CTTI HABP/VABP Pilot Study
Preliminary Planning

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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

Program

Antibacterial Drug Development (ABDD)

Projects

- Unmet Need in multi-resistant bacterial infections
- Hospital Acquired and Ventilator Associated Bacterial Pneumonia (HABP/VABP)
- Pediatric trials

Design Challenges & Barriers
- Parent/Caregiver Perceptions
- Site Networks
- Data collection
- Protocol elements
- Patient focus groups
- Expert Meetings and Think Tanks
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
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 $\leq 24$ hrs

- Prior Antibiotic A
- Prior Antibiotic B

Randomization
1. Two segments to 24 hour 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

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 if 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