CLINICAL TRIALS TRANSFORMATION INITIATIVE

October 5, 2021

Next Steps for Obtaining Novel Endpoint Reliability & Acceptance

Webinar #3 in the Developing Novel Digital Endpoints Series

Welcome and Housekeeping slide

- This webinar is being recorded and will be posted to https://ctti-clinicaltrials.org/webinars/
- All participants are muted upon entry.
- Only presenters should have their video on during presentation and panel sessions.
- Enter questions and comments into the chat during the webinar.
- There will be a Q&A session toward the end of the webinar.

Developing Novel Digital Endpoints Webinar Series

Today's Speakers

Lindsay Kehoe
CTTI

Alicia Staley
Medidata

Jennifer Goldsack
DiMe

Michelle Crouthamel
AbbVie

Introduction to CTTI

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Multi-stakeholder,

public-private partnership

co-founded by Duke University & FDA

Participation of 500+ more orgs and ± 80 member organizations

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

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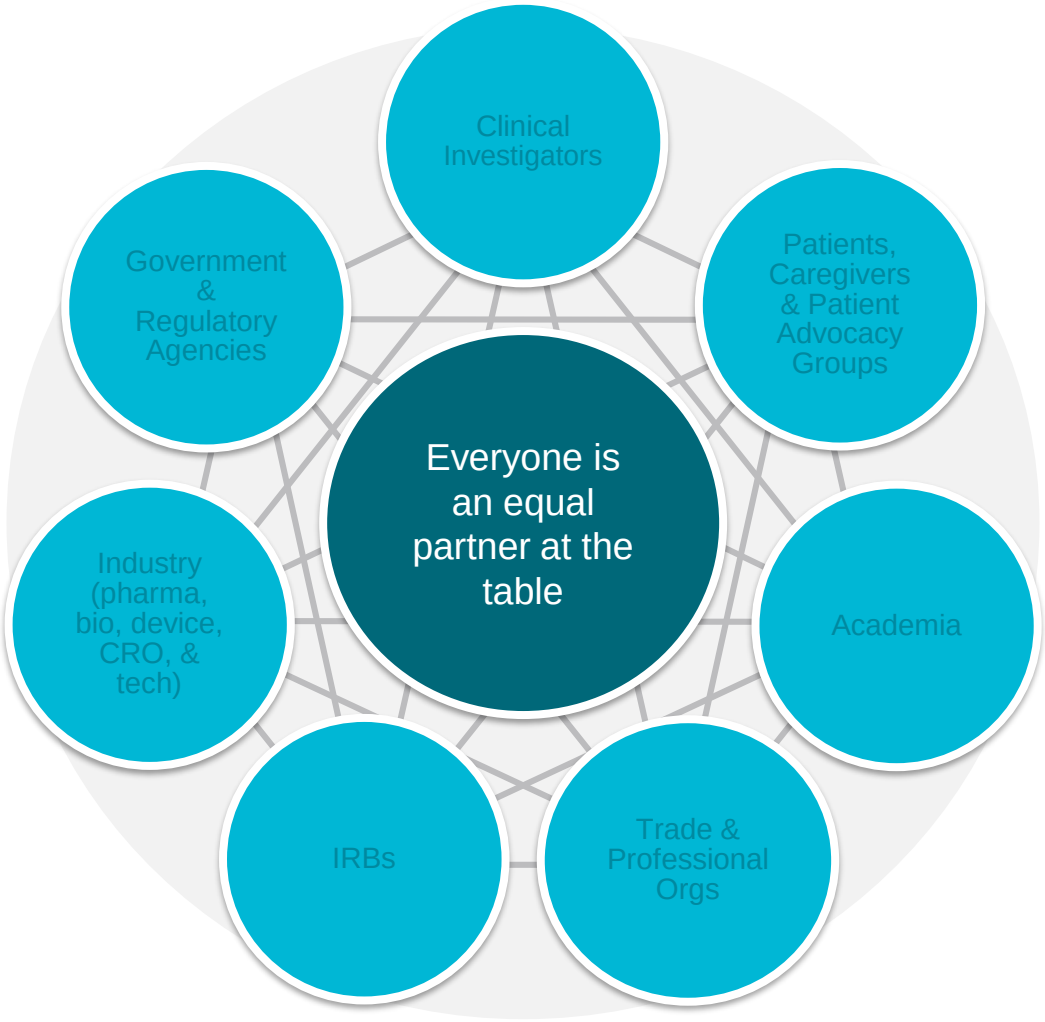
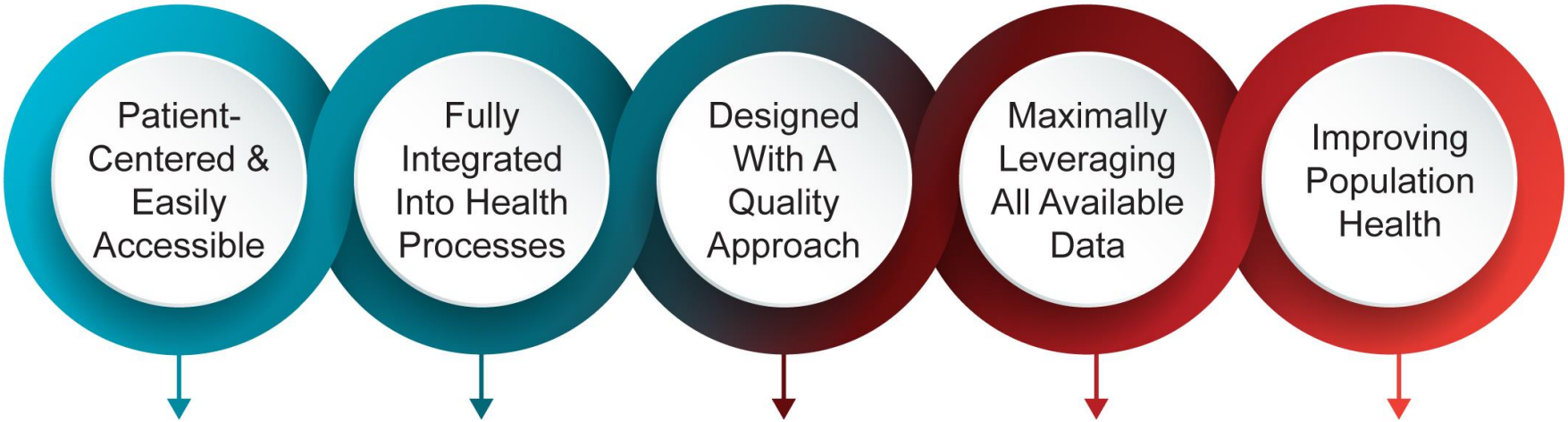
Multi-Stakeholder Collaboration



TRANSFORMING TRIALS 2030

By 2030, clinical trials need to be:



A critical part of the Evidence Generating System

https://ctti-clinicaltrials.org/who_we_are/strategic-vision/

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Portfolio of CTTI Work

Quality

- Quality by Design
- Diversity
- Stakeholder Engagement in Trial Design
- Challenges of ClinicalTrials.gov Reporting
- Informing the Update of ICH E6
- Recruitment
- Planning for Pregnancy Testing
- State of Clinical Trials Report
- Monitoring

Digital Health Trials

- Novel Endpoints
- Decentralized Clinical Trials
- Digital Health Technologies
- Engaging Patients and Sites
- Feasibility Studies Database

Novel Clinical Trial Designs

- Trials in Health Care Settings
- Disease Progression Modeling
- Real-World Data
- Registry Trials
- Master Protocols
- Antibacterial Drug Development
- Large Simple Trials
- Using FDA Sentinel for Trials

Patient Engagement

- Patient Group Engagement
- Patient Engagement Collaborative

Investigators & Sites

- Investigator Community
- Investigator Qualification
- Site Metrics

Ethics & Human Research Protection

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

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Obtaining Novel Endpoint Reliability & Acceptance

Lindsay Kehoe, CTTI

Webinar Series Recap

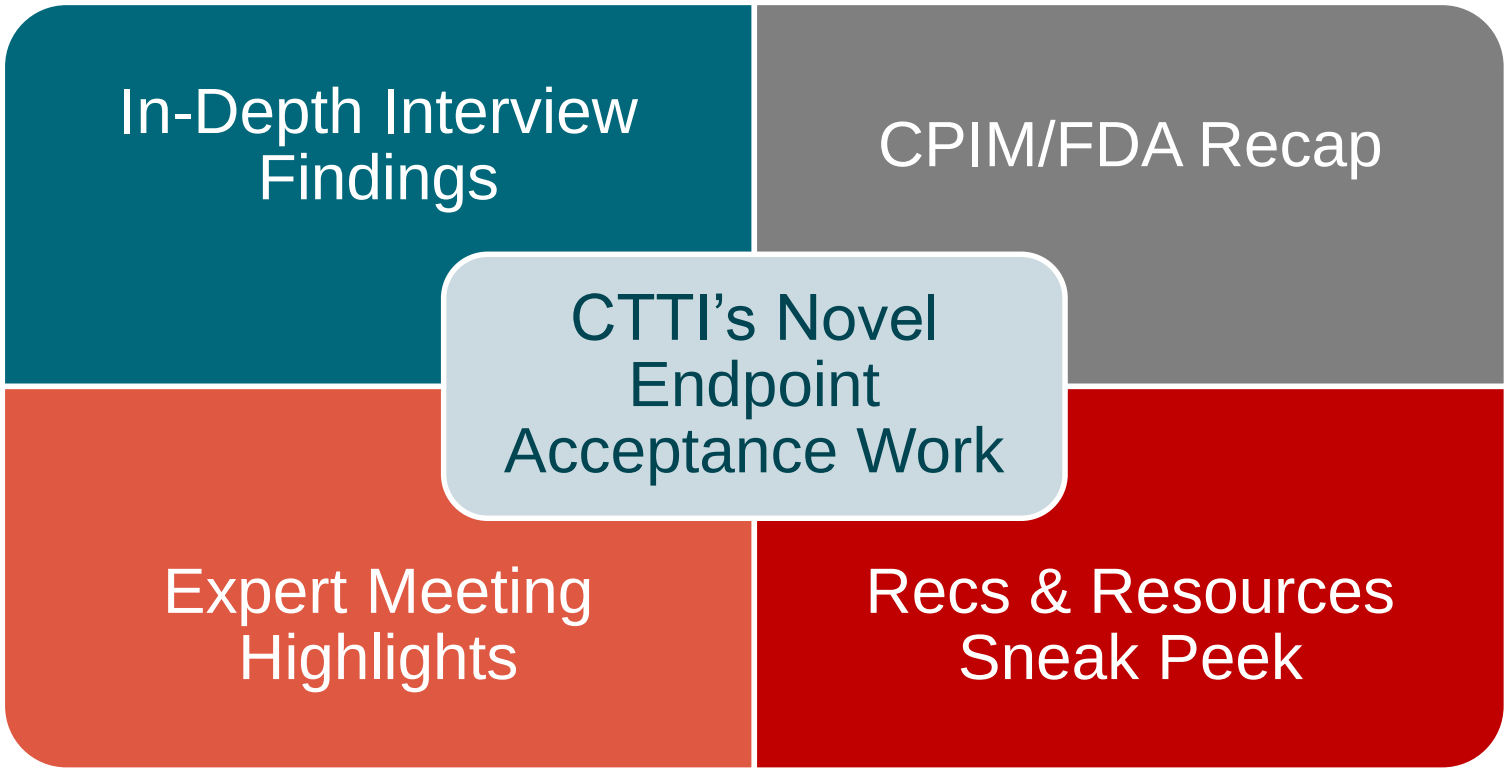
- **Webinar 1**: August 2 | Digital Endpoints
  - DiMe shared a variety of their resources to advance digital measures, including:
    - The V3 framework for digital measurement performance
    - The 5 part framework for digital measurement technologies
    - *The Playbook* to put these resources, and more, into action today

  Recording at: https://www.dimesociety.org/webinar/dime-presents-digital-endpoints-webinar/

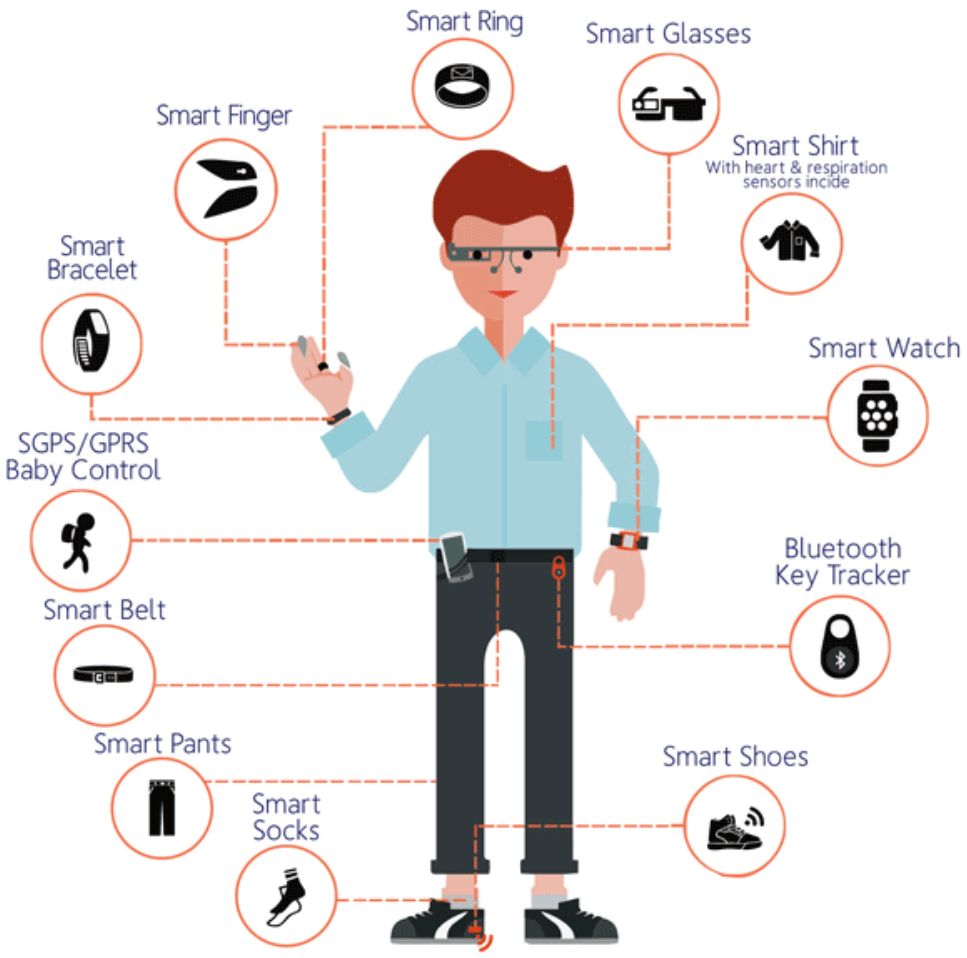
- **Webinar 2**: September 21 | Developing a Novel Measurement of Sleep in Rheumatoid Arthritis: Study Proposal for Approach and Considerations
  - TransCelerate used DiMe's V3 framework and CTTI resources in a hypothetical case to validate a sleep endpoint
    - Demonstrated key considerations and challenges for developing novel digital endpoints for use in medical product development

  Recording at: https://www.transceleratebiopharmainc.com/news-center/

Today's Webinar: Next Steps for Obtaining Novel Endpoint Reliability & Acceptance



Digital Health Technology



- Allow for a broader, holistic picture of how patients feel and function
- Can provide novel measurements, and more frequent or continuous data collection
- Able to move healthcare from the clinic to the patient
- Enhance data collection and enable decentralized clinical trials

Digital Health Trials (DHT) Program*

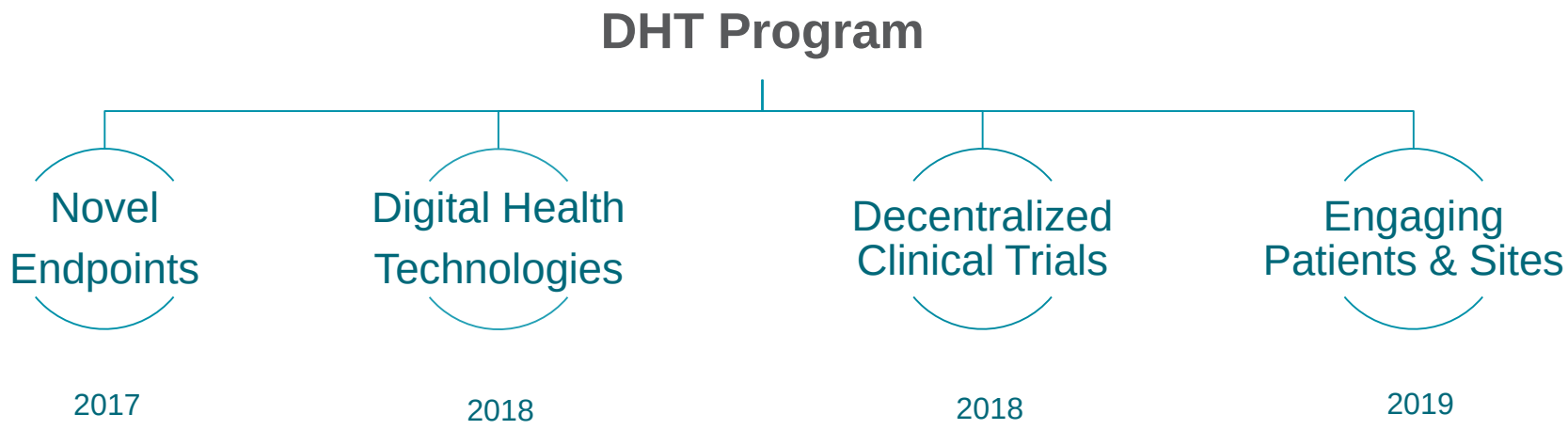
PURPOSE:

Develop evidence-based recommendations that affect the widespread adoption and use of digital health technology in clinical trials for regulatory submission.

ANTICIPATED IMPACT:

Increased number of clinical trials leveraging digital health technologies.

More efficient trials generating better quality information.



Formerly CTTI's Mobile Clinical Trials (MCT) Program

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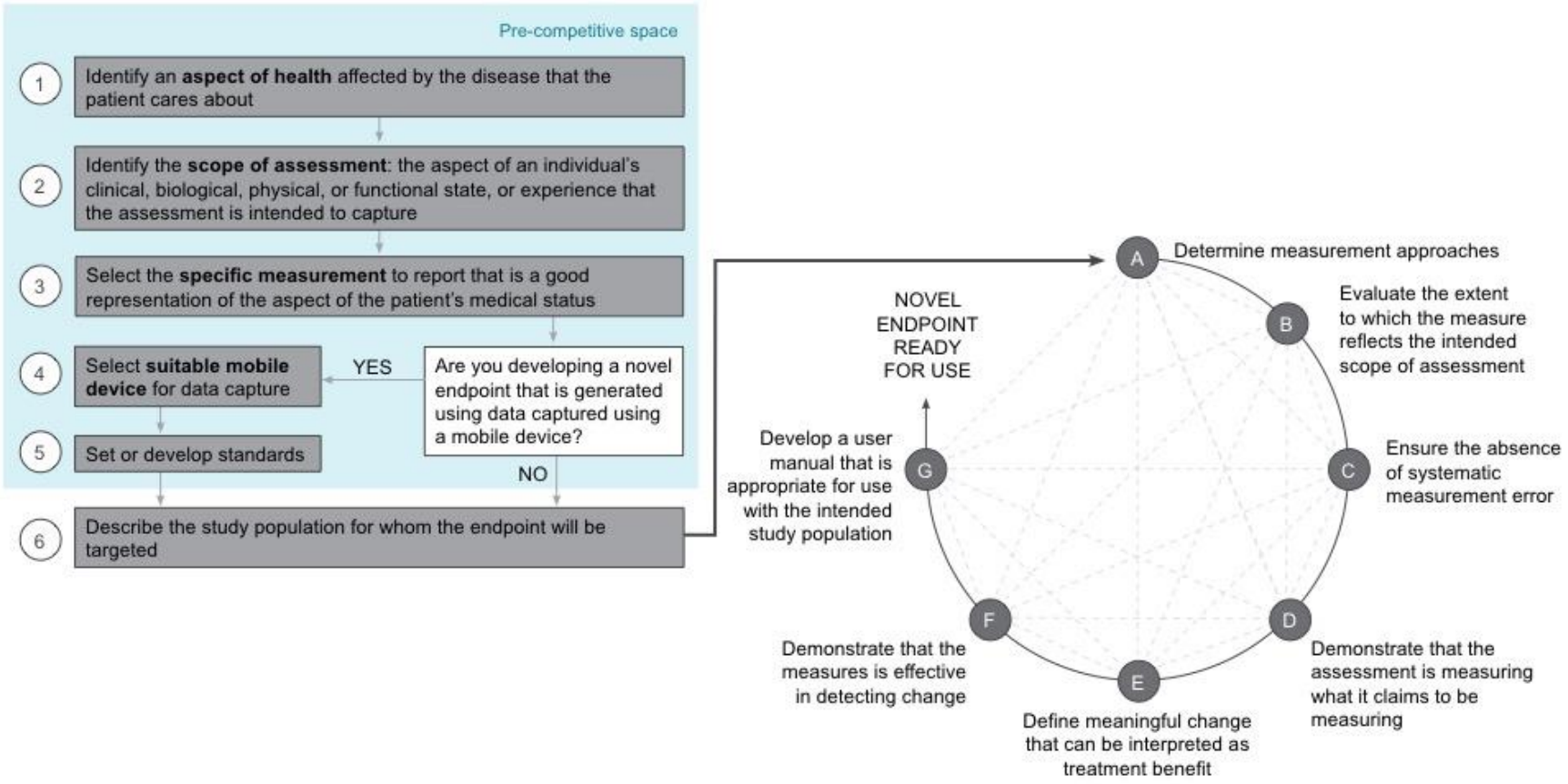
CTTI's 2017 Developing Novel Endpoints

Recommendations

- **Optimizing Novel Endpoint Selection**
  - Focus on measures that are meaningful to patients.
  - Select the technology after selecting an outcome assessment.
  - Use a systematic approach to identify key novel endpoints.
- **Practical Approaches to Novel Endpoint Development**
  - Foster collaboration among key stakeholders.
  - Create technical standards for mobile technology-derived assessments.
  - Engage with regulators.
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies.
  - Think critically about how to optimally position novel endpoints in interventional trials.

CTTI's 2017 Developing Novel Endpoints

Steps for Novel Endpoint Development



DHT-Derived Endpoints In Use Today

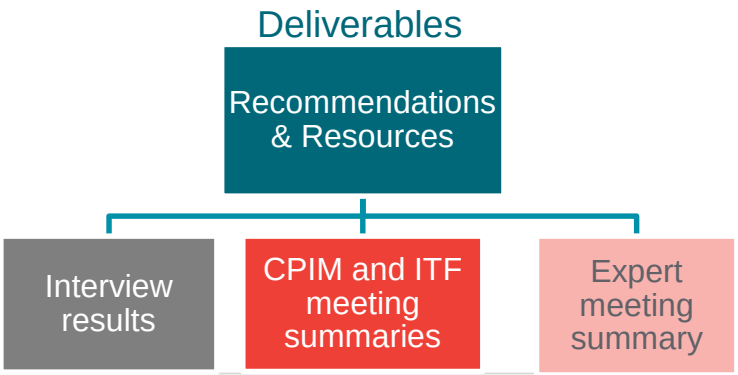
- No known clinical outcome assessments captured by a DHT have been “accepted” by FDA to support an approved label claim
- As of September 2021, there are ~225 DHT-derived endpoints listed in Digital Medicine Society’s crowdsourced Library of Digital Endpoints.
  - The majority are listed as a “secondary” endpoint
- 7 qualified Clinical Outcome Assessments (COA) under FDA’s DDT program (All are PROs)
- 6 DHT-Passive Monitoring COAs have an accepted Letter of Intent under the DDT program
- One Phase 4 study used a DHT-derived outcome to inform a label claim in Europe, and that claim was approved

Novel Endpoint Acceptance Project

- **Purpose**: Obtain reliability and acceptance of meaningful, DHT-derived novel endpoints
- **Objectives:**
  - Identify gaps and barriers and solutions to achieve regulatory acceptance for a DHT-derived endpoint
  - Describe the evidence needed to achieve regulatory acceptance for a novel, DHT-derived endpoint
  - Create a glossary for DHT-derived novel endpoints
- **Expected Impact:** Increase the use of meaningful, DHT-derived novel endpoints as key endpoints in clinical trials for labeling claims

In Scope	Out of Scope

• Clinical Outcome Assessments (COAs)*
  • *Functional outcomes*
  • *Passive and active monitoring*
  • *Technology intended for use in clinical trials*
	• Surveys (ePROs)
	• Digital therapeutics
	• Biomarkers



*Per FDA/NIH's BEST glossary, a clinical outcome describes or reflects how an individual feels, functions or survives.

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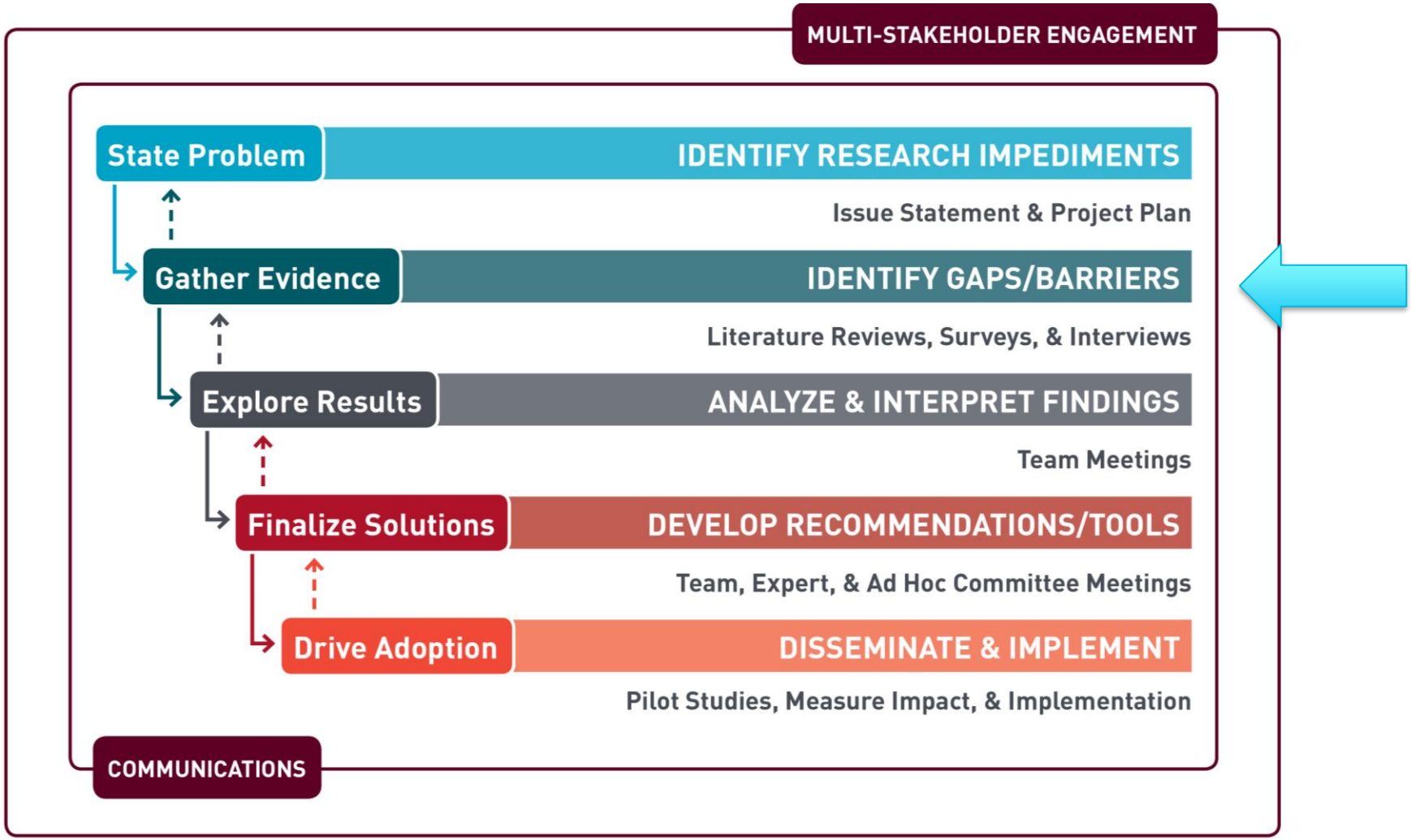
2021 Novel Endpoints Acceptance

Project Team

Team Leaders	Team Members	
Alicia Staley (Medidata) Elektra Papodopoulous (FDA) Jörg Goldhahn (ETH Zurich) Rodrigo Garcia* (EMD Serono) **Now Quentin Le Masne (EMD Serono)*	Kai Langel (Janssen) Tom Switzer (Genentech) Jeremy Wyatt (ActiGraph) Xinzhi Zhang (NIH) Andrew Potter (FDA) Sue Jane Wang (FDA) Maria Ali (George Institute for Global Health) Shelly Barnes (UCB) Steven Berman (FDA) Krishna Jhaveri (Phillips) Joy Bhosai (Duke) Matthew Diamond (FDA) Katy Eichinger (University of Rochester) Jeffrey Statland (KUMC) Michelle Crouthamel (AbbVie) Phil Green (patient)	Emily Cerciello (Crohn's & Colitis Foundation) Timothy Chen (Medidata) Sonja Cloosterman (Orikami) Andy Coravos (HumanFirst) Megan Doyle (Amgen) Cynthia Geoghegan (patient) Beatrix Friedeberg (Amgen) Elizabeth Kunkoski (FDA) Ingrid Oakley-Girvan (Medable) Lauren Oliva (Biogen) Colleen Rouse (Cleveland Clinic) **Social Science Lead** Brian Perry (CTTI) **Project Manager** Lindsay Kehoe (CTTI)

CTTI Methodology



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Key Findings from Novel Endpoint Acceptance Project

Alicia Staley, Medidata

Evidence Gathering for Novel Endpoint Acceptance Project

- In-Depth Interviews with Sponsors
- Expert Meeting
- Critical Path Innovation Meeting (CPIM)
- Innovation Task Force (ITF) Meeting (pending)
- Team discussion and consensus

In-Depth Interviews with Sponsors

11 interviews covering 11 trials

Objectives

- Describe the evidence used to support DHT-derived novel endpoints in pivotal trials for successful regulatory approvals.
- Identify gaps, barriers, and solutions to using DHT-derived novel endpoints as key endpoints in pivotal clinical trials.

Trial Selection Criteria

- a clinical trial that uses a digitally derived endpoint to support or potentially support a label claim
- the digitally derived endpoint uses a digital tool to objectively measure a functional clinical outcome
- Focused on digitally derived endpoint positioned as either primary or secondary

Topics Addressed in Interviews

- Endpoint selection process
- DHT selection process
- Validation process
- Regulatory interactions and feedback
- Recommendations from sponsors

Key Findings to Date

In-depth Sponsor Interviews

Barriers

- Sponsor uncertainty
- Burdensome qualification process
- Lack of appropriate DHTs and experienced vendors
- Lack of sharing information
- Challenges associated with interpreting meaningful change

Solutions

- Engage stakeholders early & often
- Include DHT-derived endpoints in early phase trials
- Select a DHT that is fit-for-purpose; ensure 1) there is a need, 2) it is verified and validated for the context of use, & 3) It is sensitive to measure meaningful differences
- Validate the DHT algorithm
- Monitor patient compliance throughout the trial
- Include other measures to provide context and demonstrate meaningful change

Basic Evidence Required

- DHT is accurate and reliable for a specific outcome within a similar context of use as the trial
- DHT is safe and feasible to use as intended by the patient population
- Endpoint is measuring a health concept that is meaningful
- Endpoint is able to measure change in disease progression or therapeutic effectiveness
  - Change is similar to changes in legacy COAs
  - Change is meaningful to patients, caregivers, and/or clinicians

Critical Path Innovation Meeting (CPIM)

July 16, 2021

- Informal, nonbinding meeting with the FDA to provide general advice on methodology or technology
- CTTI's Purpose: to discuss the challenges associated with the adoption of novel DHT-derived endpoints into clinical trials to support medical product approval
- Multiple offices and divisions attended including CDER, CDRH, and Oncology Center of Excellence

CPIM Meeting Take-Aways

Engage Early	• Include CDRH's Digital Health Center of Excellence as necessary to determine what is needed to use the DHT for a clinical trial
Fit-for-Purpose is a Must	• Consider whether the DHT measure corresponds to a clinically meaningful outcome
DHTs in Trials May or May Not be Regulated as a Device	• DHTs regulated as devices receive clearance or approval for a specific indication for use and may/may not be valid for use in a medical product trial depending on the context of use
Validate but Don't Conflate	• Validation of the device and clinical meaningfulness of the measurement are two separate issues
Examples of Value are Needed	• Sponsors could present specific examples of how DHTs will be used so that the agency may better understand risk and benefit

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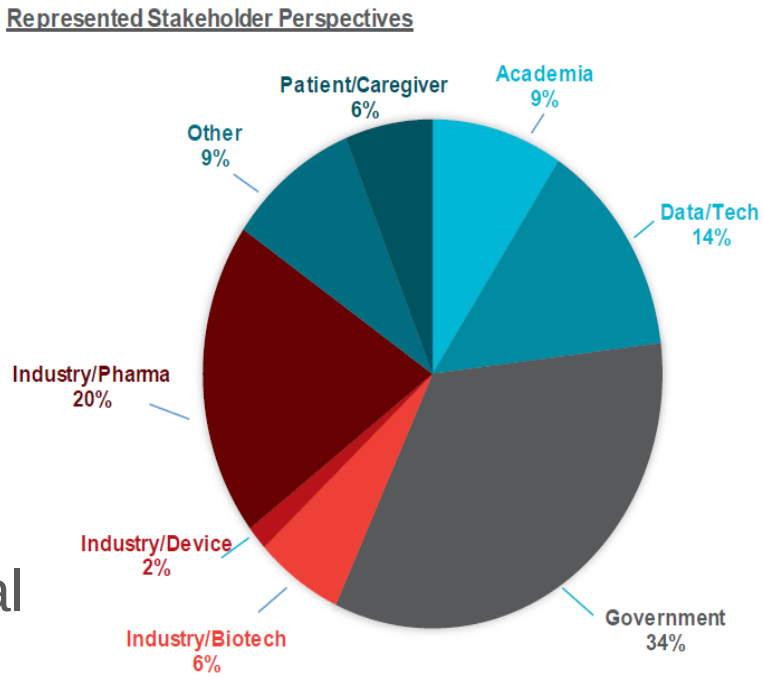
Expert Meeting

- Held July 27-28
- Meeting objectives:
  - Identify the barriers and discuss solutions to the adoption of DHT-derived endpoints into pivotal trials
  - Discuss the data needed to support that a DHT-derived endpoint is ready for a pivotal trial
  - Explore how collaboration and other new efforts can advance the adoption of DHT-derived endpoints



Key Findings to Date

Multi-Stakeholder Expert Meeting

The Time is Now	• Collaborate and develop solutions that increase the understanding and use of DHT-derived endpoints
Fit-for-Purpose is a Must	• Validly measure a concept of interest for a specific context of use in a way that is accurate, interpretable, and not misleading
"Meaningful" in More than One Way	• Have the community – including patients and clinicians – discuss what constitutes "meaningful" change
Engage Early and Often	• Engage patients, site personnel, and regulators when planning
Validate, Validate, Validate	• Validate the measure in the target population • Clinical validation will involve proper planning and alignment with stakeholders

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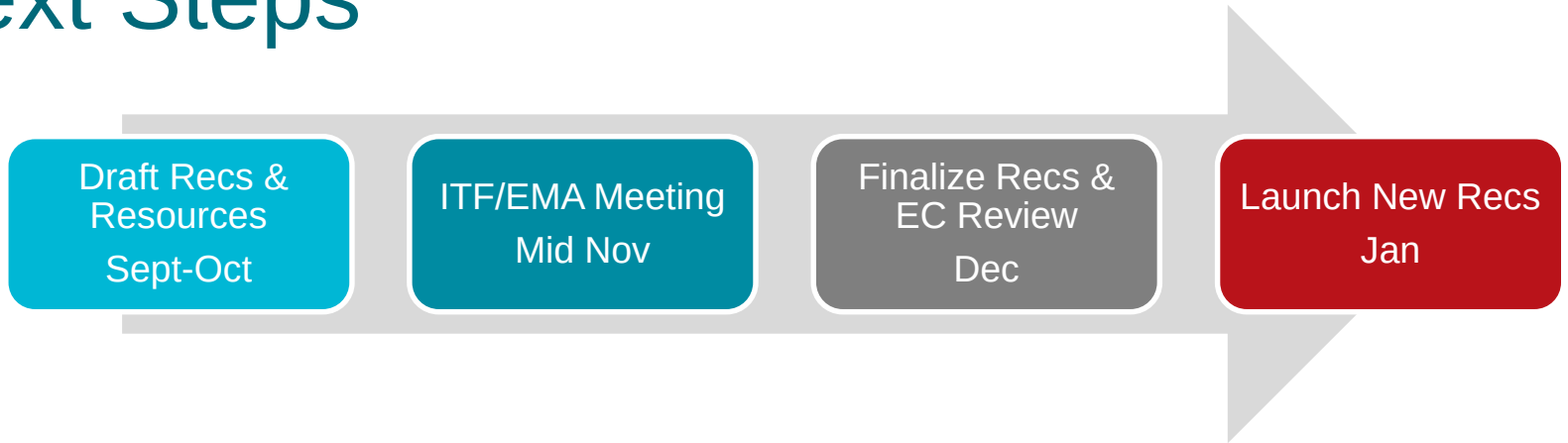
Next Steps



Refine existing recommendations and develop new resources focused on:

- Providing incentives
- Streamlining processes through collaboration
- Clarifying evidence needs

Relevant to CTTI's Transforming Trials 2030 vision:

- Patient-centered and easily acceptable
- Maximally leveraging all available data

Q&A

Poll:

1. Which aspects of CTTI's findings deserve immediate attention?

2. What are potential solutions to the CTTI findings that require immediate attention?

Discussion:

- As we try to advance the use of novel digital endpoints what would you say is the #1 lesson learned, so far?
- If you could identify one thing in the near term – say, 6 months – that is needed to advance the use of the these endpoints, what would it be?
- Describe how we'll ideally be using these novel endpoints 2 years from now and what are the 1-3 things that are critical to getting us there?

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Eager to continue the discussion? Join us at the:

DIA Digital Technology in Clinical Trials

Short Course

Oct. 21 | 9 a.m. – 1 p.m. EST

https://www.diaglobal.org/en/conference-listing/meetings/2021/10/digital-technology-in-clinical-trials

THANK YOU

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