CLINICAL TRIALS TRANSFORMATION INITIATIVE

*November 19, 2017*

# Enhancing Clinical Trial Enrollment Strategies: Early consent and enrollment

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# Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
- The presenter is an Employee of Duke University. Salary support comes from pooled membership fees of the Clinical Trials Transformation Initiative and from FDA Cooperative agreement.

# CTTI Strengths

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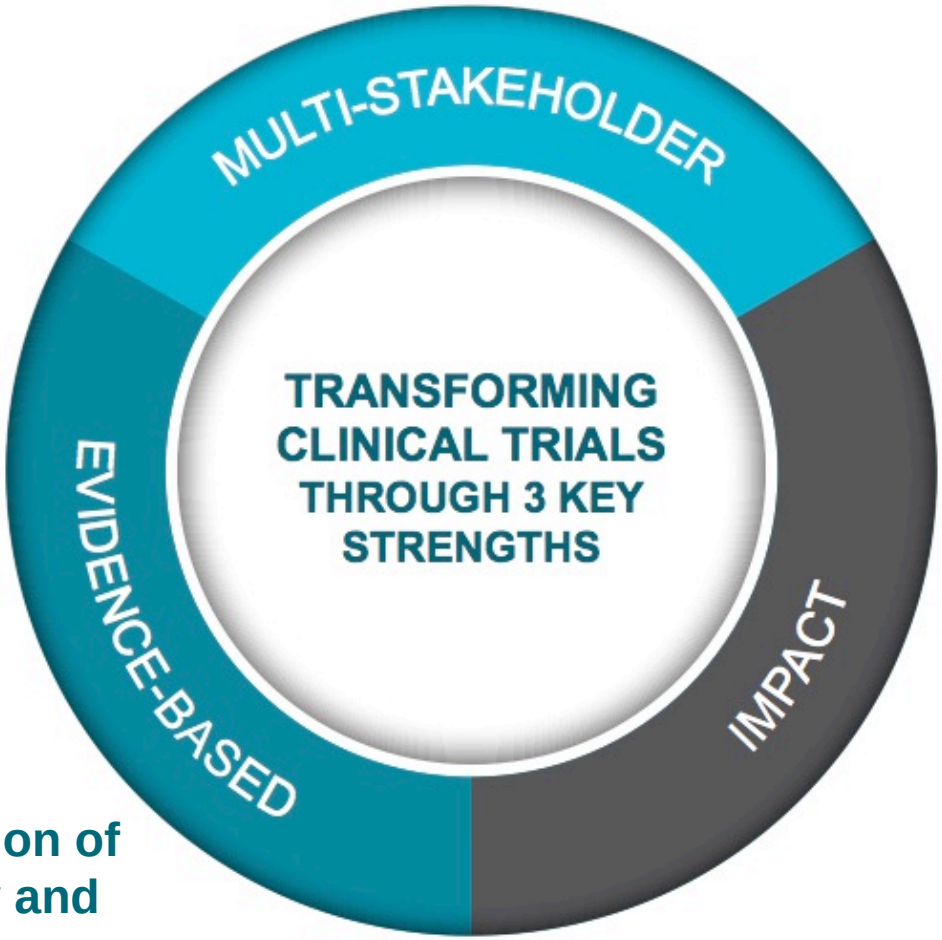


Public-private partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

**MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials**

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# CTTI Activities

## Quality

- **Quality by Design**
- Informing ICH E6 Renovation
- Diversity
- Analysis of ClinicalTrials.gov
- Recruitment
- Planning for Pregnancy Testing
- State of Clinical Trials Report
- Monitoring

## Patient Engagement

- **Patient Groups & Clinical Trials**
- Patient Engagement Collaborative

## Investigators & Sites

- Investigator Community
- Investigator Qualification
- Site Metrics

## Mobile Clinical Trials

- Novel Endpoints
- Mobile Technologies
- Decentralized Clinical Trials
- Engaging Patients and Sites

## Novel Clinical Trial Designs

- Real-World Data
- Registry Trials
- Master Protocols
- **Antibacterial Drug Development**
- Large Simple Trials
- Using FDA Sentinel for Trials

## Ethics & Human Research Protection

- **Single IRB**
- Data Monitoring Committees
- Informed Consent
- Safety Reporting

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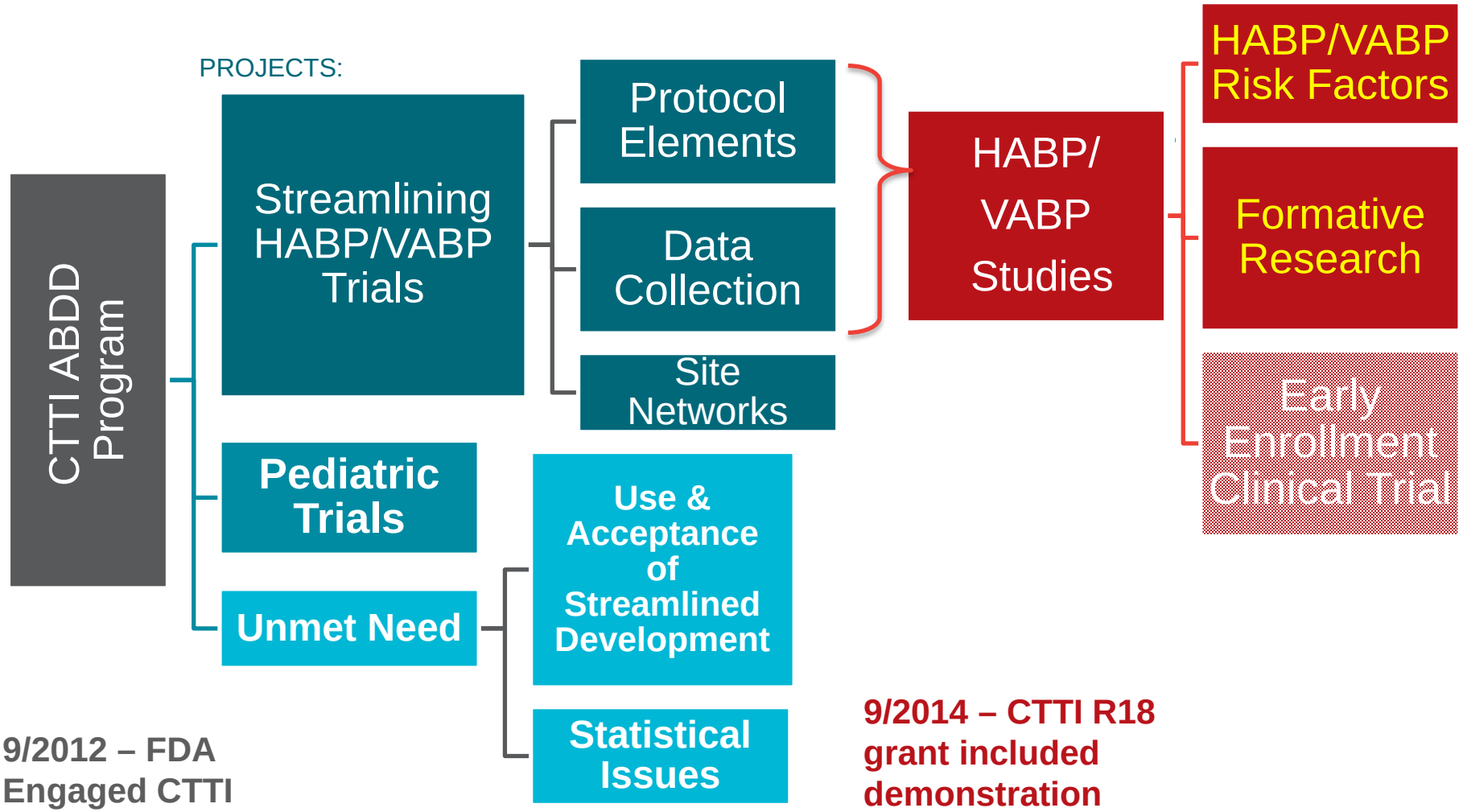
# CTTI Antibacterial Drug Development (ABDD)




**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 **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.*

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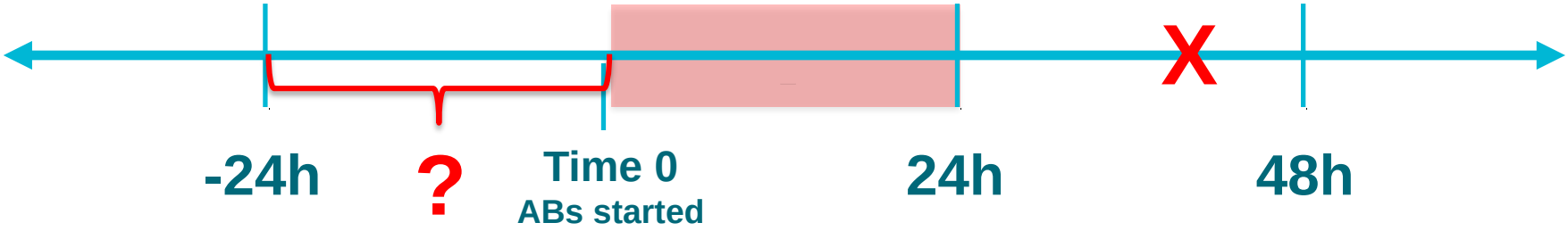
# Common Theme: Prior Antibiotic Therapy

- 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

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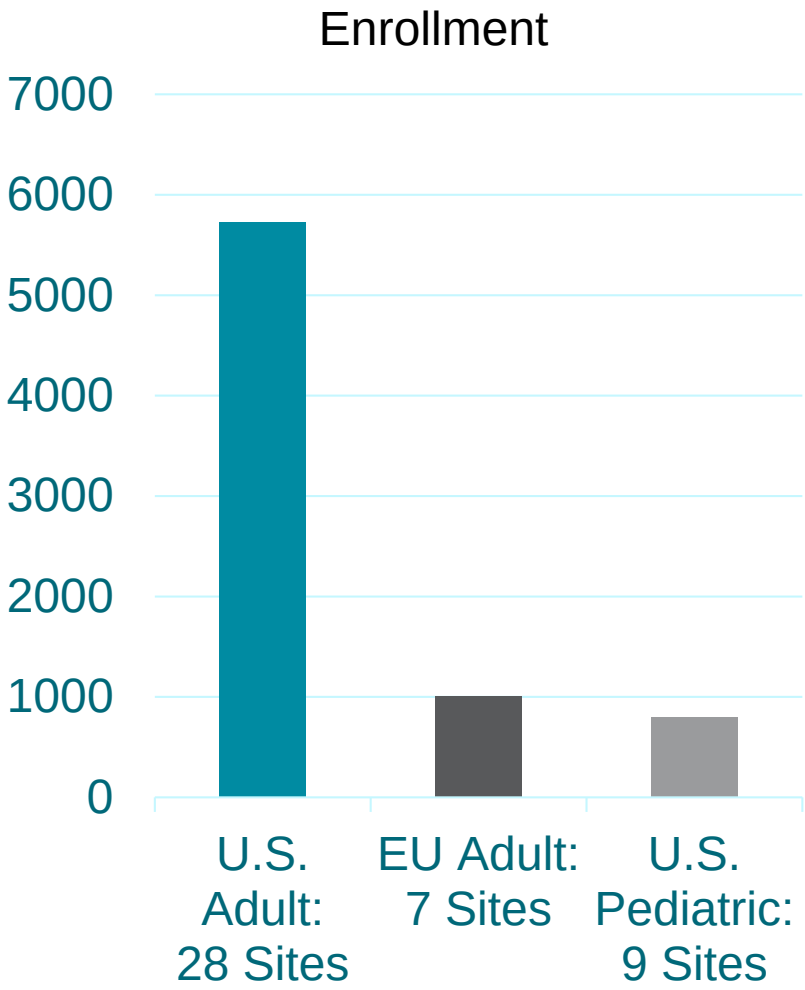
# Determining population to approach early: Risk Factors for HABP/VABP Study

- 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

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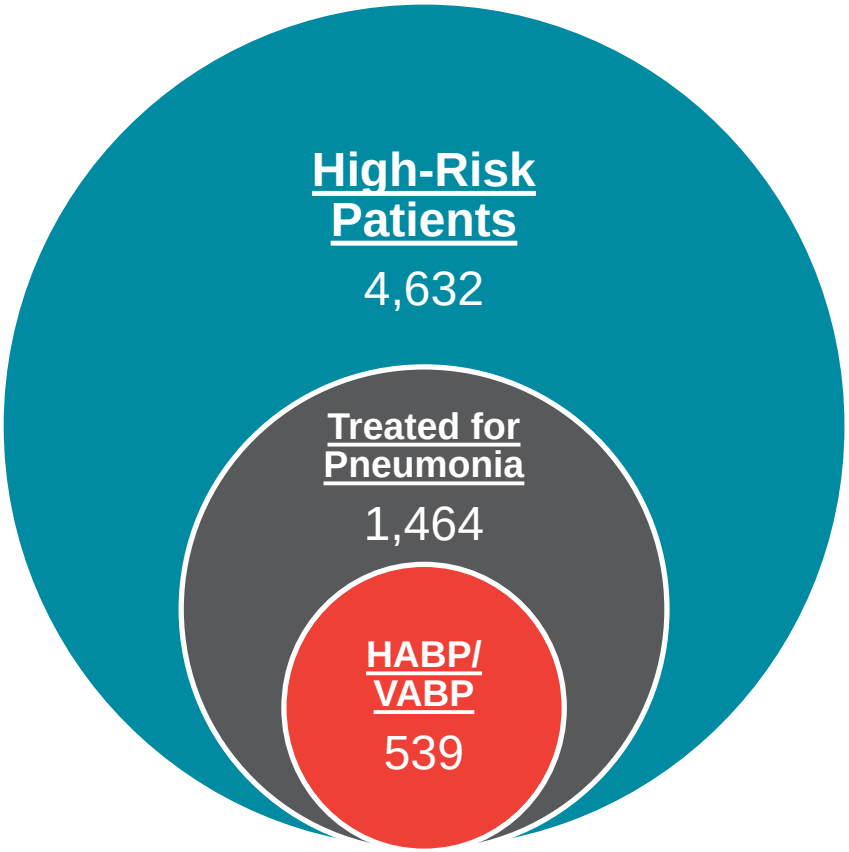
# U.S. Adult High-Risk Population*




- 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

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# 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?

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## Preliminary Research –

- Risk Factors for HABP/VABP Study and **Formative Research**

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# 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

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# 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.*

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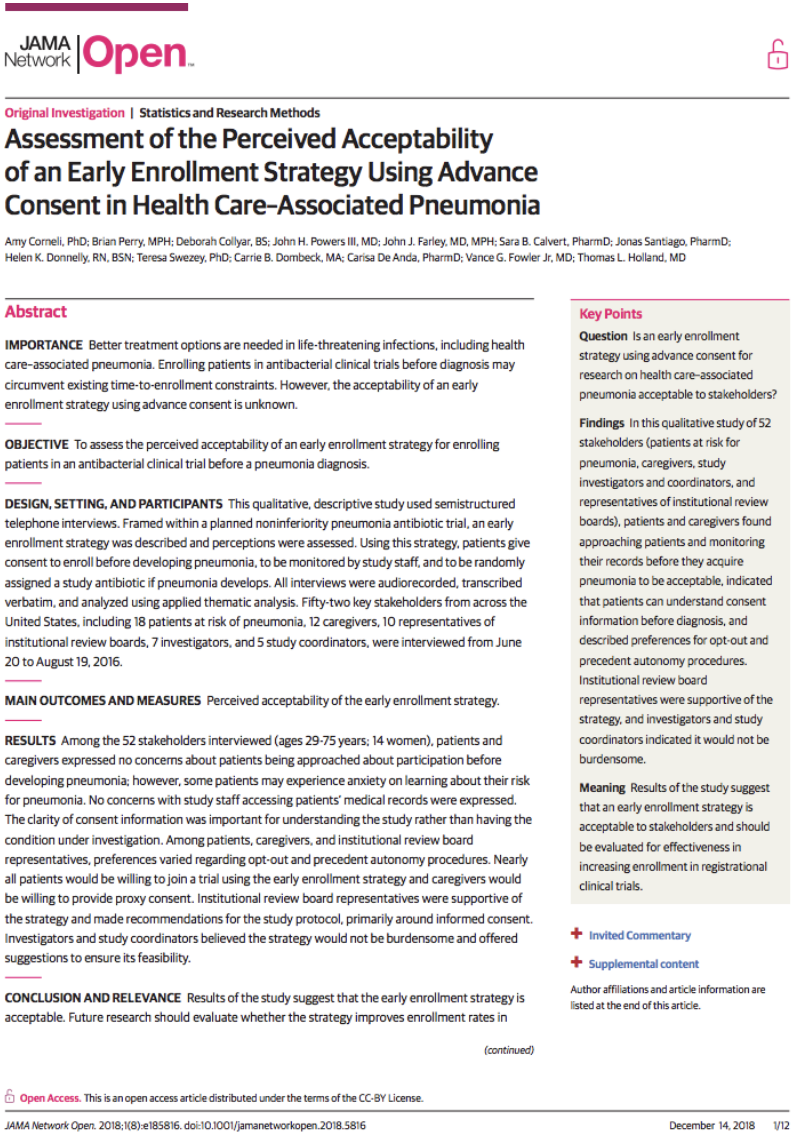
# Key Topics for Early Informed Consent

- Participants identified topics for which they would want wanted 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



JAMA Network Open

Original Investigation | Statistics and Research Methods

# Assessment of the Perceived Acceptability of an Early Enrollment Strategy Using Advance Consent in Health Care–Associated Pneumonia

Amy Corneli, PhD; Brian Perry, MPH; Deborah Collyar, BS; John H. Powers III, MD; John J. Farley, MD, MPH; Sara B. Calvert, PharmD; Jonas Santiago, PharmD; Helen K. Donnelly, RN, BSN; Teresa Swezey, PhD; Carrie B. Dombeck, MA; Carisa De Anda, PharmD; Vance G. Fowler Jr, MD; Thomas L. Holland, MD

## Abstract

**IMPORTANCE** Better treatment options are needed in life-threatening infections, including health care–associated pneumonia. Enrolling patients in antibacterial clinical trials before diagnosis may circumvent existing time-to-enrollment constraints. However, the acceptability of an early enrollment strategy using advance consent is unknown.

**OBJECTIVE** To assess the perceived acceptability of an early enrollment strategy for enrolling patients in an antibacterial clinical trial before a pneumonia diagnosis.

**DESIGN, SETTING, AND PARTICIPANTS** This qualitative, descriptive study used semistructured telephone interviews. Framed within a planned noninferiority pneumonia antibiotic trial, an early enrollment strategy was described and perceptions were assessed. Using this strategy, patients give consent to enroll before developing pneumonia, to be monitored by study staff, and to be randomly assigned a study antibiotic if pneumonia develops. All interviews were audiorecorded, transcribed verbatim, and analyzed using applied thematic analysis. Fifty-two key stakeholders from across the United States, including 18 patients at risk of pneumonia, 12 caregivers, 10 representatives of institutional review boards, 7 investigators, and 5 study coordinators, were interviewed from June 20 to August 19, 2016.

**MAIN OUTCOMES AND MEASURES** Perceived acceptability of the early enrollment strategy.

**RESULTS** Among the 52 stakeholders interviewed (ages 29-75 years; 14 women), patients and caregivers expressed no concerns about patients being approached about participation before developing pneumonia; however, some patients may experience anxiety on learning about their risk for pneumonia. No concerns with study staff accessing patients' medical records were expressed. The clarity of consent information was important for understanding the study rather than having the condition under investigation. Among patients, caregivers, and institutional review board representatives, preferences varied regarding opt-out and precedent autonomy procedures. Nearly all patients would be willing to join a trial using the early enrollment strategy and caregivers would be willing to provide proxy consent. Institutional review board representatives were supportive of the strategy and made recommendations for the study protocol, primarily around informed consent. Investigators and study coordinators believed the strategy would not be burdensome and offered suggestions to ensure its feasibility.

**CONCLUSION AND RELEVANCE** Results of the study suggest that the early enrollment strategy is acceptable. Future research should evaluate whether the strategy improves enrollment rates in

*(continued)*

## Key Points

**Question** Is an early enrollment strategy using advance consent for research on health care–associated pneumonia acceptable to stakeholders?

**Findings** In this qualitative study of 52 stakeholders (patients at risk for pneumonia, caregivers, study investigators and coordinators, and representatives of institutional review boards), patients and caregivers found approaching patients and monitoring their records before they acquire pneumonia to be acceptable, indicated that patients can understand consent information before diagnosis, and described preferences for opt-out and precedent autonomy procedures. Institutional review board representatives were supportive of the strategy, and investigators and study coordinators indicated it would not be burdensome.

**Meaning** Results of the study suggest that an early enrollment strategy is acceptable to stakeholders and should be evaluated for effectiveness in increasing enrollment in registrational clinical trials.

+ Invited Commentary
+ Supplemental content

Author affiliations and article information are listed at the end of this article.





- For additional details about acceptability of early enrollment strategy:

  Corneli A, et al.

  JAMA Netw Open. 2018;1(8):e185816. doi:10.1001/jamanetworkopen.2018.5816

- Survey data and final consent text will be submitted by the end of the year for publication

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# 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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