CTTI History and Methodology
ABDD Program History

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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Clinical trials in crisis

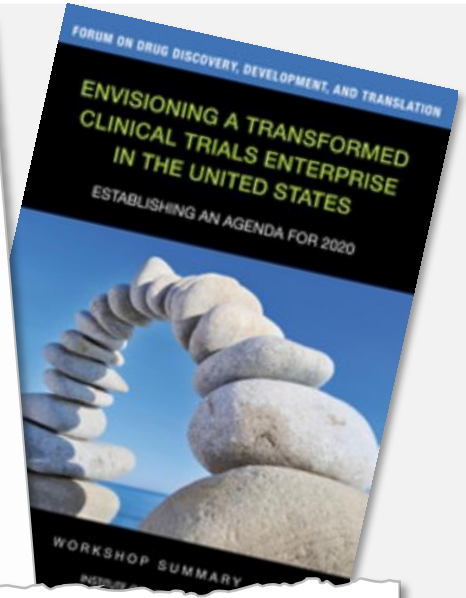
REPORT TO THE PRESIDENT

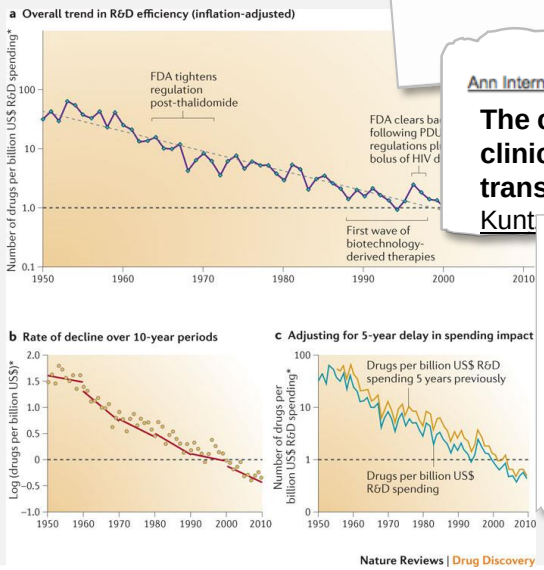
TRANSFORMATION AND OPPORTUNITY: THE FUTURE OF THE U.S. RESEARCH ENTERPRISE

Executive Office of the President

President's Council of Advisors on Science and Technology

NOVEMBER 2012





Ann Intern Med. 2013 Jun 18;158(12):914-5. doi: 10.7326/0003-4819-158-12-201306180-00011.

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.

Kunt

Addressing This Need

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To identify and promote practices that will *increase the quality and efficiency* of clinical trials

Public-Private Partnership
Co-Founded by FDA and Duke
involving all stakeholders
70+ members

CTTI Membership

How CTTI Works

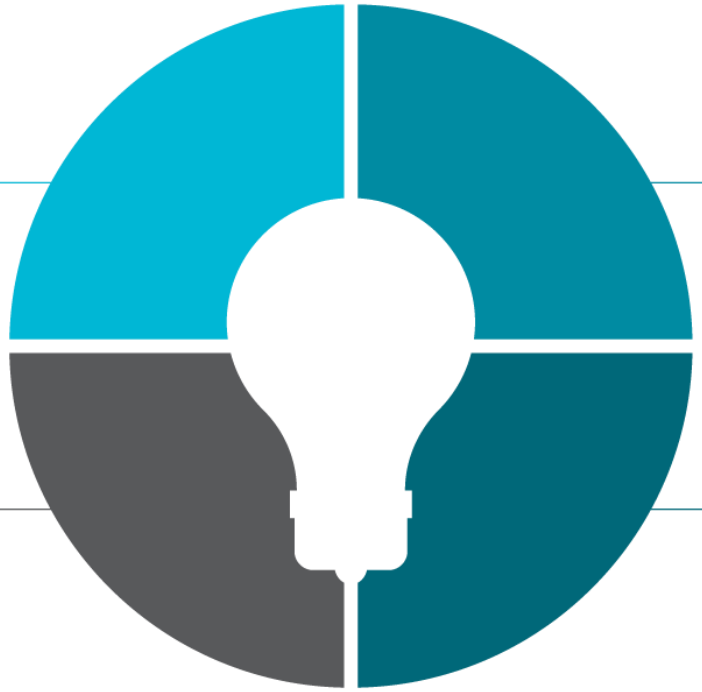
- ***Engage & value*** all stakeholders equally
- ***Understand incentives*** to maintain non-value added activities and have solutions that are mindful of those incentives
- ***Plant the seeds for change*** throughout all phases of a project
- ***Develop actionable***, evidence-based, consensus driven recommendations
- ***Create and share*** knowledge, tools & resources to facilitate change that improves clinical trials

CTTI Recommendations

- CTTI projects focus on streamlining and accelerating clinical trials, while ensuring the highest standards of quality and human subjects protection. We provide **actionable**, **evidence-based**, **consensus-driven** **recommendations designed to:**

Accelerate study start-up times & streamline protocols

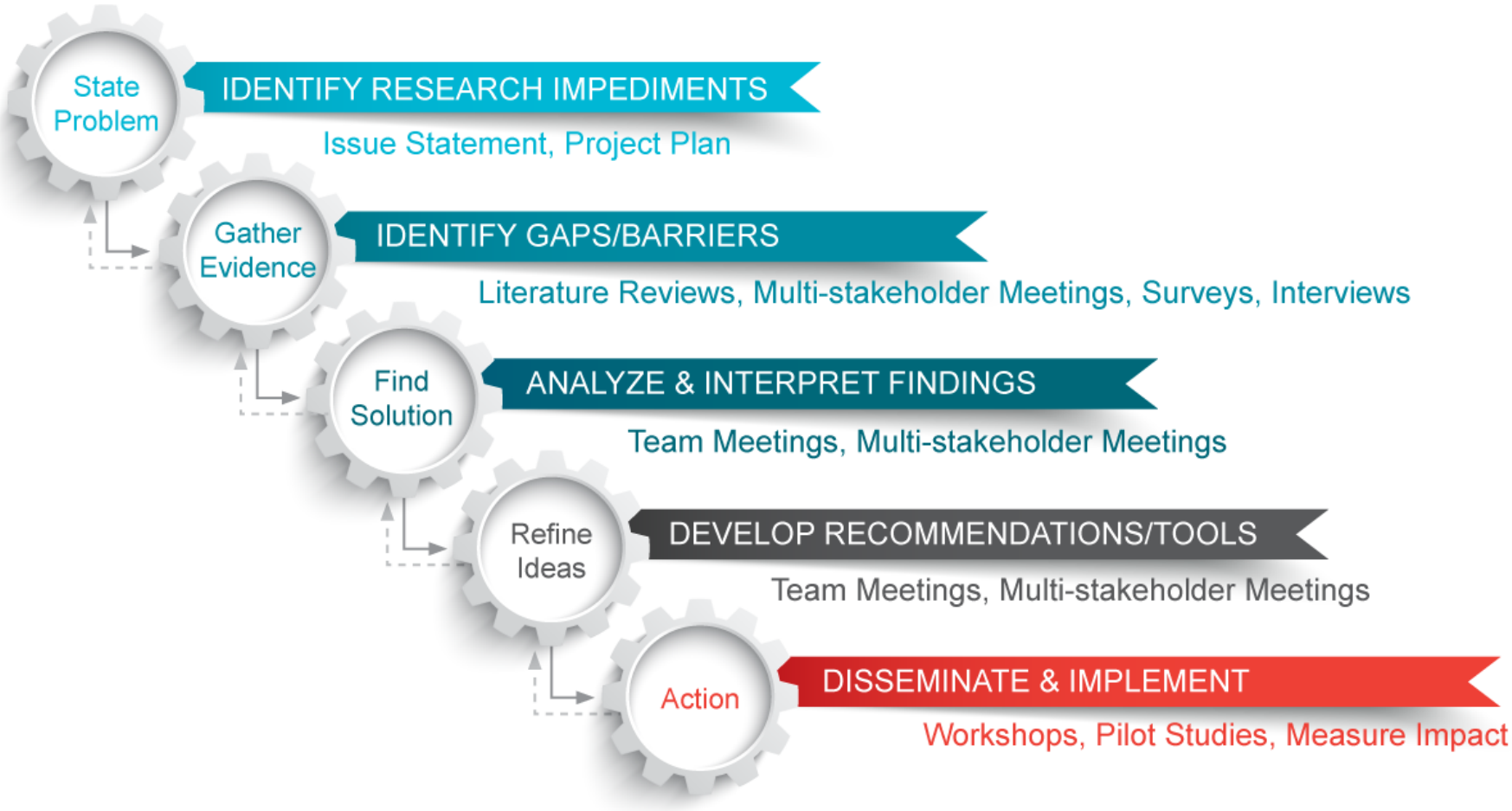
Enhance the quality of clinical trials without adding undue burden



Leverage new technologies to improve efficiency of clinical trials

Identify streamlined strategies to meet regulatory requirements

CTTI Methodology



Portfolio of CTTI Projects

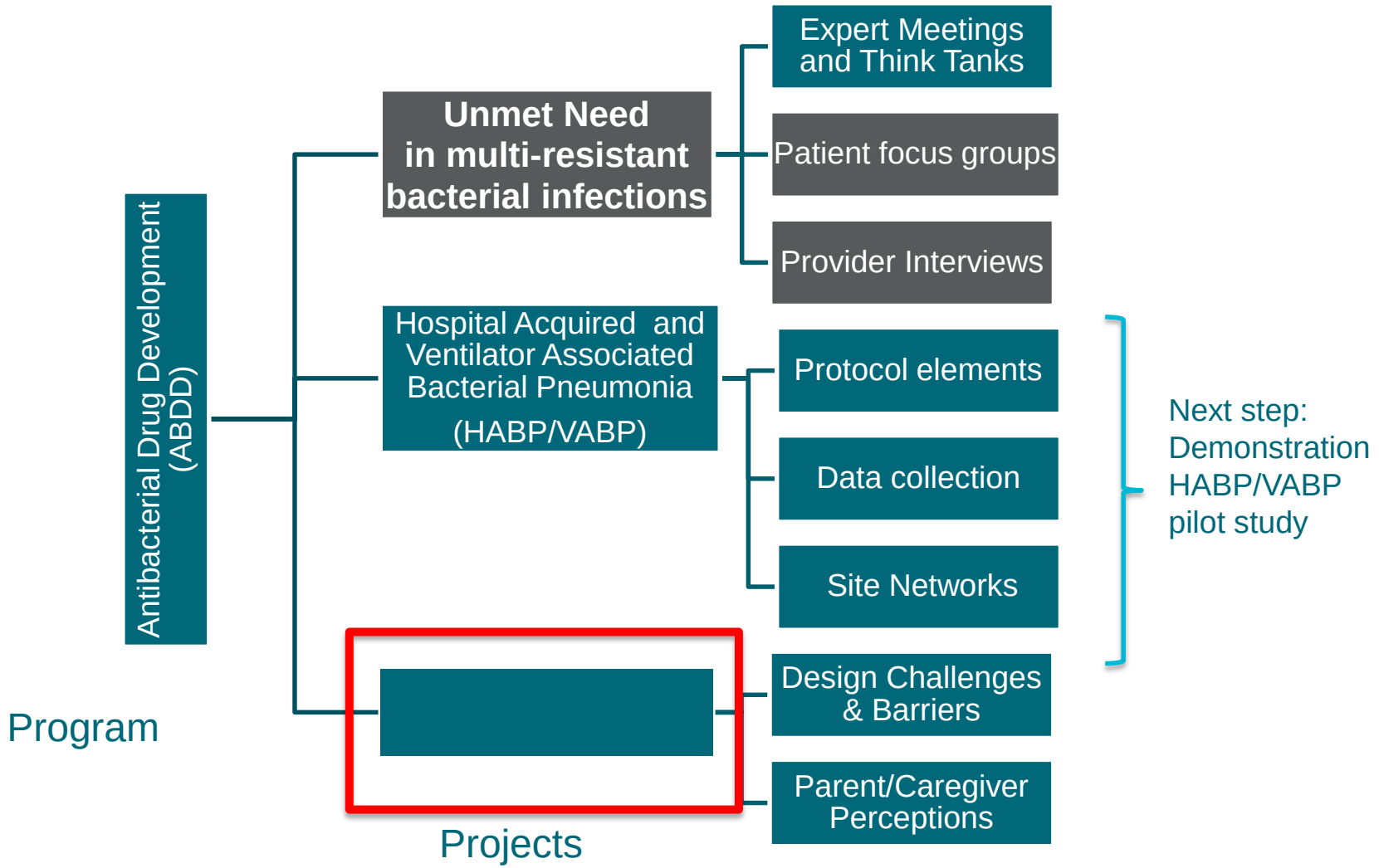
	Investigational plan	Study start up	Study conduct	Analysis and dissemination	Specialty areas
Completed projects	• Large simple trials • Uses of electronic data	• Central IRB • Site metrics	• Adverse event reporting • IND safety • Monitoring		• Long-term opioid data

CTTI Program: Antibacterial Drug Development (ABDD)

Background:

- Prevalence of antibacterial resistance continues to rise
- Pressing need for drug development in this area
- Resistant infections are a burden to society with serious consequences of morbidity and mortality and healthcare costs
- **In 2012, FDA established a task force and engaged CTTI and other organizations to tackle this issue on several fronts**

ABDD Program and Projects



Streamlining HABP/VABP

- Recommendations to be released in July
  - Simultaneous with a supplemental CID publication
    - Outlines the work done to date
    - Looks ahead to the pilot study
    - Reflects on the importance of site networks and PPPs to advance the development of new antibiotics

The Risk Factor Study

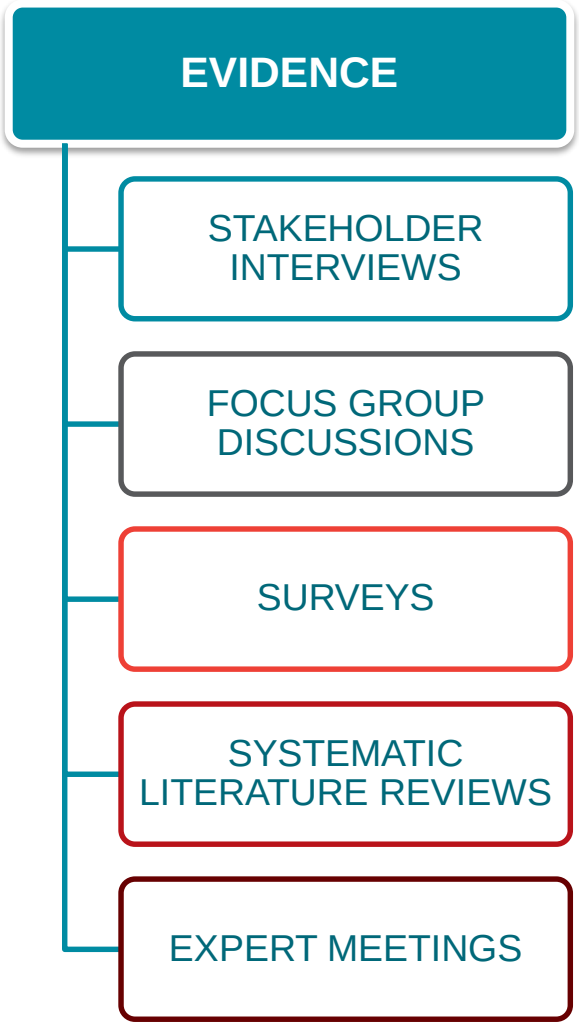
- Prospective, multicenter observational study
  - Define the pop at highest risk of HABP/VABP
  - 5 of 30 US adult sites enrolling
  - 45 total adult sites planned
    - 10-15 in the EU (thru COMBACTE/CLINnet)
  - 10 Peds sites from the PTN
  - >200 patients enrolled as of 4/4/16
- Part of planning for the Early Enrollment Pilot Study, which will incorporate many CTTI Recommendations, including Streamlining HABP/VABP and others

Early Enrollment Pilot Study

- Objective:
  - Conduct a study that will lead to improve HABP/VABP trial feasibility
- Design:
  - Randomized trial comparing early & traditional enrollment strategies
    - Approach & consent patients at high risk, many before they're symptomatic
- Rationale:
  - Identify & enroll high risk patients at the time they meet criteria for a diagnosis of HABP/VABP but before they have received >24^{O} of effective antibiotic therapy

Evidence guides the journey to solutions

- We use quantitative & qualitative research methods, selecting those best aligned with each project's objectives, to:
  - Identify/describe "what is going on" to gain a better understanding of a particular phenomenon
  - Move beyond individual views to a more complete and objective understanding of the disincentives and motivators for change
- Equipped with data, we then challenge assumptions, identify roadblocks, build tools and develop recommendations to change the way people think about and conduct clinical trials.



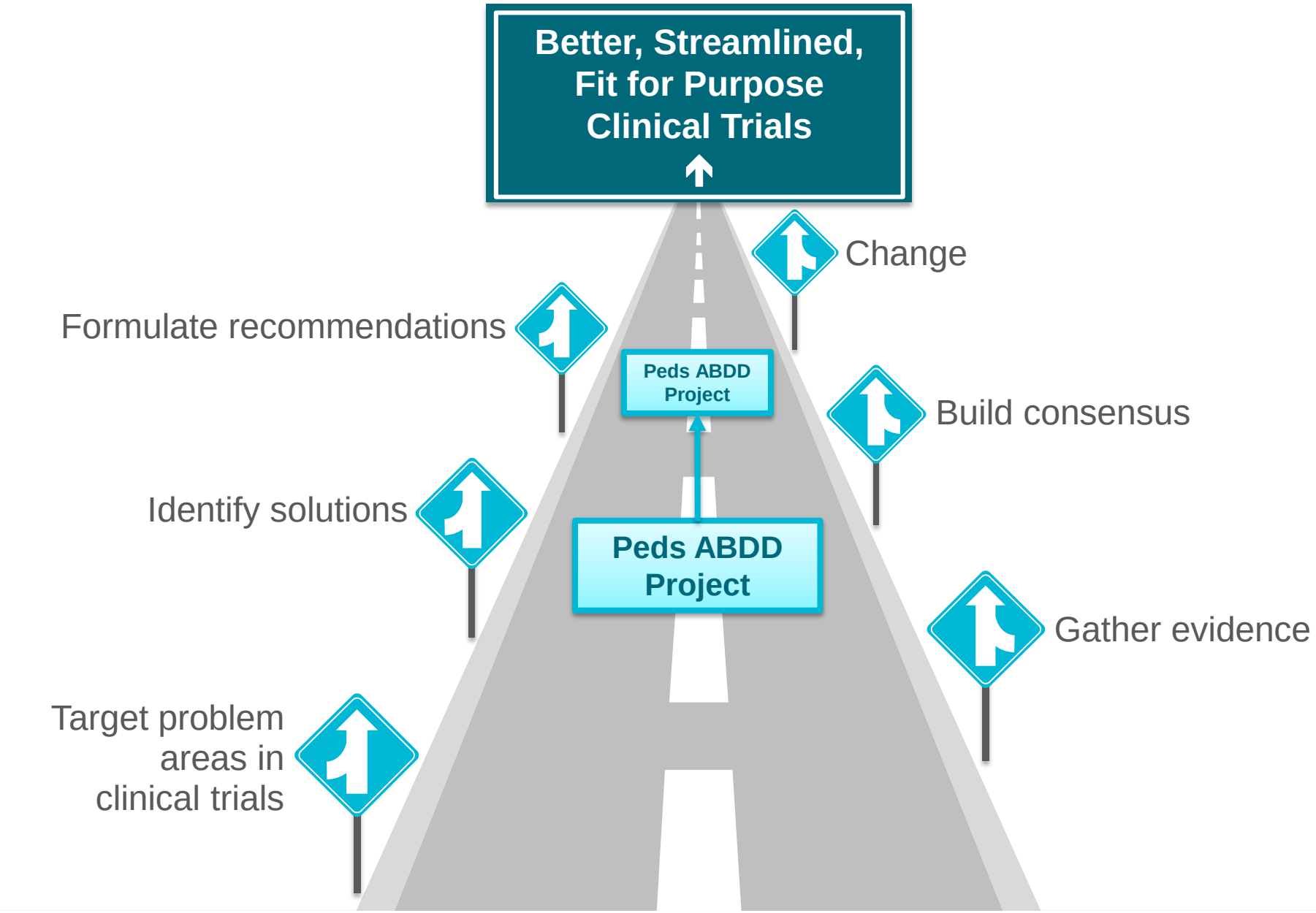
Team Members

- **Team Leaders:**
  - Danny Benjamin (Duke)
  - Sumathi Nambiar (FDA)
  - Gary Noel (J&J)

- **Team Members:**
  - John Bradley (UCSD)
  - John Farley (FDA)
  - Breck Gamel (Patient Advocate)
  - Ethan Hausman (FDA)
  - Hasan Jafri (MedImmune)
  - Brian Smith (Duke)
  - Edward Spindler (The Med Co)
  - Pamela Tenaerts (CTTI)
  - Rosemary Tiernan (FDA)
  - Chris Wheeler (FDA)
  - Kunyi Wu (FDA)
  - Kimberly Bergman (FDA) *(former)*
  - Raafat Bishai (AstraZeneca) *(former)*
  - Katherine Laessig (FDA) *(former)*
  - Jonas Santiago (FDA) *(former)*

Meeting Objectives

- Present findings
- Identify remaining gaps that may require further exploration
- Present and obtain feedback on draft considerations to improve the successful conduct and execution of pediatric antibacterial drug trials
- Develop initial consensus on the mechanisms for improving the conduct and execution of pediatric trials of antibacterial drugs


Better, Streamlined, Fit for Purpose Clinical Trials
Change
Formulate recommendations
Peds ABDD Project
Build consensus
Identify solutions
Peds ABDD Project
Gather evidence
Target problem areas in clinical trials

The Issue

- **PREA**:
  - NDAs and BLAs (or supplements) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration ***are required to contain pediatric assessments unless*** the applicant has obtained a waiver or deferral.
  - To comply, most AB developers are required to conduct pediatric trials to determine dosing, efficacy, and safety
  - However, designing trials and establishing AB dosages in pediatric populations is challenging

What We Need to Know

- ***Identify scientific and operational challenges in conduct of pediatric antibacterial trials*** to facilitate appropriate dosing and pharmacokinetic understanding of new agents

Objectives

- Identify scientific and operational issues in pediatric antibacterial drug trial conduct and enrollment
- Develop ***actionable*** recommendations to address scientific and operational challenges in the design and conduct of clinical trials of antibacterial drugs in children
- Quantify PREA and BPCA compliance

Methods

- Conduct semi-structured interviews with parents to identify the enrollment challenges with pediatric antibacterial drug trials
- Review pediatric antimicrobial drugs trials in ClinicalTrials.gov (utilizing the AACT database) to determine the landscape of these trials
  - Compare to FDA accounts of BPCA and PREA trials conducted and ongoing
- Conduct an expert survey and semi-structured interviews of diverse stakeholders to further characterize barriers

Anticipated Impact

- Higher quality, more efficient pediatric antibacterial drug trials due to
  - Better design and conduct
  - More efficient enrollment
  - Increased compliance with Best Pharmaceuticals for Children Act (BPCA) and PREA

Some Terms

- Extrapolation of Efficacy:
  - Under PREA, if the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be “extrapolated” from adult data. Thus, depending on a number of factors, a drug may be considered to be effective in the pediatric population when it has been demonstrated to be effective in adults. This is often the case with antibacterial drugs for some or all pediatric age groups. As a result, clinical trials in children may often enroll a smaller number of patients than adult trials
    - Extrapolation does NOT apply to safety

“Consensus”

- An effort in which affected parties (stakeholders) seek to reach agreement on a course of action to address an issue or set of related issues
  - Decision making by agreement rather than majority vote
  - Inclusive of all necessary interests when possible
  - Decision-makers are accountable to their constituents & the process
  - Committed to implementation of what is agreed to
- Elements:
  - All parties agree with the proposed decision(s) and are willing to implement
  - No one will block or obstruct the decision(s) or implementation
  - Everyone will support and implement

Thank you.

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