CTTI HABP/VABP Pilot: Proposed Study Designs

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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

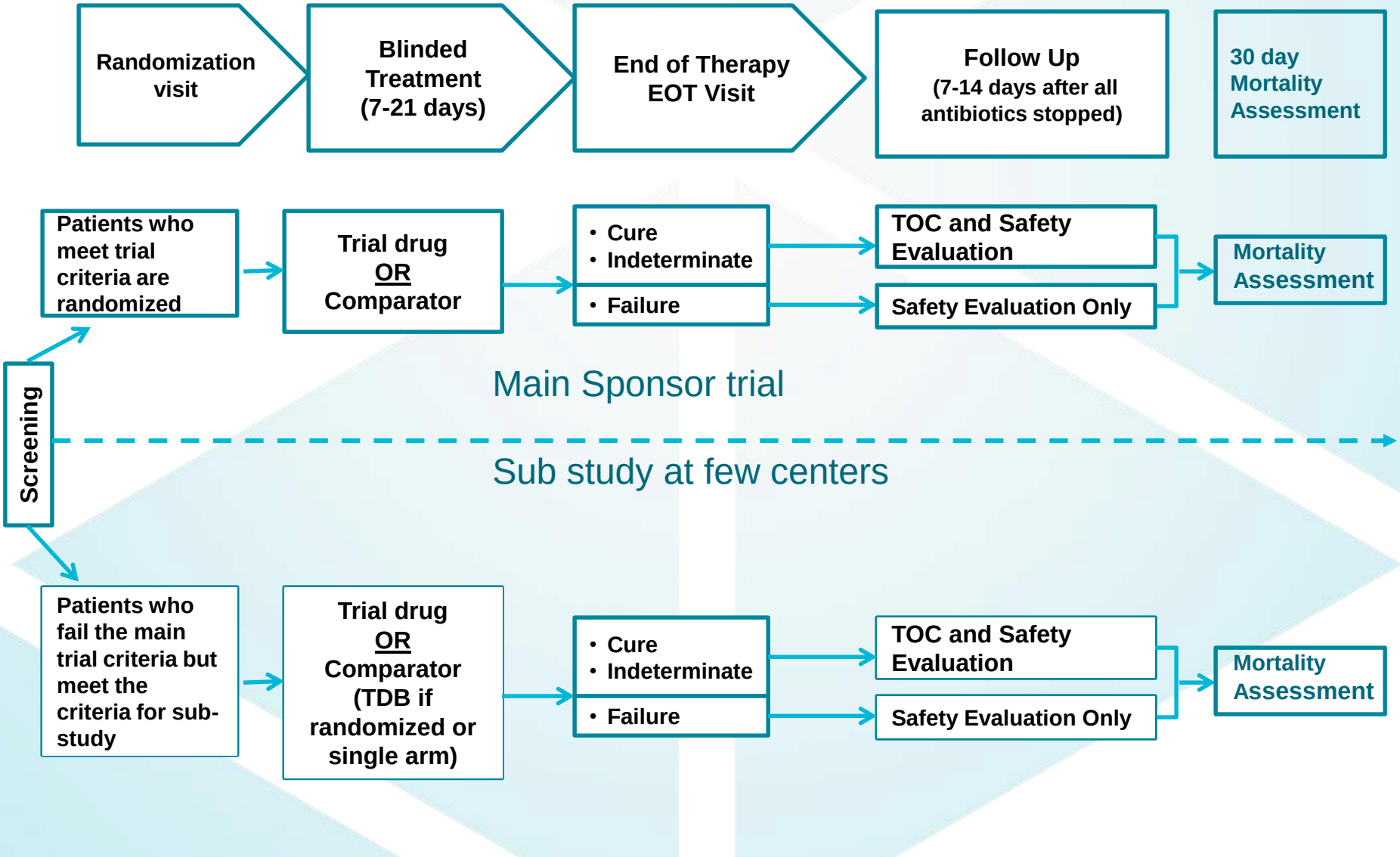
Pros:

- Answers relevant drug question and streamlining question

Cons:

- Complex design

Design D: HABP/VABP Trial Substudy



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

Study Design	Pros	Cons
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.

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