CTTI HABP/VABP Pilot Study

Preliminary Planning

Sara Bristol Calvert, PharmD

Senior Clinical Project Manager, CTTI

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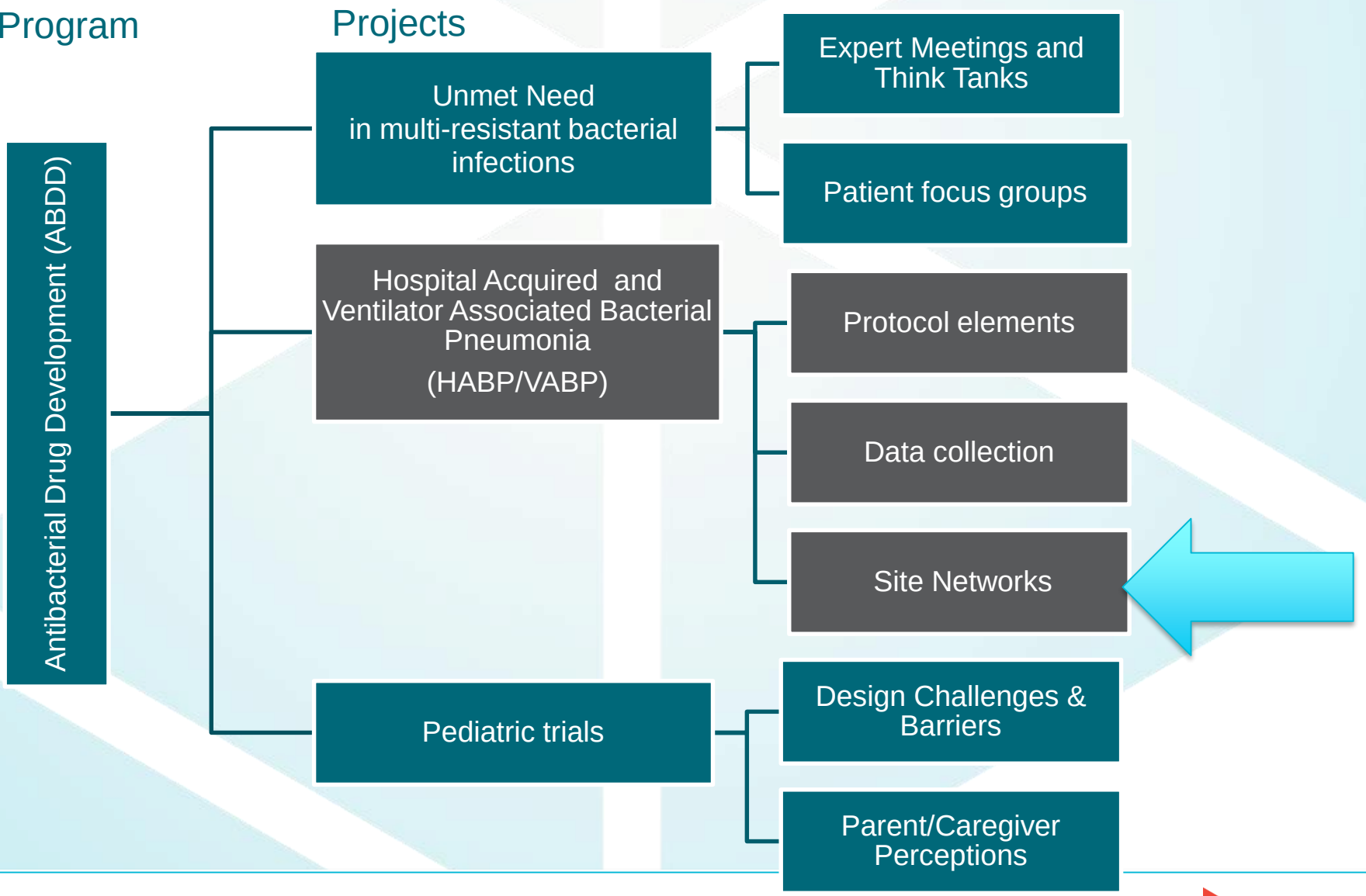
CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

Preliminary Work – Pilot Study Planning

- ID site networks
- Financial analysis (Tufts CSDD)
- Collected eligibility criteria and schedule of events from recent/current/planned HABP/VABP clinical trials
- Study coordinator meeting
- Conversations with clinical trials stakeholders

ABDD Program and Projects



Site Networks

2013-2014

- Pre-identification of sites capable of doing HABP/VABP studies
  - 52 Sites identified – 32 US, 20 ROW

Current

- Setting up master trial agreements (MTA) with sites

Next

- Add Protocol/budget specific amendments to MTAs
- If Central IRB, IRB Authorization Agreements between sites and central IRBs

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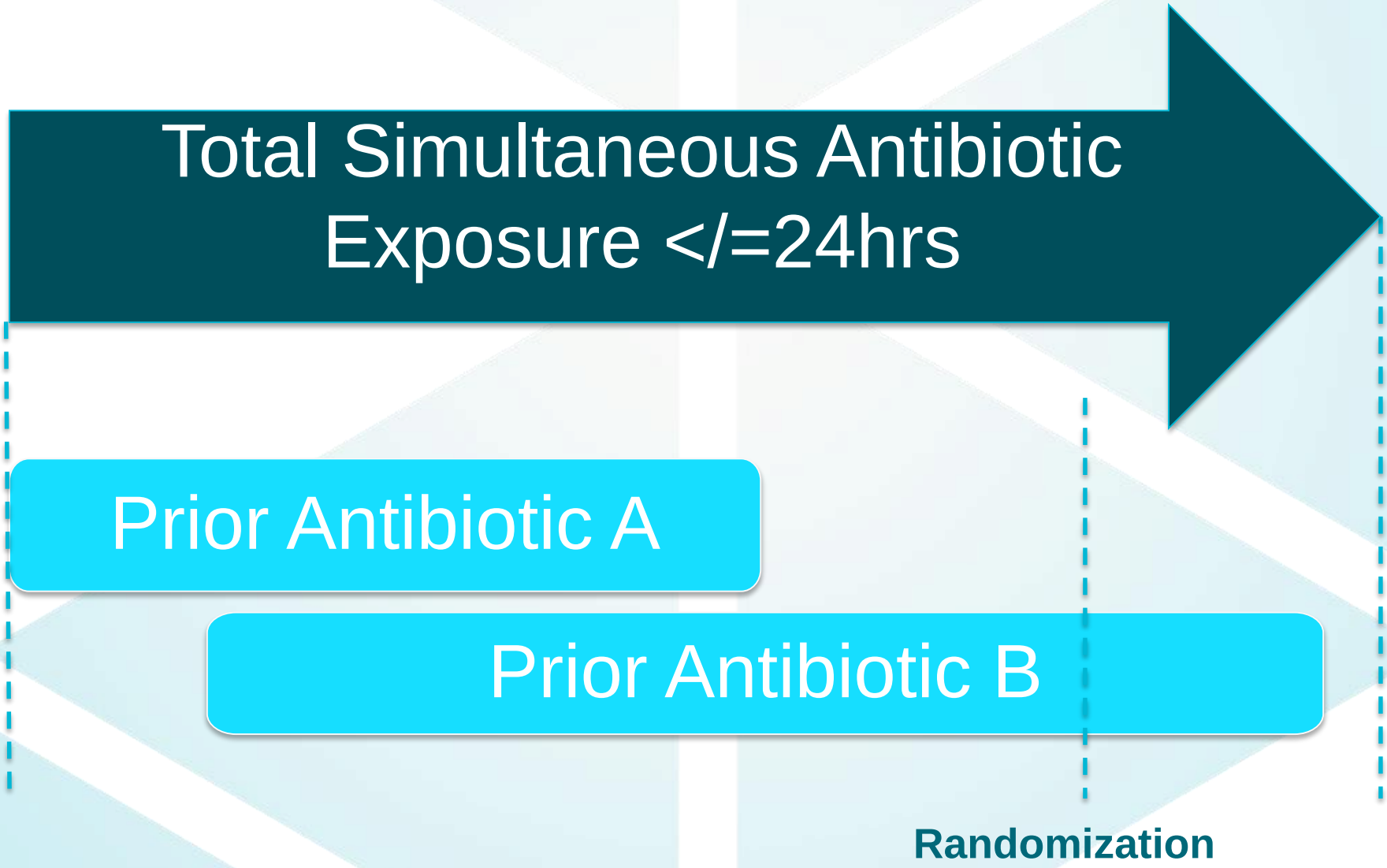
Clinical Research Coordinator Meeting

- Attendees:
  - 6 Clinical Research Coordinators (CRC)
    - 4 Pulmonary and Critical Care Medicine
    - 2 Infectious Disease
  - 2 Clinical Research Associates
- Currently or recent trial experience included VABP, CABP, C. difficile, UTI, influenza, and ARDS
- Guided discussion about operational challenges in the conduct of clinical trials with critically ill patients
  - Notably those with serious infections (i.e. HABP/VABP)
  - Reviewed summaries of eligibility criteria and schedule of events from HABP/VABP trials

CRC Meeting: Challenges to enrollment

1. **Prior antibiotic therapy >24hrs**
2. Restrictive enrollment criteria
3. Buy-in from clinical providers
4. Diagnosis of HABP, VABP, or nosocomial infection


Total Simultaneous Antibiotic Exposure </=24hrs
Prior Antibiotic A
Prior Antibiotic B
Randomization

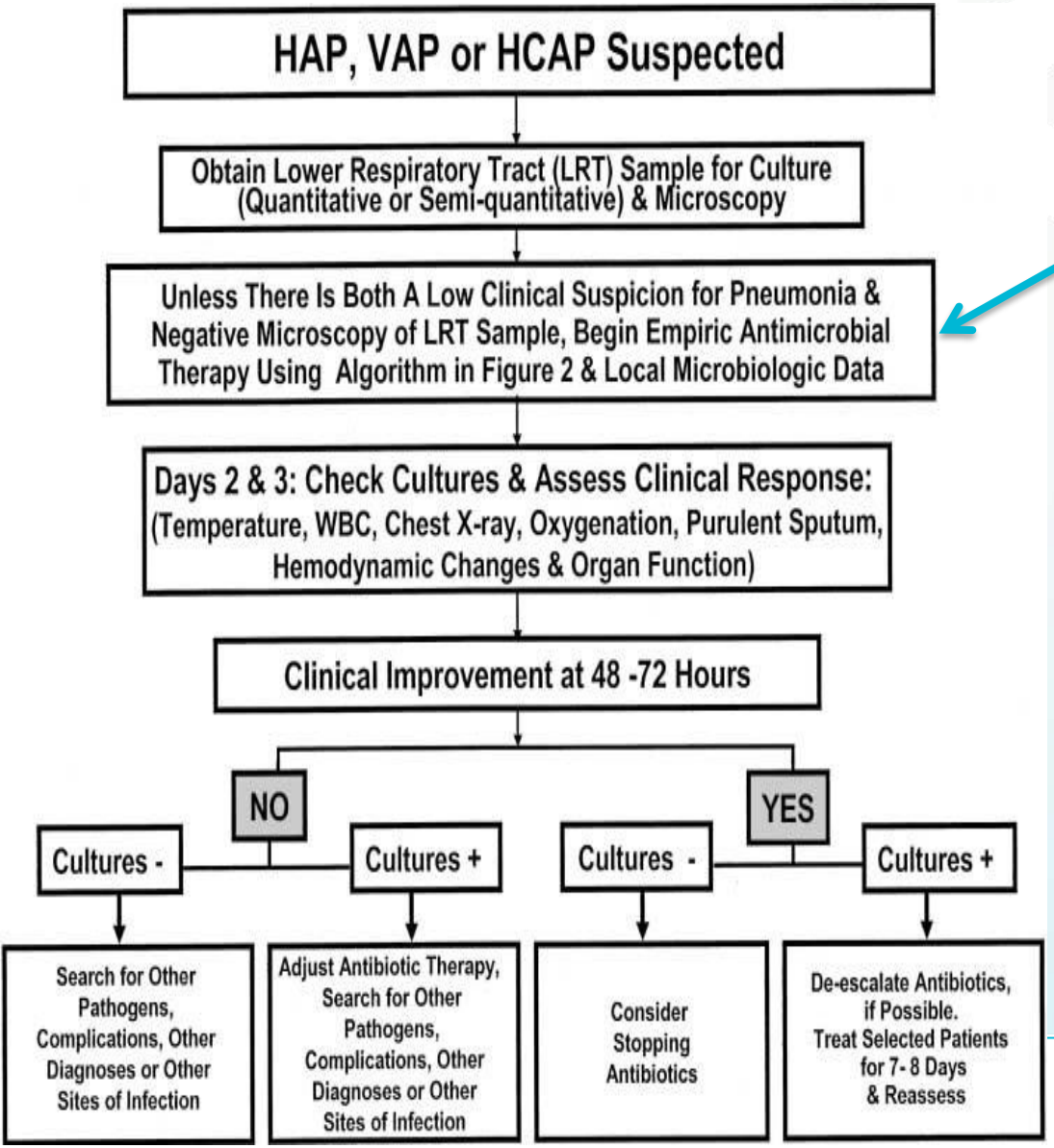
1. Two segments to 24hour window

- Finding eligible patients who have not had >24 hours of antibiotics
  - Locating & identifying eligible patients
  - Approval to approach and enroll from clinical care team
  - Clinical care/guidelines to start antibiotics as soon as pneumonia expected
    - “IV bag hung is before chest x-ray is read”
  - Getting consent from legally authorized representative (LAR)
  - All labs/tests/procedures to confirm enrollment
- Randomization to start of study drug
  - Obtaining study drug from pharmacy

1. Potential solutions to 24 hour barrier

- Extend PAT >24 hours: allow a 12-18 hour timeframe after randomization to receive the first dose
- Identify patients ASAP:
  - Speak with clinical pharmacists after rounds
  - Automatic notifications to identify eligible patients
    - Emails when *Bronchoalveolar lavage* (*BAL*) ordered or cultures are ordered
    - Notifications programmed to eligibility criteria
- LAR consents via telephone/photos via text message

1. Potential solutions to 24 hour barrier



- Provide study drug in conjunction with clinical standard of care
- Enroll in randomized study before the pathogen is known and acknowledge that some will not be dropped or excluded from analysis

https://www.thoracic.org/statements/resources/mtpi/guide1-29.pdf

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2. Expand eligibility criteria

- Blanket exclusion of immune compromised tough
  - Include remote transplant patients > 5 years ago, if no rejection suspected in ≥ 6 months
- Include chronic ventilator patients
  - Acknowledged these are patients with different bugs
- Allowing renal impairment and dialysis patients when possible
- Allow patients to be enrolled who are in other studies (e.g. in observational or “blood draw” studies)

3. Buy-in from clinical providers

- Use proven sites
- Respected PI/Key opinion leader
- Enlist help of clinical pharmacists (sometimes as sub-I)
- Trial networks can be helpful (ARDSNet mentioned)
- Experienced study coordinators

4. Diagnosis of HABP, VABP, or nosocomial infection

- Related to clinical care team buy-in
- Difficulty obtaining buy-in when hospital acquired infections involve penalties
  - "My patient doesn't have *THAT*"
- Suggestions:
  - Don't use HABP, VABP, or nosocomial in study title
  - Conduct as "Screening study" that shifts to clinical trial if the person develops an infection

Additional Coordinator Feedback

- Separate trials for increasing enrollment and streamlining trial operations
- Collecting less data would reduce burden
- Enrollment is the major issue
  - “Less data doesn’t help of there are no patients enrolled”
- Create simple checklists for pre-screening/screening to get true data on screen fails
- Compensate sites for pre-screening and screening efforts - % coordinator effort