Enhancing Clinical Trial Enrollment Strategies: Early consent and enrollment

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CTTI Strengths

Public-private partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials
CTTI Antibacterial Drug Development (ABDD)

PROJECTS:

- Streamlining HABP/VABP Trials
- Protocol Elements
- Data Collection
- Site Networks
- Pediatric Trials
- Use & Acceptance of Streamlined Development
- Statistical Issues
- HABP/VABP Studies
- HABP/VABP Risk Factors
- Formative Research
- Early Enrollment Clinical Trial

9/2012 – FDA Engaged CTTI in ABDD

9/2014 – CTTI R18 grant included demonstration studies

HABP/VABP = hospital-acquired and ventilator-associated bacterial pneumonia
Why CTTI Started Thinking About Early Consent

- Urgent need for new antibiotics to treat HABP/VABP
  - Increasing rates of infection with multidrug-resistant pathogens
  - Demonstrated limitations of many available antibiotics

- Few ongoing or planned HABP/VABP trials
  - Average enrollment estimates of 1-2 patients/site/year\(^1\)
  - Estimated costs of almost $90,000 per patient enrolled\(^2\)

CTTI Streamlining HABP/VABP Trials Projects

- Included \textit{patient} recommendation to approach patients at risk of developing HABP/VABP earlier - ideally before critically ill - to discuss preferences related to research participation\(^3\)

Request for CTTI to conduct a demonstration study that could lead to improved HABP/VABP clinical trial feasibility

\(^1\)Barriere SL. CID 2010;51(Supplement 1):S4-S9. \(^2\)Stergiopoulos et al, CID 2018;66(1):72-80. \(^3\)Knirsch et al, CID 2016;63(S2):s29-36
Common Theme: Prior Antibiotic Therapy

Theme from Streamlining HABP/VABP work, multi-stakeholder project team discussions, and focus group with experienced study coordinators.

Challenge to enrollment – the need to exclude patients who have received > 24 hours of prior effective antibiotic therapy (PAT).

Even when patient identified before 24 hours of PAT, difficult to complete all enrollment procedures before window closes:
- Consent
- Labs
- Study drug availability
Can Enrollment into HABP/VABP trials be Improved by Beginning Consent Before the Patient Develops HABP/VABP?

Early Enrollment = Approach AND consent patients at high risk for developing pneumonia
- Before 24 hours of antibiotics
- Many before pneumonia symptoms develop

Planned to conduct a study comparing: Early Enrollment vs. Standard Enrollment
Early Enrollment: Acceptable & Feasible?

Which patients have highest likelihood of developing pneumonia?

What concerns would IRBs have about the early enrollment strategy?

How burdensome would this be to trial investigators and study coordinators?

How would patients and caregivers feel about enrolling in a clinical trial before they have the condition under investigation?

What do patients want to know about this approach so they can make an informed decision about participating?

Preliminary Research –

- Risk Factors for HABP/VABP Study and Formative Research
Determining population to approach early: Risk Factors for HABP/VABP Study

Population: ICU patients hospitalized ≥48 hours
- requiring invasive or non-invasive ventilation – “follow the oxygen”
- and/or receiving antibiotics for suspected pneumonia

> 7500 total patients enrolled

<table>
<thead>
<tr>
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<th>Enrollment</th>
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<tbody>
<tr>
<td>U.S. Adult: 28 Sites</td>
<td>7000</td>
</tr>
<tr>
<td>EU Adult: 7 Sites</td>
<td>5000</td>
</tr>
<tr>
<td>U.S. Pediatric: 9 Sites</td>
<td>3000</td>
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U.S. Adult High-Risk Population*

- High-risk = >12 hours of treatment with invasive or non-invasive mechanical ventilation, or high levels of supplemental oxygen within the past 7 days (4,632)

- Treated (1,464)

- 11.6% met HABP/VABP criteria from FDA Draft Guidance (569)

- HABP/VABP remains common in critically ill patients

*Study lasted approx. 8 months
HABP/VABP Risk Associations

- Multivariable logistic model developed

- Key patient characteristics and treatment exposures associated with increased risk of HABP/VABP development
  - ICU admission diagnosis
  - receipt of enteral nutrition
  - documented aspiration risk
  - admission source
  - receipt of systemic antibacterials in last 90 days

- Combining high-risk criteria plus associated factors above could be used to prospectively identify patients for an early enrollment strategy
Early Enrollment: Acceptable & Feasible?

- Which patients have highest likelihood of developing pneumonia?
- What concerns would IRBs have about the early enrollment strategy?
- How burdensome would this be to trial investigators and study coordinators?
- How would patients and caregivers feel about enrolling in a clinical trial before they have the condition under investigation?
- What do patients want to know about this approach so they can make an informed decision about participating?

Preliminary Research –
- Risk Factors for HABP/VABP Study and Formative Research
Formative Research: Modified Delphi Approach

**In-depth Interviews** (n=52)
- Acceptability of and preferences for components of an early enrollment clinical trial
- Key topics to explain in informed consent

**Online Survey #1** (n=41)
- Importance of sentences used to describe key concepts in consent text; suggested revisions

**Online Survey #2** (n=40)
- Overall agreement on language to include in consent text

*Participants – patients, caregivers, investigators, study coordinators, IRB members*
Results: patients and legally authorized representatives

An early consent and enrollment strategy was overwhelmingly accepted

- Found it acceptable to monitor patients’ medical records before they acquire pneumonia
- Can understand consent information before diagnosed with condition under investigation
- Would participate in an early enrollment trial using approved antibiotics.
Results: investigator/IRB

- May improve the efficiency of clinical trial conduct for HABP/VABP and other conditions
  - Most site personnel believed the EE strategy would improve recruitment
- None of the IRB members raised concerns about the early enrollment strategy

Honestly, this sounds fairly straightforward. It doesn't sound like it’s going to cause a great deal of concern….

So, there would have to be a discussion of the possibility, the percentage, the chance that that might happen. So, I don't see this as being an unusually concerning study.
Key Topics for Early Informed Consent

- Participants identified topics for which they would want detailed information in a consent form:
  - Rationale for the early consent and enrollment strategy
  - Non-inferiority study design
  - Reassurances—i.e., what will happen if the study drug appears not to be working

- Participants were asked how they would explain that information

- Surveys were then utilized to develop and obtain agreement on text to be included in informed consent

- We then finalized text for describing each of the topics above in a consent form
For additional details about acceptability of early enrollment strategy:

Survey data and final consent text will be submitted by the end of the year for publication
Other Potential Applications of the Early Consent Approach

Conditions for which future eligibility is predictable and/or time is of the essence

- Other ICU-acquired infections or infections that tend to recur
  - UTI, *C. difficile*, bloodstream infections
- Chronic conditions with frequent exacerbations
  - Sickle cell disease with recurrent vaso-occlusive crises
  - Bleeding disorders
- Conditions in which patients have recurrent episodes of decisional incapacity
  - Hepatic encephalopathy in patients with liver disease
  - Patient with COPD or asthma with frequent presentations with respiratory failure
  - Psychiatric disease
Conclusion and Next Steps

An early consent and enrollment strategy
- May improve the efficiency of clinical trial conduct for HABP/VABP and other conditions
- Was overwhelmingly accepted by key stakeholders

Prospectively identifying patients requiring high levels of respiratory support plus additional risk factors may assist in identifying patients for an early enrollment strategy

Developing Tools to assist HABP/VABP trial planning:
- Template consent language for early enrollment
- Publicly sharing risk factor study data
- Trial planning tool – view remaining population numbers by modifying eligibility criteria
THANK YOU.

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