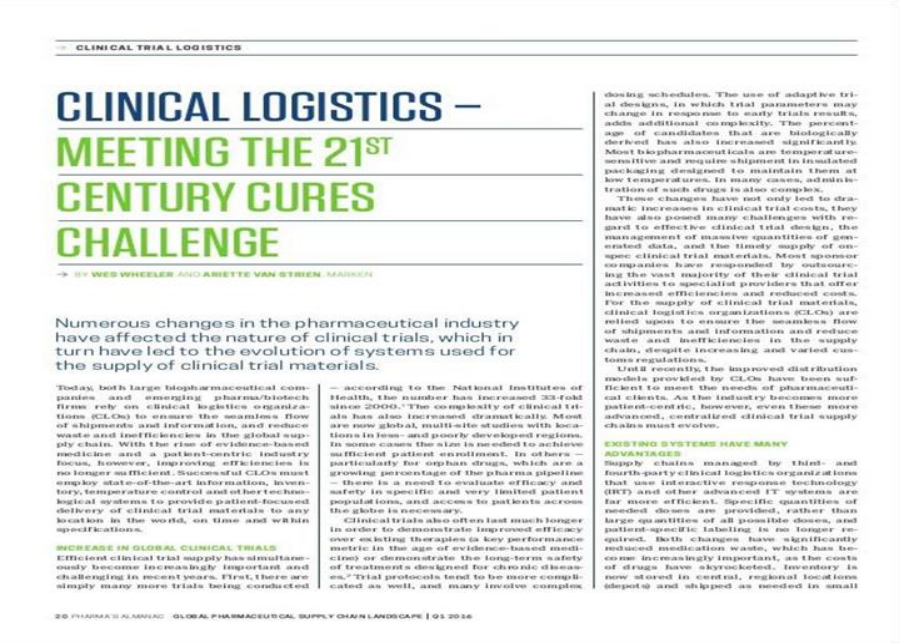
CLINICAL TRIALS TRANSFORMATION INITIATIVE

October 2, 2017

Introduction to CTTI

Clinical Trials in Crisis



CLINICAL TRIAL LOGISTICS

CLINICAL LOGISTICS – MEETING THE 21ST CENTURY CURES CHALLENGE

BY WES WHEELER AND ARIETTE VAN STRIEN, MARKEN

Numerous changes in the pharmaceutical industry have affected the nature of clinical trials, which in turn have led to the evolution of systems used for the supply of clinical trial materials.

Today, both large biopharmaceutical companies and emerging pharma/biotech firms rely on clinical logistics organizations (CLOs) to ensure the seamless flow of shipments and information, and reduce waste and inefficiencies in the global supply chain. With the rise of evidence-based medicine and a patient-centric industry focus, however, improving efficiencies is no longer sufficient. Successful CLOs must employ state-of-the-art information, inventory, temperature control and other technological systems to provide patient-focused delivery of clinical trial materials to any location in the world, on time and within specifications.

INCREASE IN GLOBAL CLINICAL TRIALS

Efficient clinical trial supply has simultaneously become increasingly important and challenging in recent years. First, there are simply many more trials being conducted — according to the National Institutes of Health, the number has increased 33-fold since 2000.[1] The complexity of clinical trials has also increased dramatically. Most are now global, multi-site studies with locations in less- and poorly developed regions. In some cases the size is needed to achieve sufficient patient enrollment. In others — particularly for orphan drugs, which are a growing percentage of the pharma pipeline — there is a need to evaluate efficacy and safety in specific and very limited patient populations, and access to patients across the globe is necessary.

Clinical trials also often last much longer in order to demonstrate improved efficacy over existing therapies (a key performance metric in the age of evidence-based medicine) or demonstrate the long-term safety of treatments designed for chronic diseases.[2] Trial protocols tend to be more complicated as well, and many involve complex dosing schedules. The use of adaptive trial designs, in which trial parameters may change in response to early trials results, adds additional complexity. The percentage of candidates that are biologically derived has also increased significantly. Most biopharmaceuticals are temperature-sensitive and require shipment in insulated packaging designed to maintain them at low temperatures. In many cases, administration of such drugs is also complex.

These changes have not only led to dramatic increases in clinical trial costs, they have also posed many challenges with regard to effective clinical trial design, the management of massive quantities of generated data, and the timely supply of on-spec clinical trial materials. Most sponsor companies have responded by outsourcing the vast majority of their clinical trial activities to specialist providers that offer increased efficiencies and reduced costs. For the supply of clinical trial materials, clinical logistics organizations (CLOs) are relied upon to ensure the seamless flow of shipments and information and reduce waste and inefficiencies in the supply chain, despite increasing and varied customs regulations.

Until recently, the improved distribution models provided by CLOs have been sufficient to meet the needs of pharmaceutical clients. As the industry becomes more patient-centric, however, even these more advanced, centralized clinical trial supply chains must evolve.

EXISTING SYSTEMS HAVE MANY ADVANTAGES

Supply chains managed by third- and fourth-party clinical logistics organizations that use interactive response technology (IRT) and other advanced IT systems are far more efficient. Specific quantities of needed doses are provided, rather than large quantities of all possible doses, and patient-specific labeling is no longer required. Both changes have significantly reduced medication waste, which has become increasingly important, as the costs of drugs have skyrocketed. Inventory is now stored in central, regional locations (depots) and shipped as needed in small

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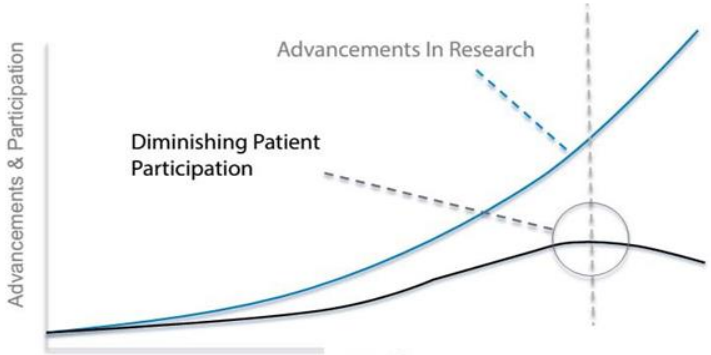

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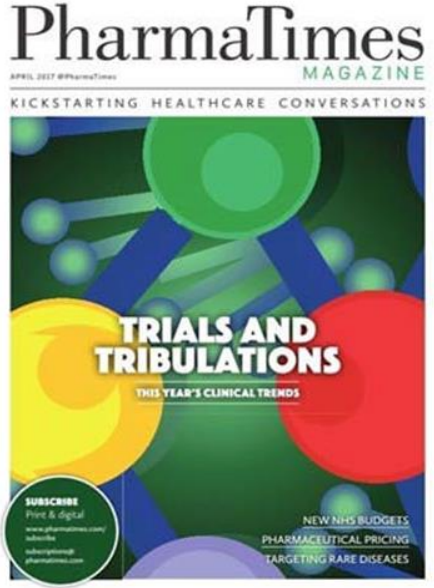

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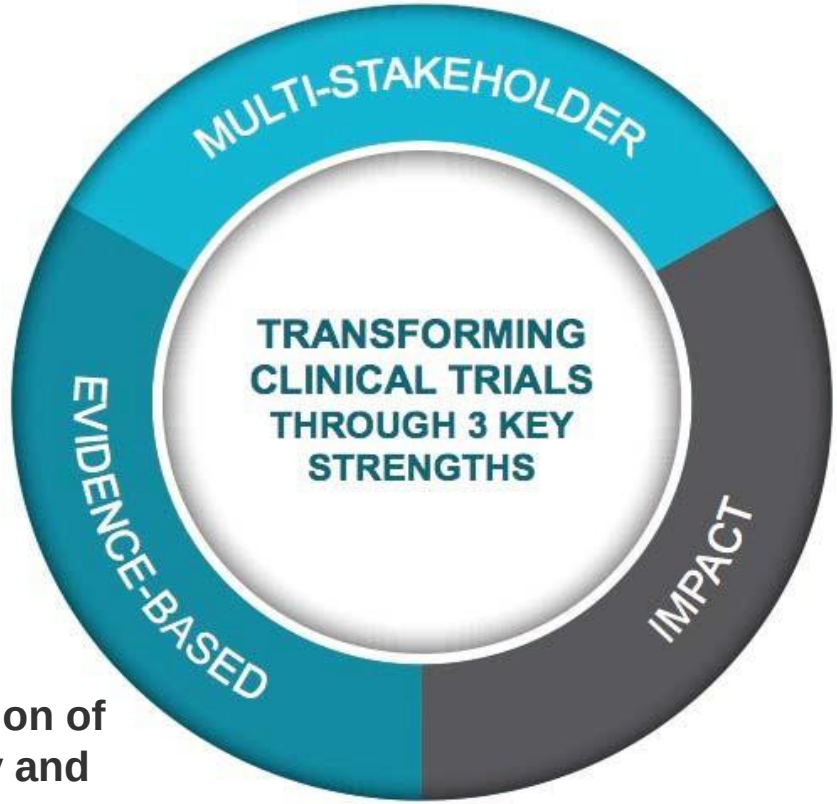
Addressing This Need

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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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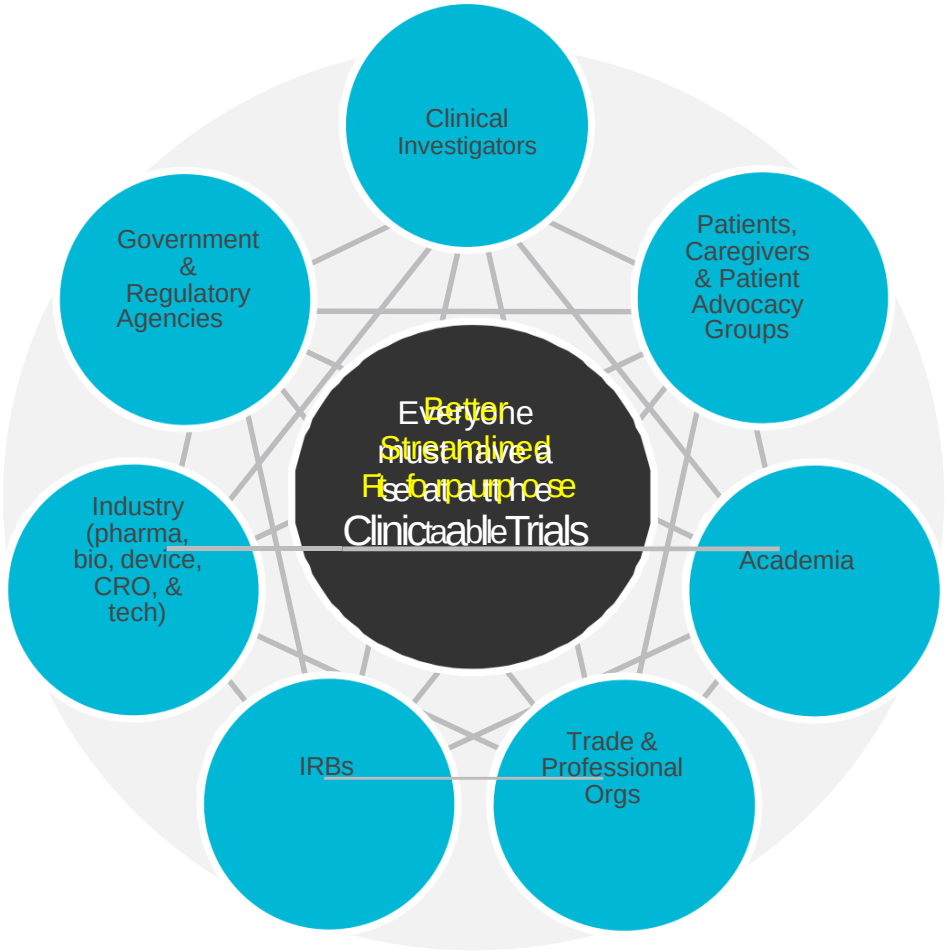
Multi-Stakeholder



CTTI Membership

*Version: Sept. 26, 2017

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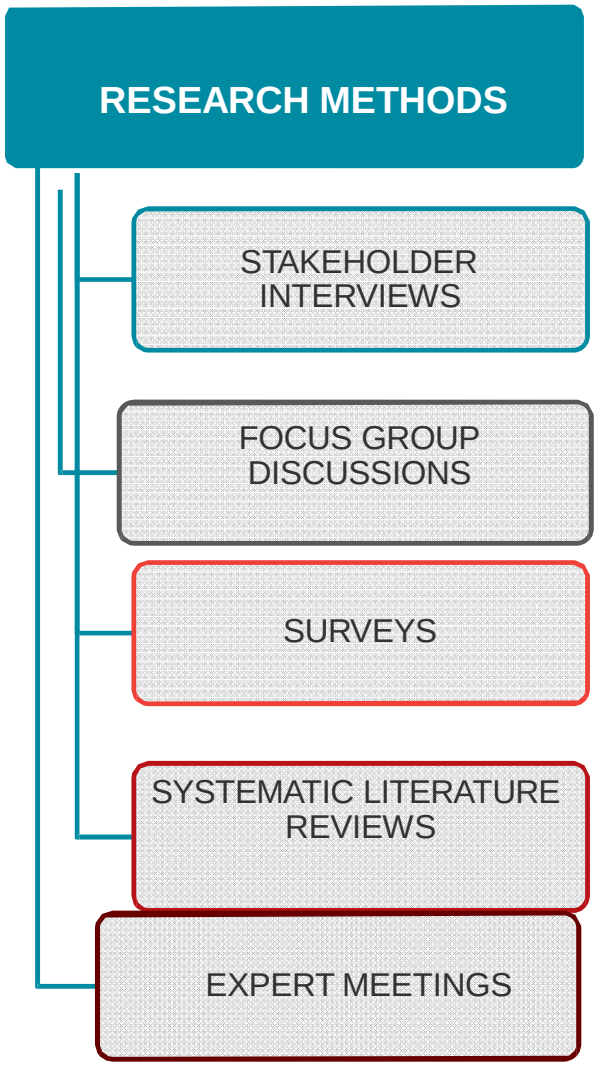
Evidence-Based

- 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.



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Real-World Impact within Organizations

- CTTI's Central IRB tools & recommendations are used by:
  - Celgene Corporation
  - National Institute of Neurological Disorders and Stroke (NIH)
  - Northwell Health

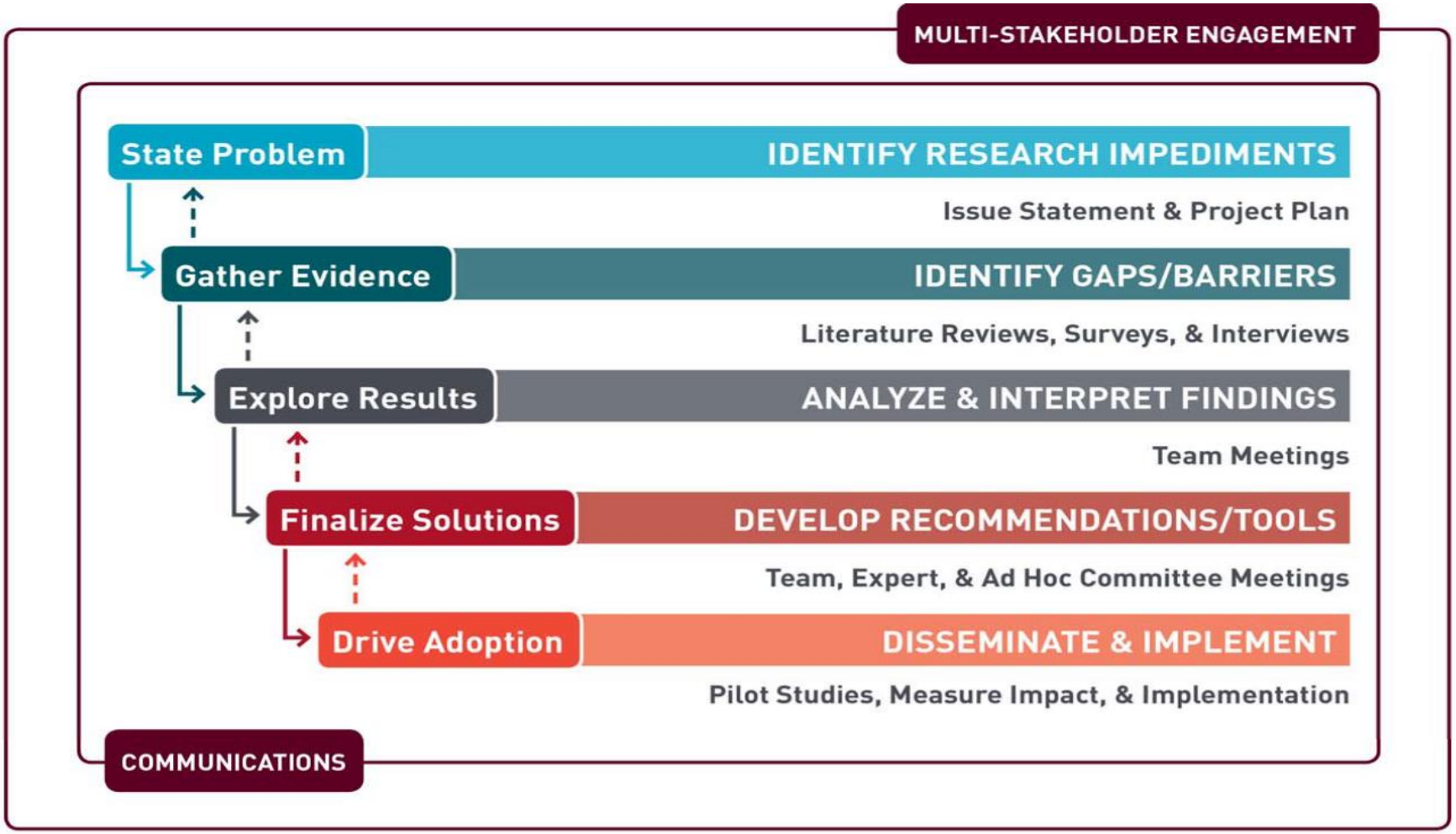
- CTTI's Quality by Design framework is used by:
  - AstraZeneca
  - DCRI
  - The Medicines Company
  - PCORNET
  - Pfizer
  - Seattle Genetics
  - Target Health Inc
  - University of Oxford

Real-World Impact at the Policy Level

- CTTI and its work have been cited in:
  - NIH Policy
  - Several FDA guidance documents
  - An EMA reflection paper
  - HR 21st Century Cures & corresponding Senate effort

CTTI Projects

Project Methodology



Project Portfolio

Areas of Strategic Focus:	SYSTEMATIC EVIDENCE GENERATION	PATIENTS AS EQUAL PARTNERS	EFFICIENT & QUALITY TRIALS	PUBLIC HEALTH CONCERN	SAFE & ETHICAL TRIALS
Active Projects:	MCT Legal & Regulatory MCT Mobile Devices MCT Stakeholder Perceptions Real World Evidence State of Clinical Trials	Patient Groups & Clinical Trials	Investigator Qualification	ABDD HABP/VABP Studies	
Complete Projects:	Large Simple Trials MCT Novel Endpoints Registry Trials		GCP Training Investigator Community Monitoring Quality by Design Recruitment Site Metrics	ABDD Peds Trials ABDD Streamlining HABP/VABP Trials ABDD Unmet Need Long-Term Opioid Data	Central IRB, Central IRB Adv DMCs Informed Consent Pregnancy Testing IND Safety, IND Safety Adv SAE Reporting

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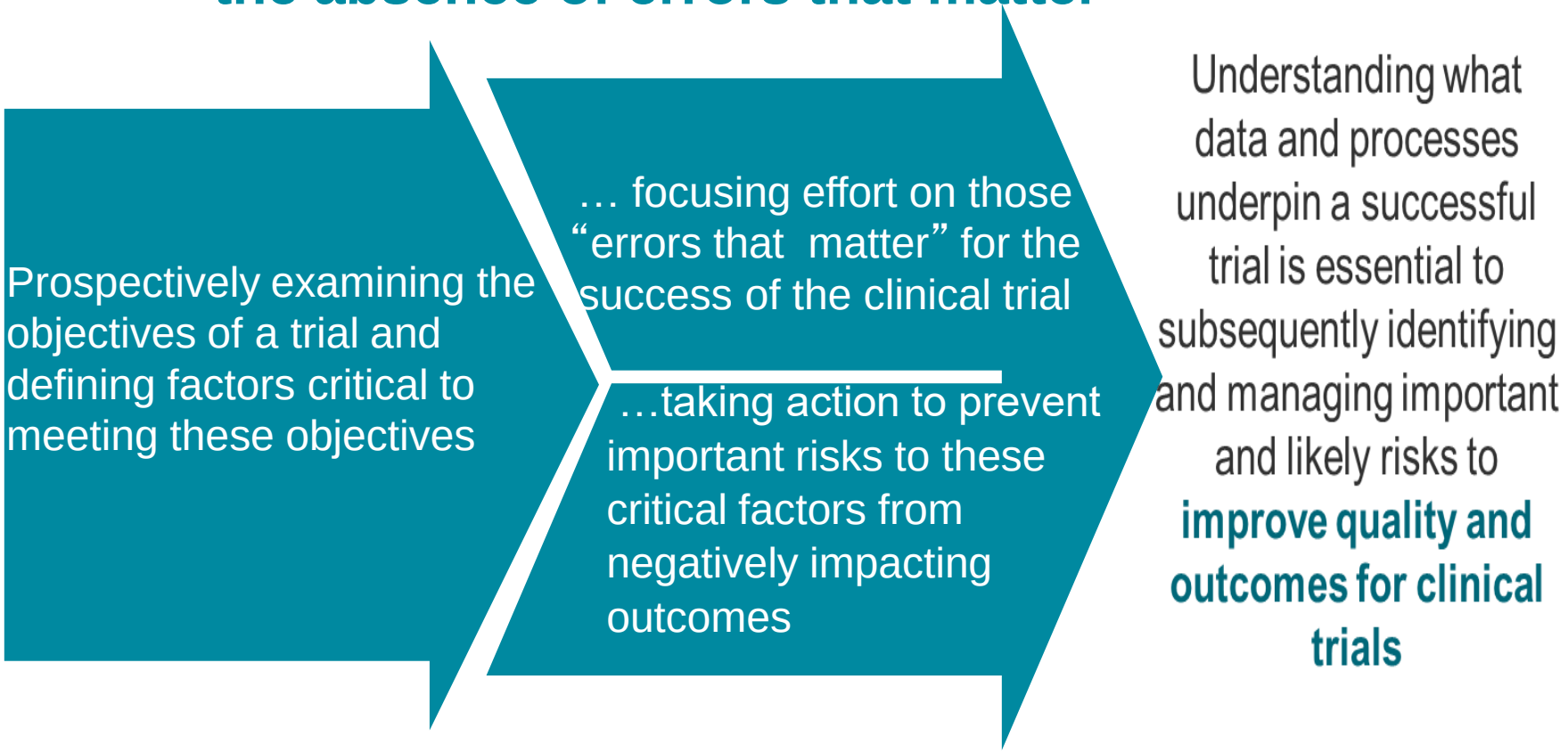
Quality by Design: QbD Defined

"Quality" in clinical trials is defined as the absence of errors that matter



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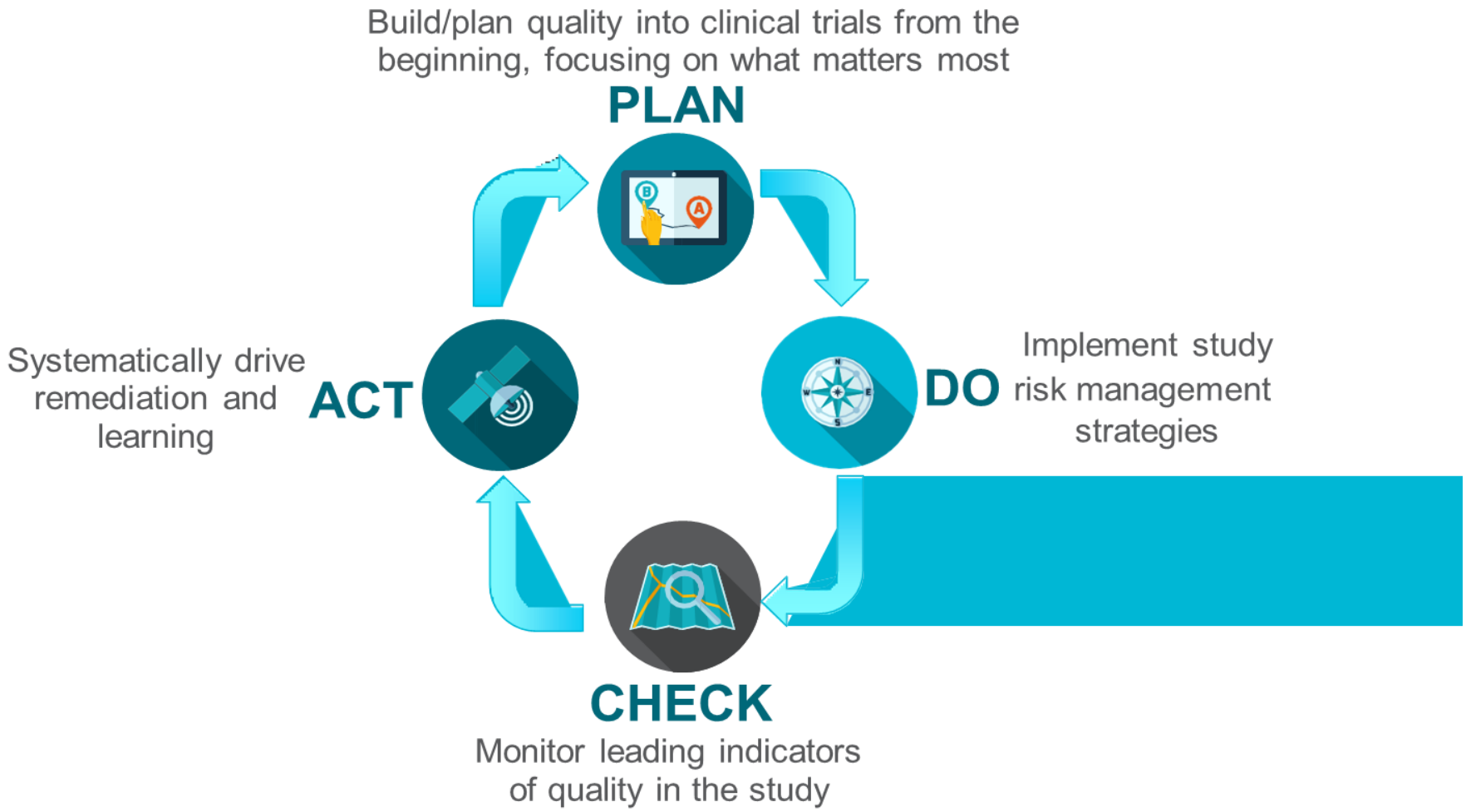
QbD Implementation: Plan, Do, Check, Act



QbD Recommendations

"Quality" is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients)

- **Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists**
- **Focus effort on activities that are essential to the credibility of the study outcomes**
- **Involve the broad range of stakeholders in protocol development and discussions around study quality**
- **Prospectively identify and periodically review the critical to quality factors**

Investigator Community: Characteristics of "One-and-Done" Investigators

Time to lead trial takes away from other necessary activities

- Long work hours
- Unpredictable work hours
- Trial time makes it difficult to devote time to:
  - Clinical and non-clinical activities
  - Activities fostering academic promotion

Too much time required to lead trial

- Amount of time to implement trial in general
- Time required by investigator to support trial and staff
- Amount of time required by staff to support trial
- Amount of time required to prepare for trial set up

Burden of data and safety reporting

- Amount
- Method
- Frequency

Dissatisfaction with trial finance

- Sponsor/site contract negotiations
- Sponsor/site budget negotiations
- Final contract
- Final site budget
- Schedule of site payments

Surprise Finding: *44% of "one and done" investigators wanted to conduct more trials*

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Investigator Community: Characteristics of Successful Active Investigators

- Sufficient and well-trained staff
- Strong commitment and work ethic
- Institutional support
- Ability to recruit patients
- Business knowledge and experience
- Strong reputation
- Ability to network
- Ability to be realistic when selecting protocols/recruitment

Investigator Community Recommendations Overview

- Develop site-based research infrastructure and staff
- Optimize trial execution and conduct
- Improve site budget and contract negotiations
- Identify additional trial opportunities for interested investigators

Investigator Qualification

Purpose

- To critically evaluate current approaches to investigator qualification, including GCP training, and issue recommendations on efficient and effective methods for investigators to become qualified to conduct clinical trials.


Investigator Qualification
Quality by Design
Investigator Community

CTTI's Approach to Expert Meetings

- Everyone participate, no one dominate
- Disagree without being disagreeable Stay open to new ways of doing things
- Respect each others' thinking and value their contributions
- Articulate hidden assumptions
- Listen for the future to emerge

THANK YOU.

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TRIALS
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www.ctti-clinicaltrials.org