be a representative sample
- If substudy is also a randomized trial (test vs. comparator), screen failures for safety reasons may not be eligible to participate
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Pros</th>
<th>Cons</th>
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| **A: Streamlined Multicenter RCT of X vs. Y** | *Relevant drug X vs. Y question*  
*Novel analytic approach – superiority design?*  
*Faster/cheaper to complete than design B* | *Relies on historical controls to test streamlining* |
| **B: RCT of “traditional” vs. “streamlined” protocol** | *Directly compares trial streamlining approach to traditional approach*  
*Novel clinical response endpoint evaluation* | *Runs inefficient trial in 1 arm*  
*Only some streamlining elements could be tested (e.g. central IRB not feasible)*  
*Only obs data on treatment regimen*  
*Complicated randomization/consent* |
| **C: Factorial** | *(X vs. Y) and (streamlined vs. traditional)*  
*Answers drug and streamlining questions* | Complex design |
| **D: Substudy of HABP/VABP clinical trial** | *Assumed cost and time savings by using existing study infrastructure*  
*Direct comparison of enrollment and cost advantages of streamlined vs. parent study* | *Locating parent study and buy-in from investigators*  
*May not be a representative sample (only failures of main study)*  
*If substudy a randomized trial (test vs. comparator), screen failures for safety reasons may not be eligible to participate* |
Thank you.