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)

Patients who meet trial criteria are randomized → Trial drug OR Comparator → Cure • Indeterminate • Failure → TOC and Safety Evaluation

Mortality Assessment

Temporary Disposition Board (TDB) if randomized or single arm

Safety Evaluation Only

Patients who fail the main trial criteria but meet the criteria for sub-study → Trial drug OR Comparator

Main Sponsor trial

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