



CLINICAL
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INITIATIVE

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Enhancing Clinical Trial Enrollment Strategies:

Early consent and enrollment

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Disclaimer

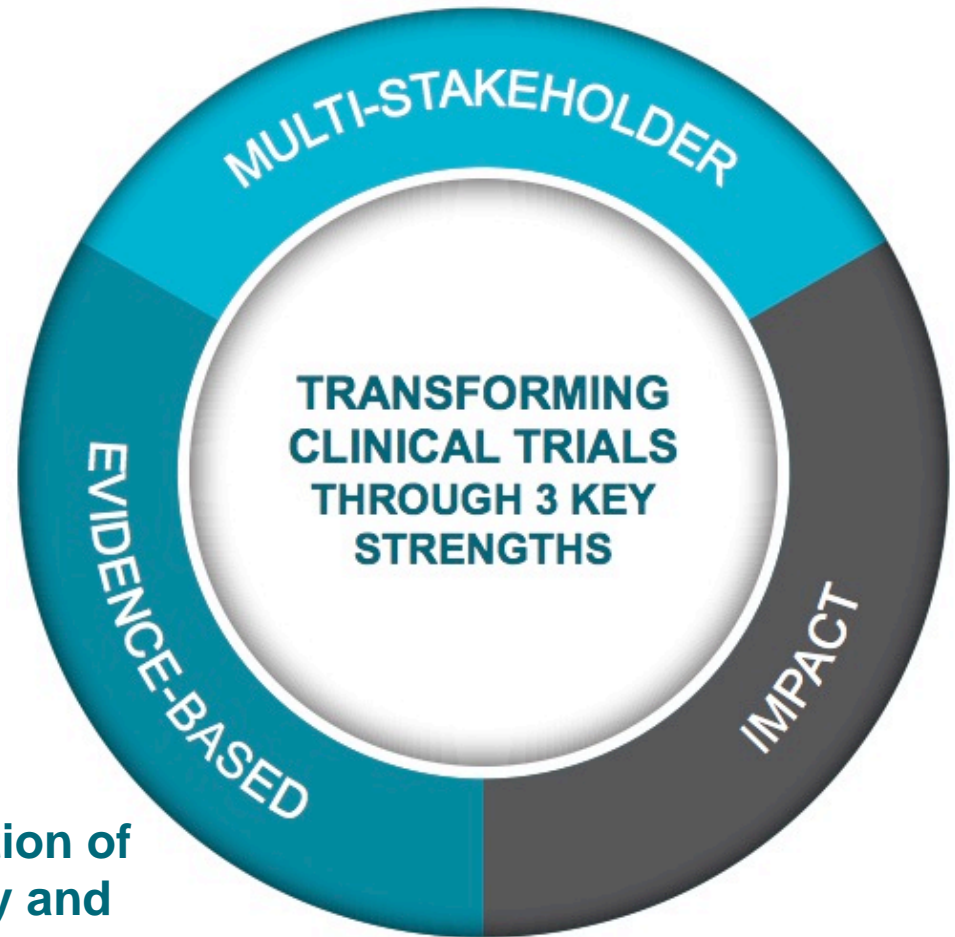
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CTTI Strengths



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 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

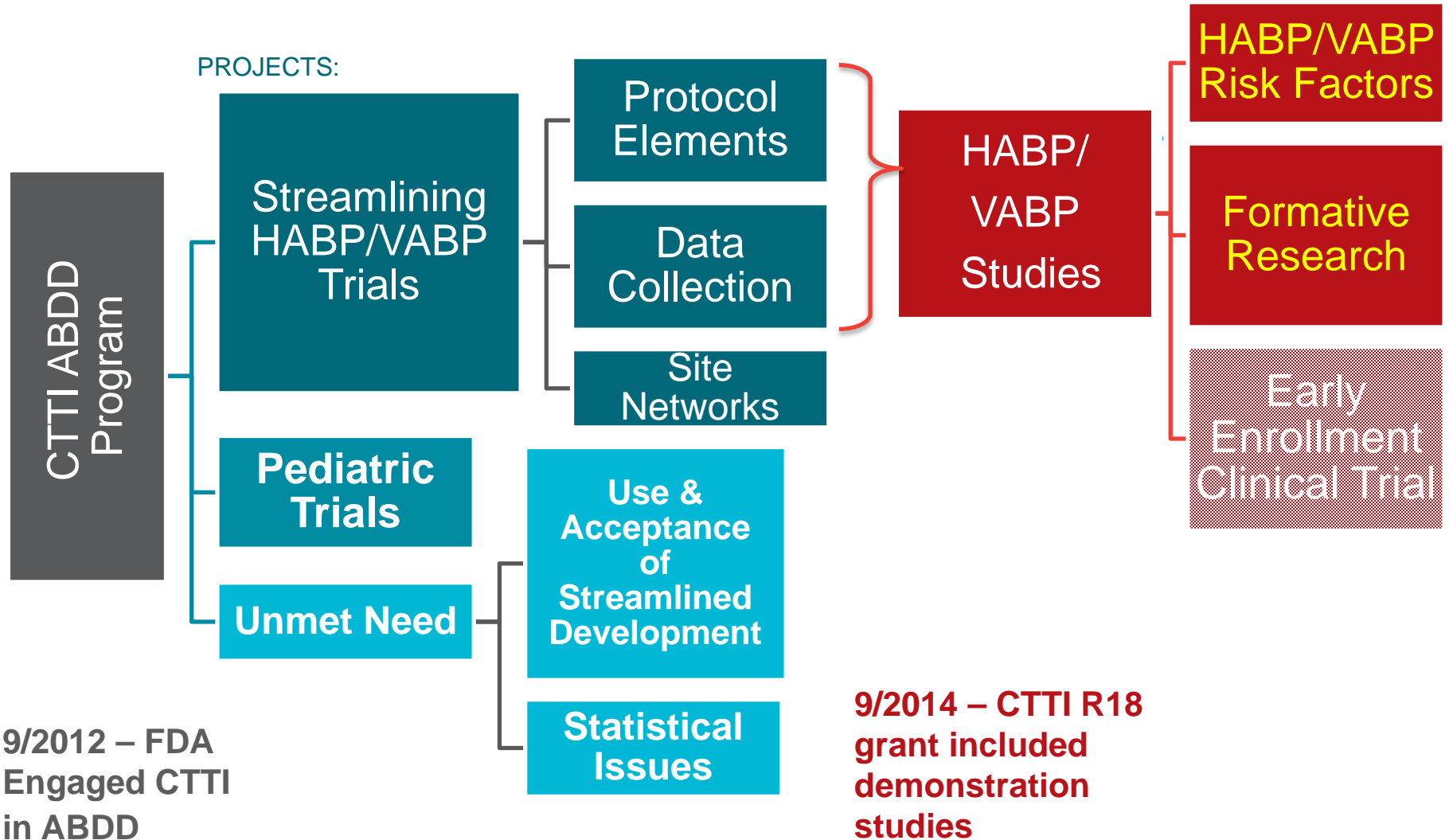
Novel Clinical Trial Designs

- ▶ 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

CTTI Antibacterial Drug Development (ABDD)



HABP/VABP = hospital-acquired and ventilator-associated bacterial pneumonia

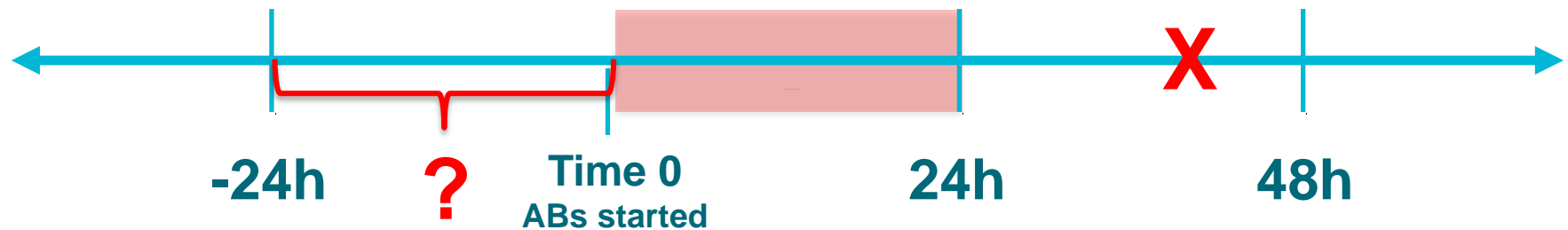
Why CTTI Started Thinking About Early Consent

- 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/year¹
 - Estimated costs of almost \$90,000 per patient enrolled²
- 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 participation³
- Request for CTTI to conduct a demonstration study that could lead to improved HABP/VABP clinical trial feasibility

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?

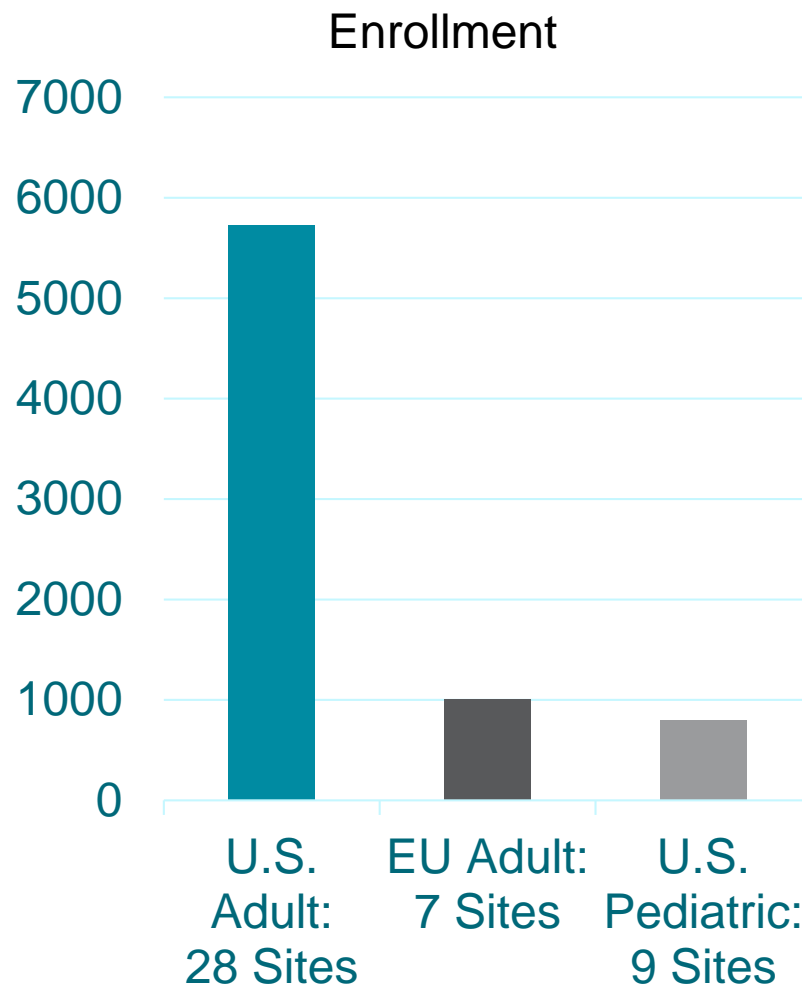
Preliminary Research –

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

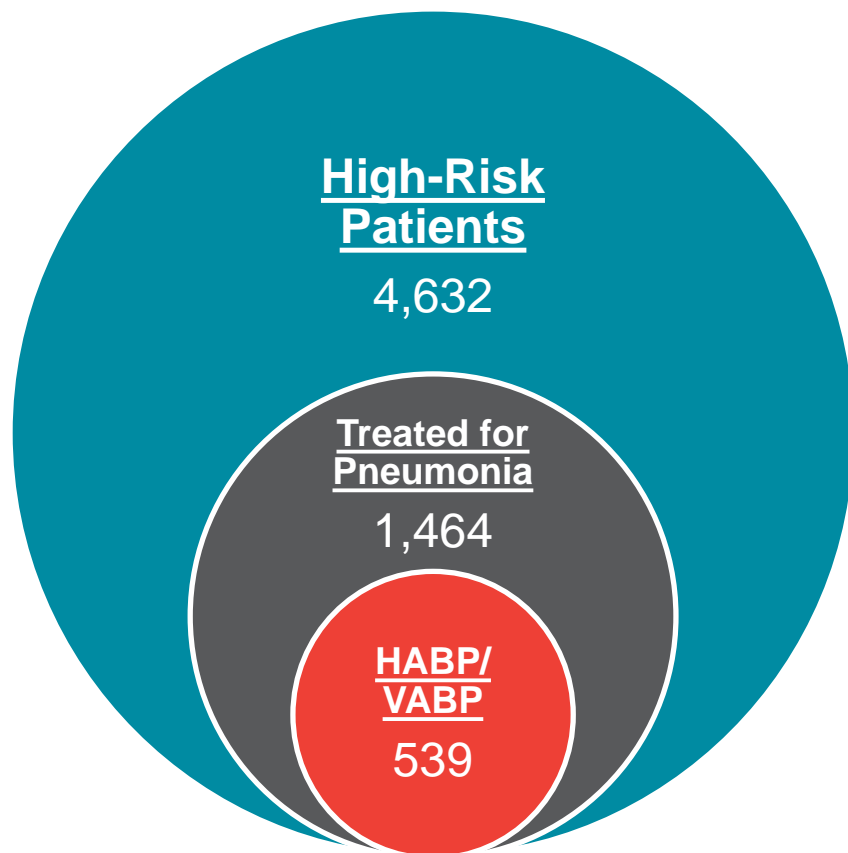
Determining population to approach early: Risk Factors for HABP/VABP Study

- 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



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**

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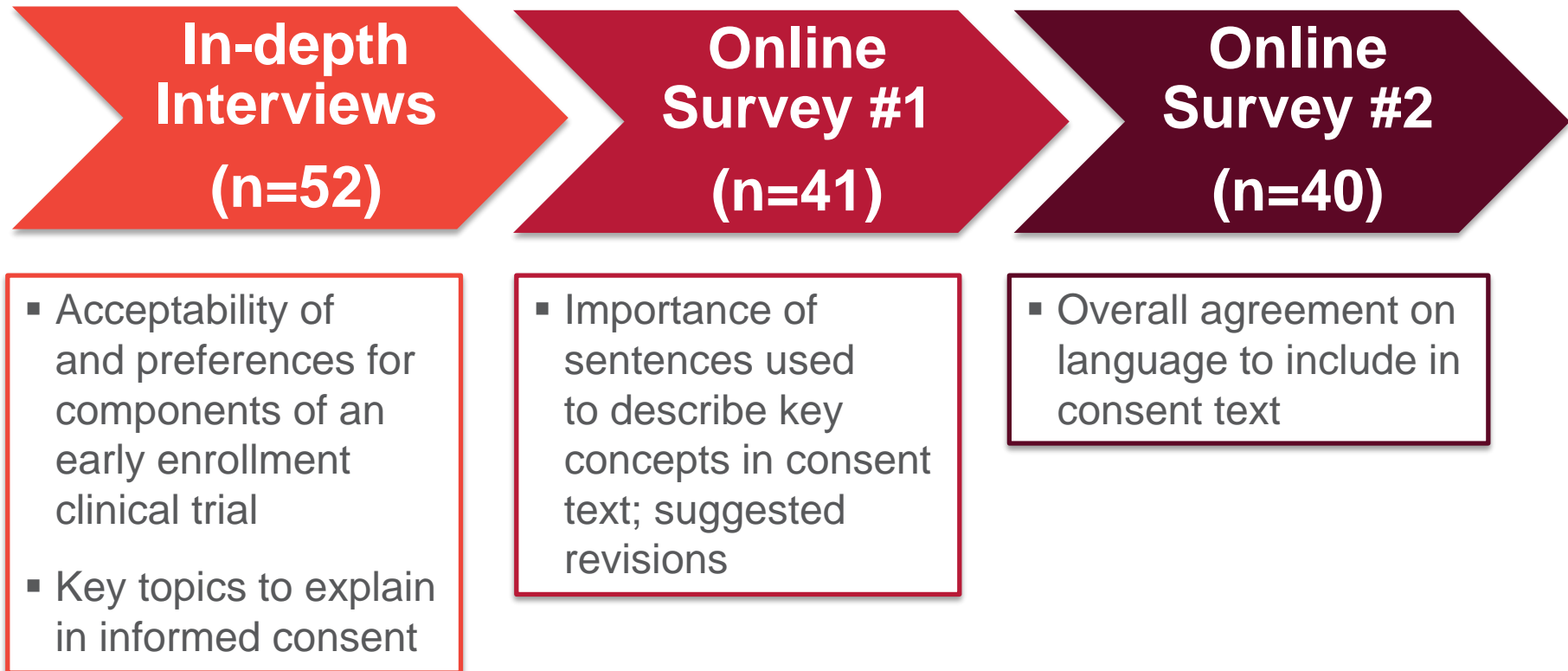
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Preliminary Research –

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Formative Research: Modified Delphi Approach



*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 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**



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 registration 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

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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www.ctti-clinicaltrials.org