CLINICAL TRIALS TRANSFORMATION INITIATIVE

July 20th, 2018

Developing Technology-Derived Novel Endpoints for Use in Clinical Trials: CTTI Recommendations & Case Examples

Rob DiCicco, PharmD | TransCelerate BioPharma, Inc.
Jen Goldsack, MChem, MA, MBA | CTTI
Will Herrington, MD, MRCP, MBBS, MA | University of Oxford

Webinar Outline

- The need for recommendations
- CTTI recommendations and resources on the selection, development, and inclusion of technology-derived novel endpoints in clinical trials
- Where is our field right now with regards to adopting these novel endpoints and how will CTTI's work continue to drive advancement?
- Why is CTTI so committed to driving the adoption of technology-derived novel endpoints in clinical trials and what other work are they doing to drive their adoption?

Benefits of Technology-Derived Endpoints

- Clinical trials appear to be behind other industries in adopting mobile technologies to improve quality and efficiency

Benefits of Technology-Derived Endpoints

- Potential scientific and efficiency benefits of mobile technology-derived endpoints:
  - Prospective
  - Objective
  - Sensitive
  - Patient-centric
  - Real-world
  - Prolonged measurements
  - Minimal interference with trial participant's daily lives
  - May increase the pool of people willing to volunteer

Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

Multi-Stakeholder Collaboration

1. Patients and patient groups
2. Clinical academic groups
3. Technology developers
4. Regulators
5. Industries developing interventions (sponsors)

CTTI Strengths

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
Co-founded by Duke University & the 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

Mobile Clinical Trials (MCT) Program

PURPOSE:

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

ANTICIPATED IMPACT:

Increased number of clinical trials leveraging mobile technologies

4 PROJECTS

**Scope: FDA-regulated clinical trials after the time of initial research volunteer consent*

CTTI

The MCT Novel Endpoints Project Team

Team Leaders	Team Members	Project Manager
Lauren Bataille (MJFF)	Ashish Naryan (Northwell)	Jen Goldsack (CTTI)
Rob DiCicco (GSK)	Elektra Papodopoulous (FDA)	**Social Science Lead**
Cheryl Grandinetti (FDA)	Theresa Strong (FPWR)	Brian Perry (CTTI)
Will Herrington (Oxford)	Komathi Stem (monARC Bionetworks)	**EC Champion**
Martin Landray (Oxford)	Ken Skodacek (FDA)	John Alexander (Duke)
Kaveeta Vasisht (FDA)	Nirav 'Rav' Sheth (MC10)	
	Marc Walton (Janssen)	

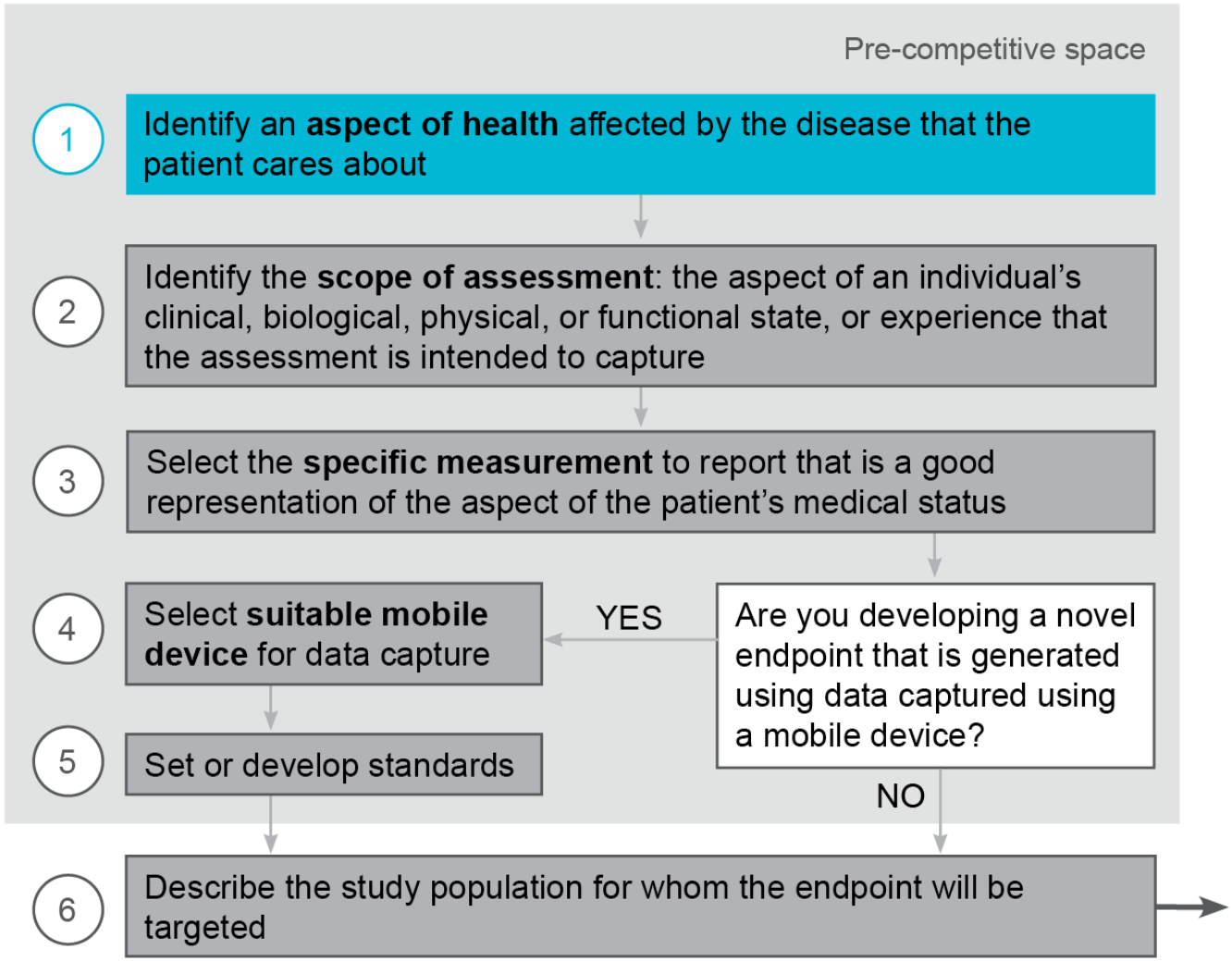
Download the Recommendations & Resources

- Visit https://www.ctti-clinicaltrials.org/projects/novel-endpoints to access and download the full suite of CTTI's MCT Novel Endpoints Recommendations and Resources

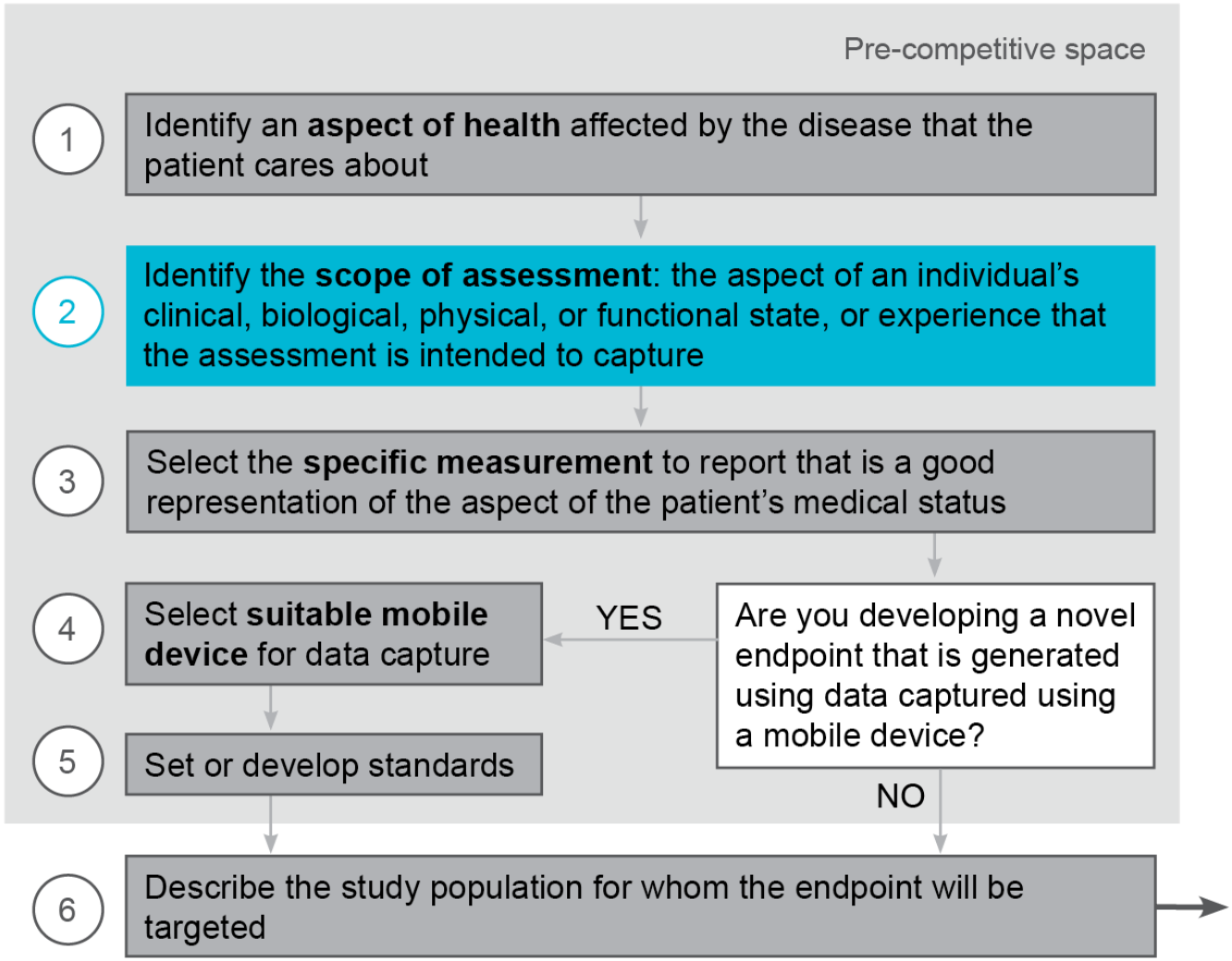
Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

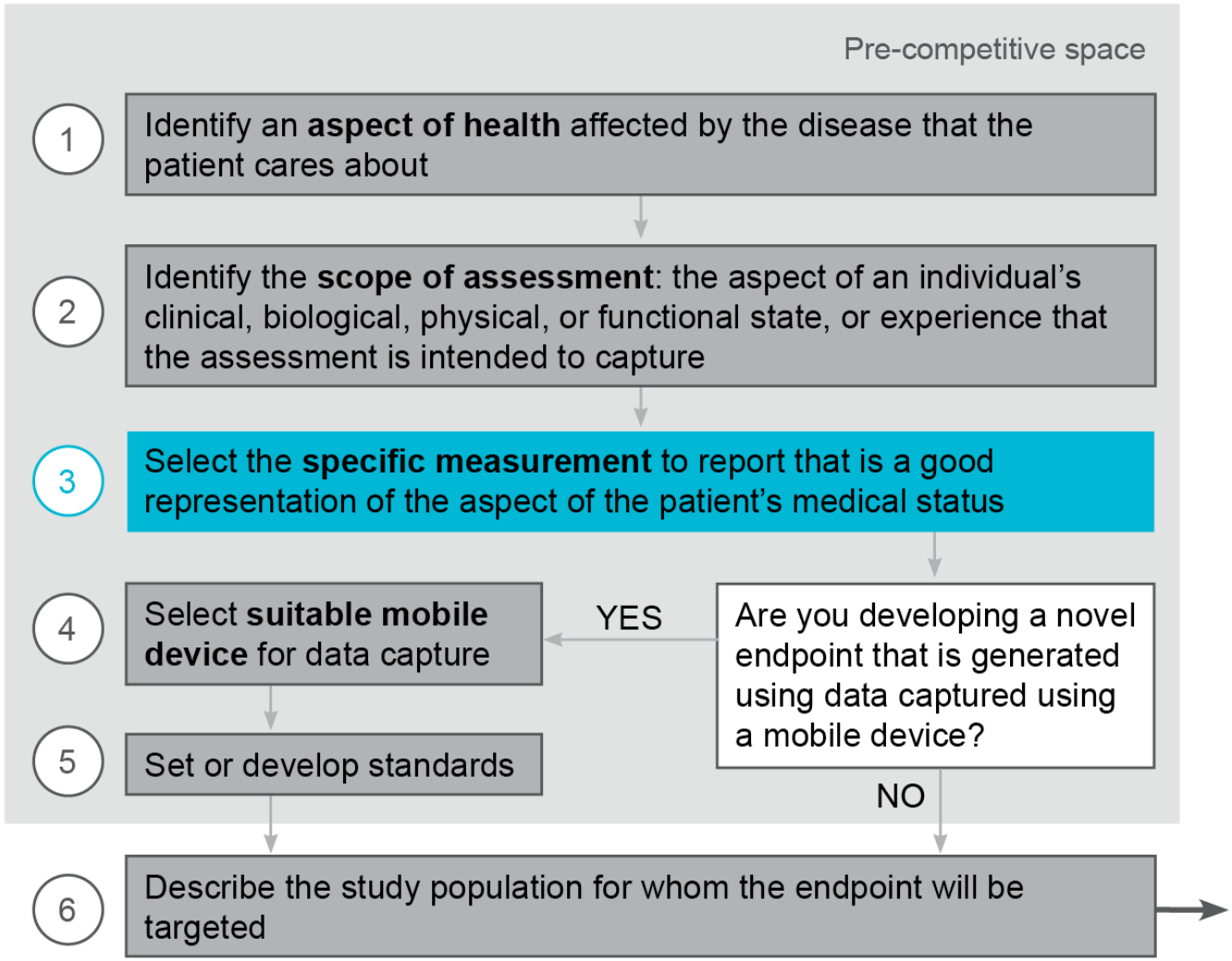
Steps for Novel Endpoint Development



Steps for Novel Endpoint Development



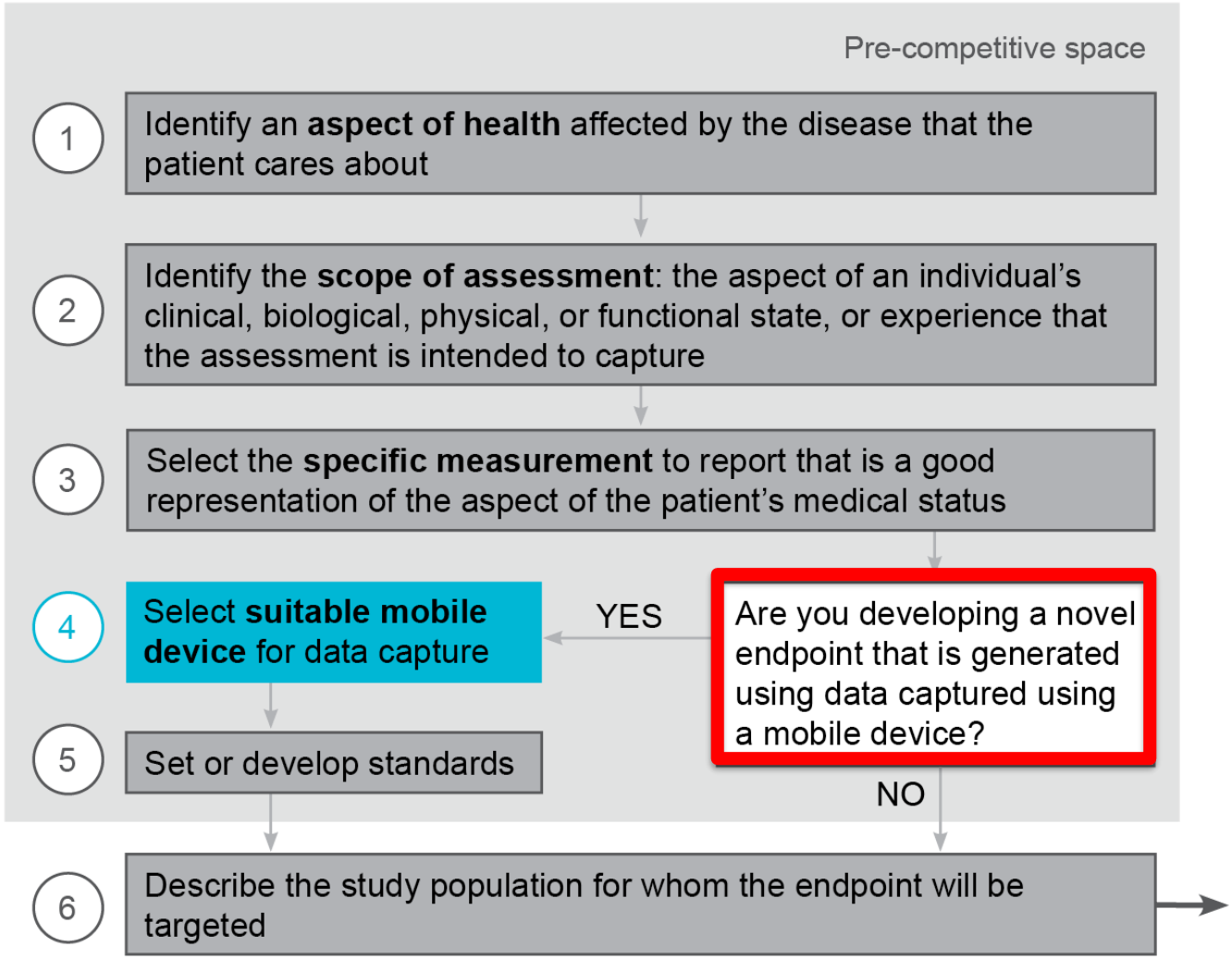
Steps for Novel Endpoint Development



Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

Steps for Novel Endpoint Development



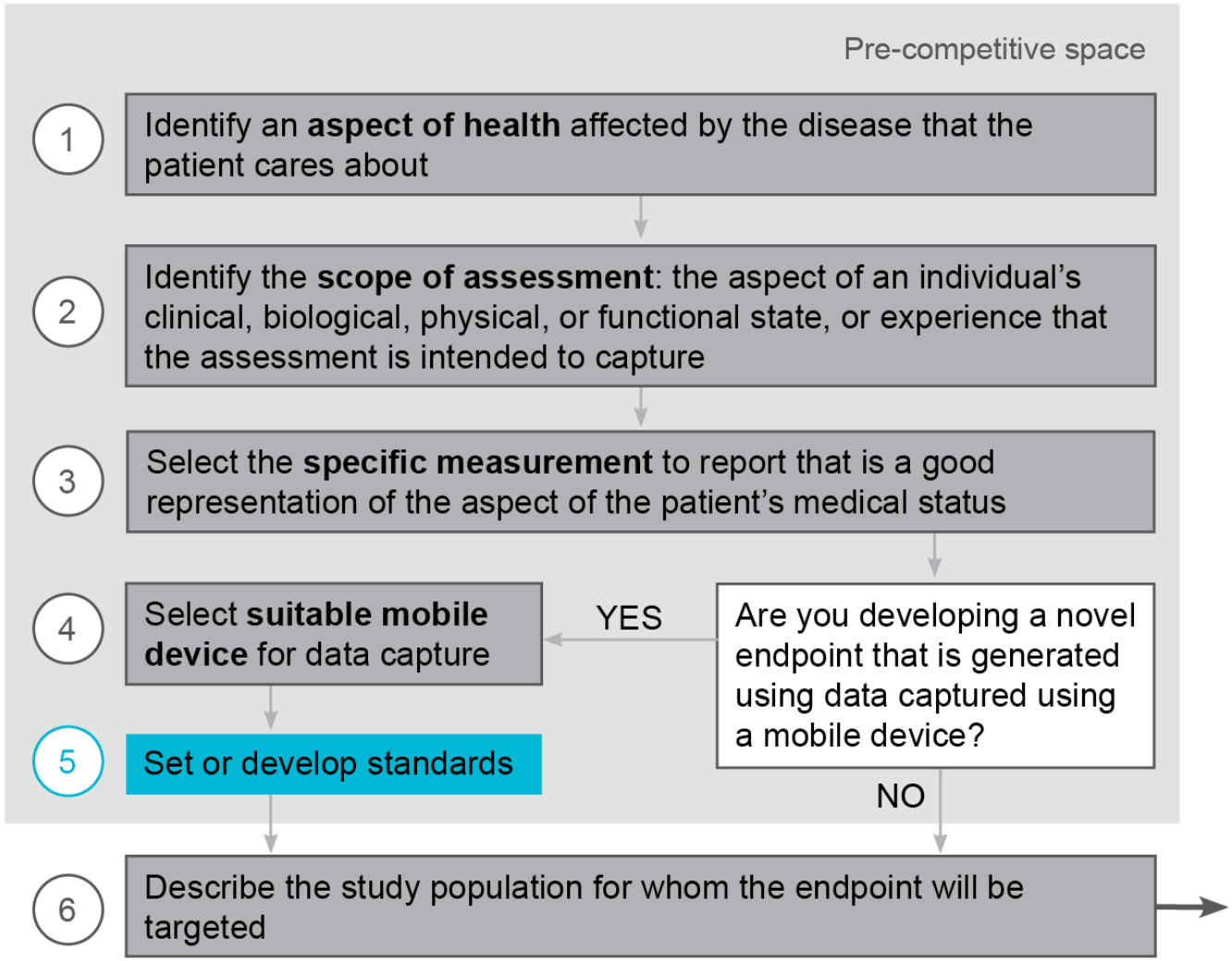
Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

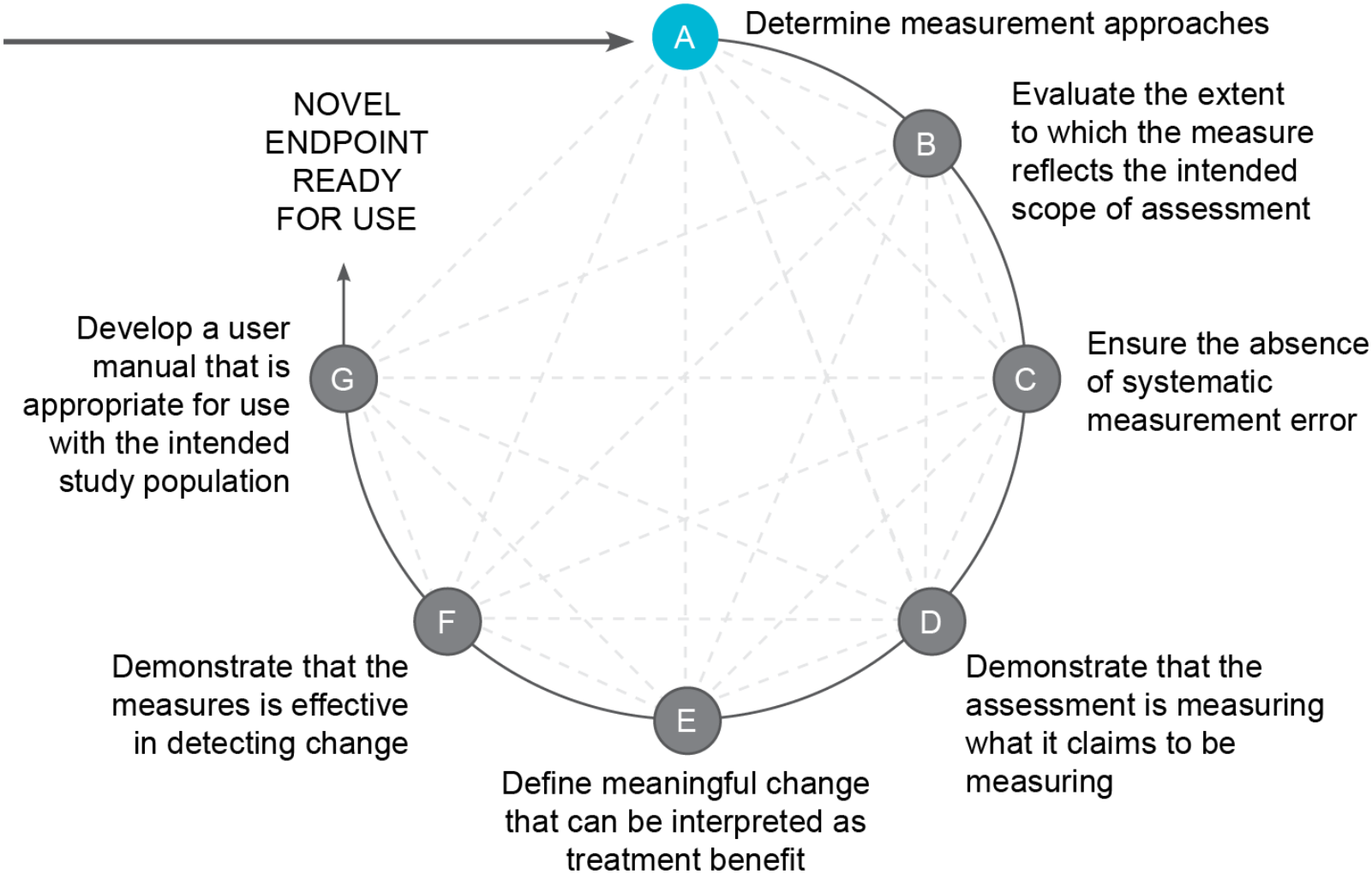
Steps for Novel Endpoint Development



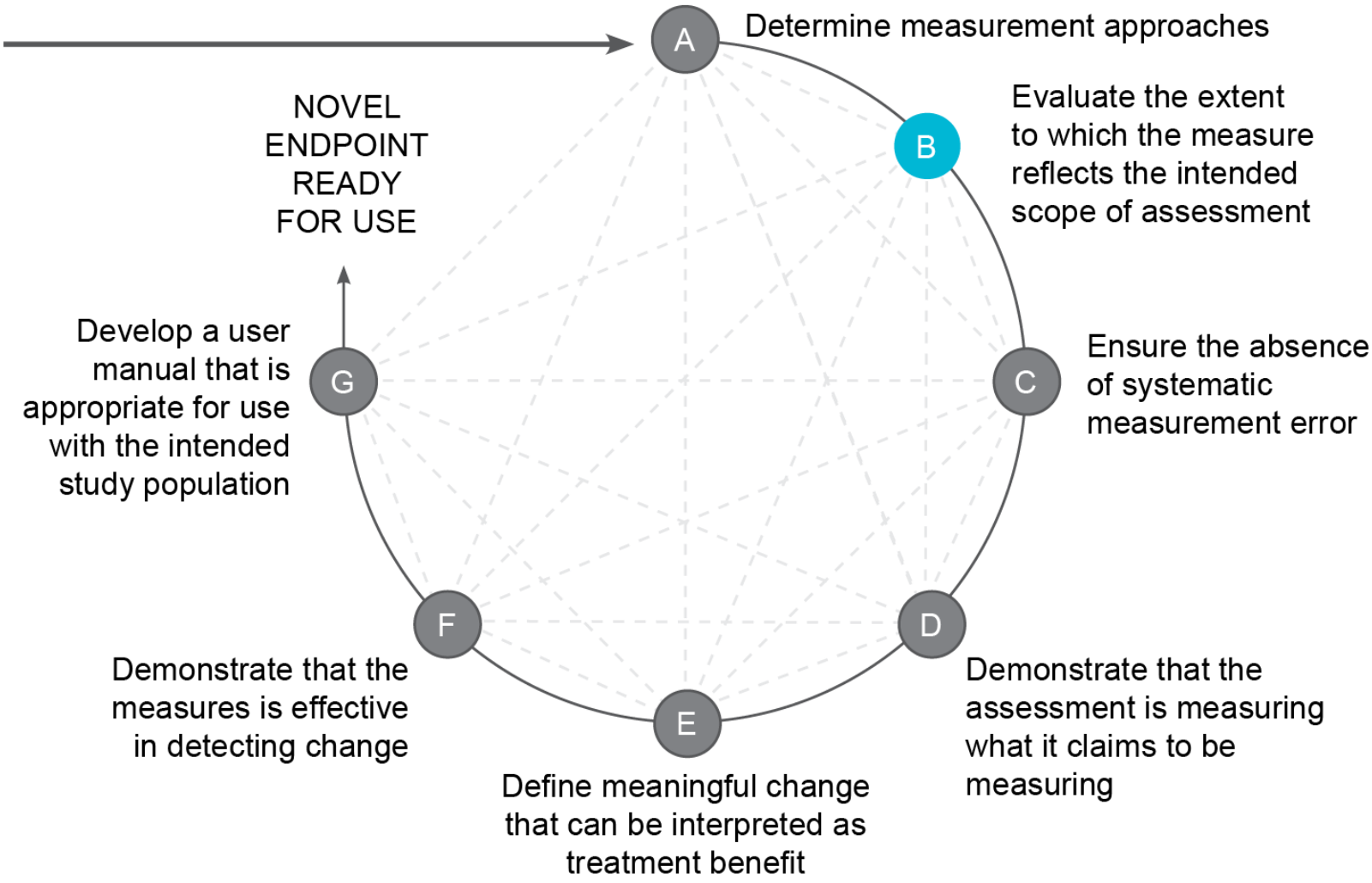
Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

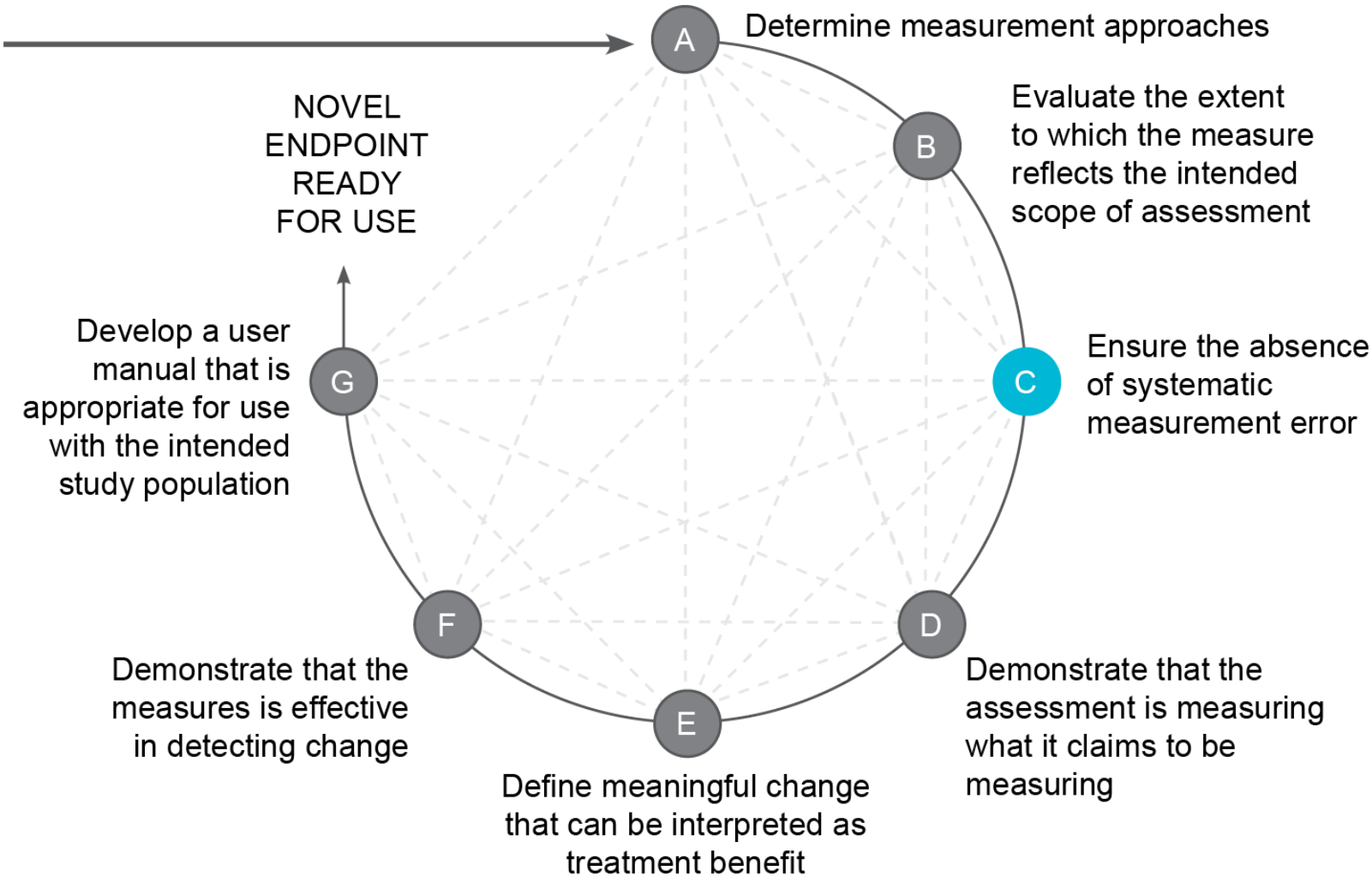
Steps for Novel Endpoint Development



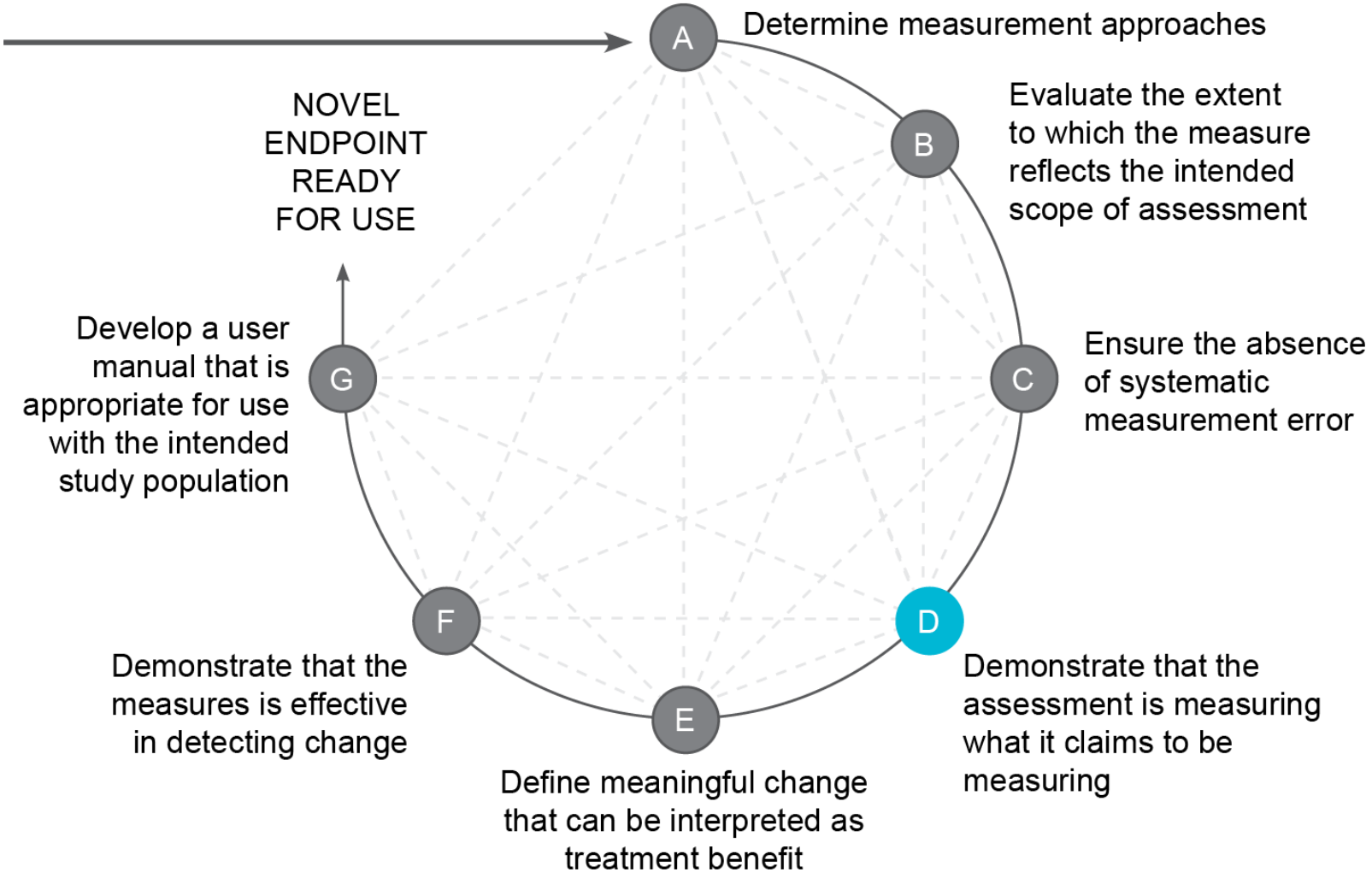
Steps for Novel Endpoint Development



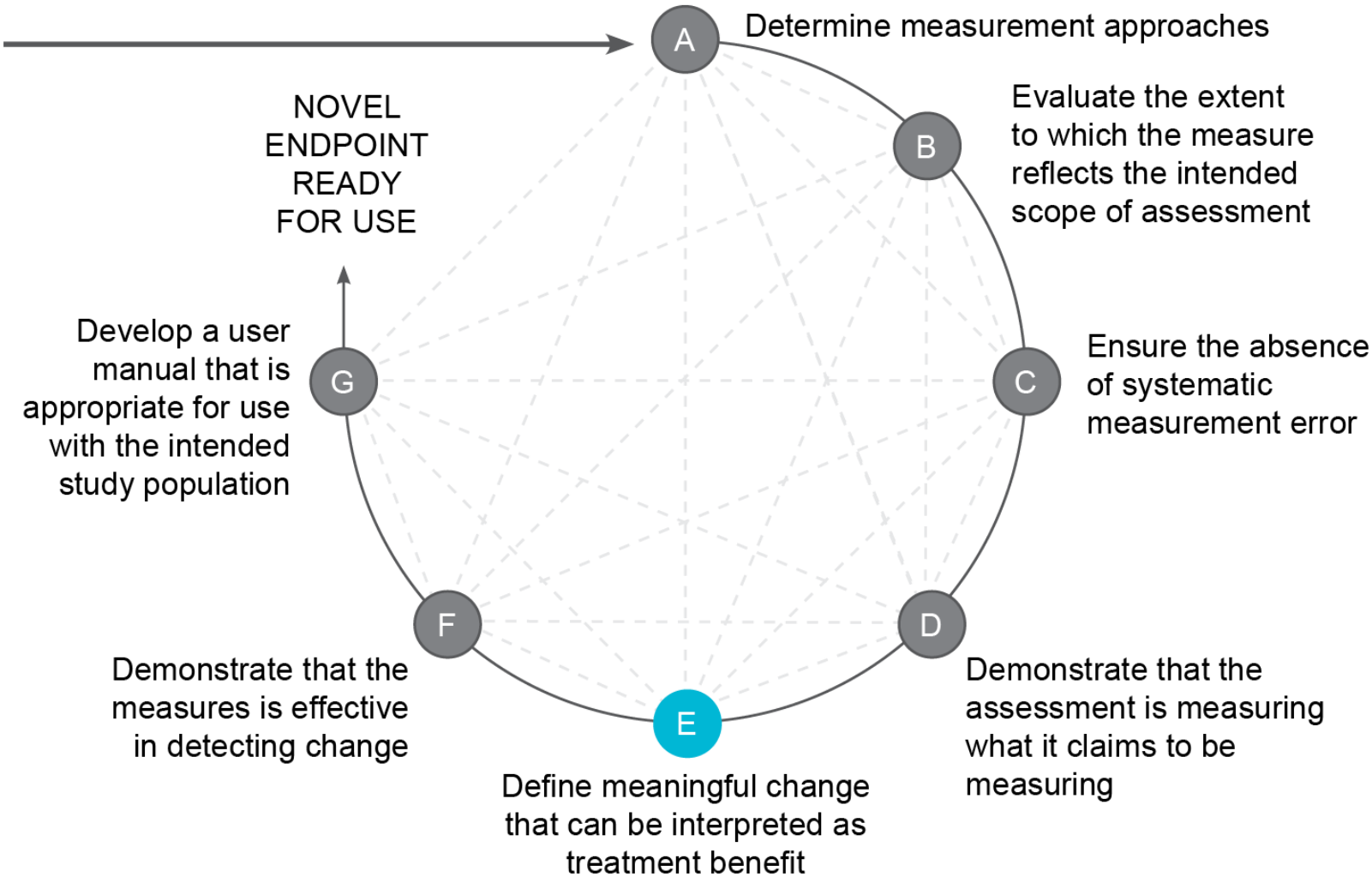
Steps for Novel Endpoint Development



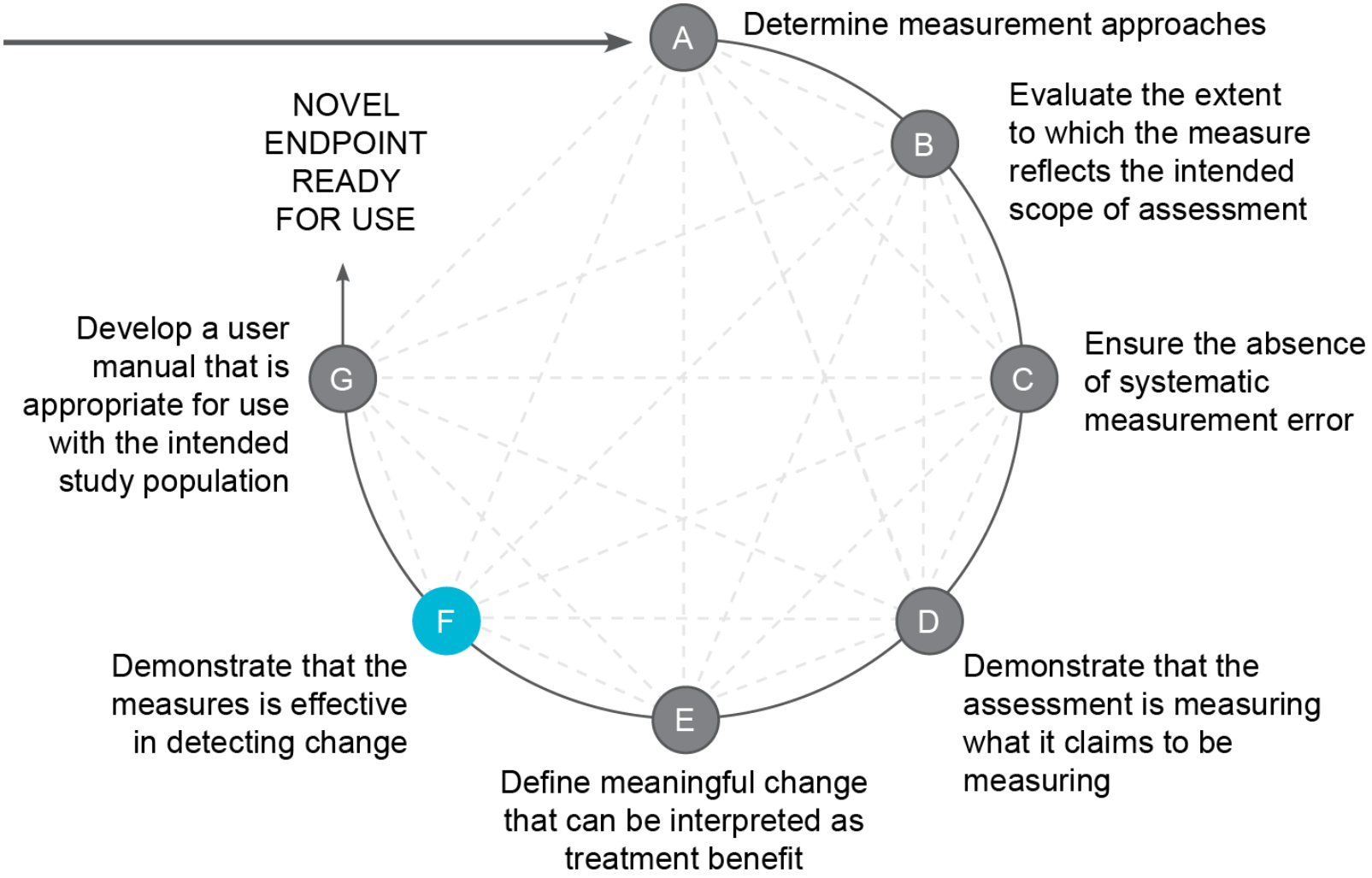
Steps for Novel Endpoint Development



Steps for Novel Endpoint Development



Steps for Novel Endpoint Development



Recommendations: Summary

- **Foster collaboration among key stakeholders**
- **Optimize novel endpoint selection**
  - Focus on measures that are meaningful to patients
  - Select the device after selecting an outcome assessment
  - Use a systematic approach to identify key novel endpoints
- **Approach novel endpoint development process practically**
  - Create technical standards for mobile technology-derived assessments
  - Engage regulators throughout the process
  - Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies
  - Critically position novel endpoints in interventional trials

MCT Novel Endpoints Products

- **Recommendations** for selecting, developing, and incorporating novel endpoints using mobile technologies for use in clinical trials
- **Selection tool** to support decisions between viable novel endpoints for development
- **Quick reference guide** to interacting with FDA regarding novel endpoint development

MCT Novel Endpoints Products

- **Flowchart** is supported by **detailed description** of novel endpoint development
  - Approaches to executing each step
  - Considerations at each step
  - Links to tangible examples demonstrating each step
- Four **use cases** providing tangible examples
  - Parkinson's disease
  - Diabetes
  - Heart failure
  - Duchenne's muscular dystrophy

Download the Recommendations & Resource

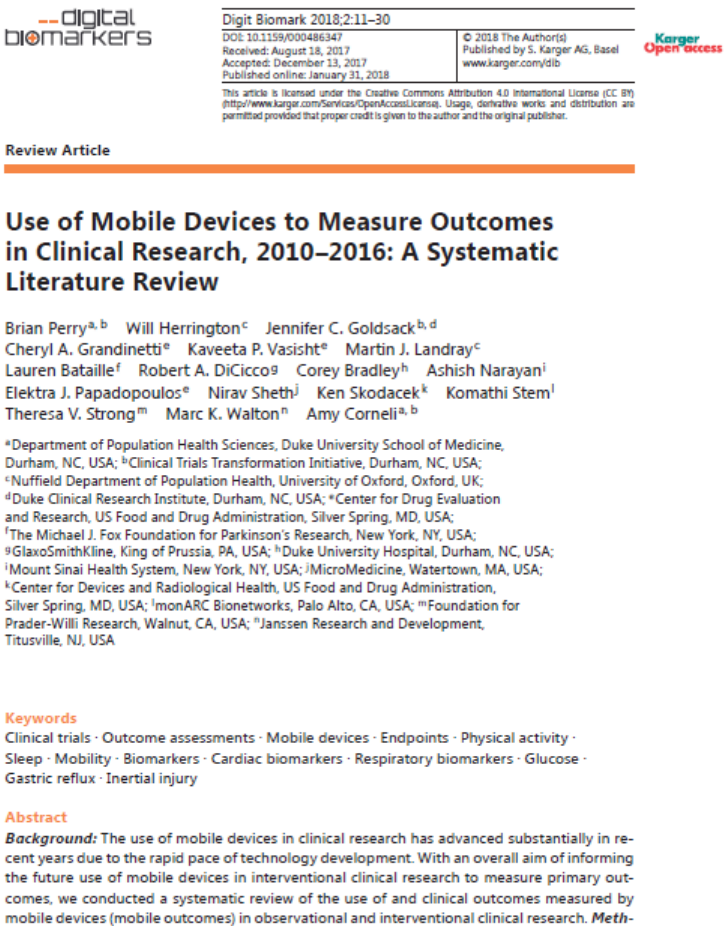
- Visit https://www.ctti-clinicaltrials.org/projects/novel-endpoints to access and download the full suite of CTTI's MCT Novel Endpoints Recommendations and Resources

Where is our Field Right Now?
How is CTTI Driving Adoption of its Work?

Rob DiCicco
TransCelerate BioPharma Inc.

How Should We Think about Mobile?

Multi-Stakeholder Collaboration is Needed



digital biomarkers

Digit Biomark 2018;2:11–30
DOI: 10.1159/000486347
Received: August 18, 2017
Accepted: December 13, 2017
Published online: January 31, 2018

Review Article

Use of Mobile Devices to Measure Outcomes in Clinical Research, 2010–2016: A Systematic Literature Review

Brian Perry[a, b] Will Herrington[c] Jennifer C. Goldsack[b, d]
Cheryl A. Grandinetti[e] Kaveeta P. Vasisht[e] Martin J. Landray[c]
Lauren Bataille[f] Robert A. DiCicco[g] Corey Bradley[h] Ashish Narayan[i]
Elektra J. Papadopoulos[e] Nirav Sheth[j] Ken Skodacek[k] Komathi Stem[l]
Theresa V. Strong[m] Marc K. Walton[n] Amy Corneli[a, b]

[a]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA; [b]Clinical Trials Transformation Initiative, Durham, NC, USA; [c]Nuffield Department of Population Health, University of Oxford, Oxford, UK; [d]Duke Clinical Research Institute, Durham, NC, USA; [e]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; [f]The Michael J. Fox Foundation for Parkinson's Research, New York, NY, USA; [g]GlaxoSmithKline, King of Prussia, PA, USA; [h]Duke University Hospital, Durham, NC, USA; [i]Mount Sinai Health System, New York, NY, USA; [j]MicroMedicine, Watertown, MA, USA; [k]Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, MD, USA; [l]monARC Bionetworks, Palo Alto, CA, USA; [m]Foundation for Prader-Willi Research, Walnut, CA, USA; [n]Janssen Research and Development, Titusville, NJ, USA

Keywords
Clinical trials · Outcome assessments · Mobile devices · Endpoints · Physical activity · Sleep · Mobility · Biomarkers · Cardiac biomarkers · Respiratory biomarkers · Glucose · Gastric reflux · Inertial injury

Abstract
Background: The use of mobile devices in clinical research has advanced substantially in recent years due to the rapid pace of technology development. With an overall aim of informing the future use of mobile devices in interventional clinical research to measure primary outcomes, we conducted a systematic review of the use of and clinical outcomes measured by mobile devices (mobile outcomes) in observational and interventional clinical research. ***Meth-***

- Mobile devices are widely used in clinical research
- Utility in interventional trials to assess therapeutic benefit has been limited
- Consolidation of evidence supporting **clinically meaningful specific outcomes**
- Standardization of use
  - Data capture
  - Placement

CTTI

A Systematic Review: The Use of Mobile Technologies

Therapeutic area	Interventional trials N=22 n(%)	Observational studies N=66 n(%)	All publications N=88 n(%)
Cardiology	4(18)	16(24)	20(23)
Diabetes	5(28)	8(12)	13(15)
Sleep	3(14)	7(11)	10(11)
Obesity	0(0)	9(14)	9(10)
Geriatrics	0(0)	9(14)	9(10)
Neurology	1(5)	3(5)	4(5)
Reproductive and peripartum health	2(9)	2(3)	4(5)
Orthopedics	1(5)	3(5)	4(5)
Pulmonology	0(0)	3(5)	3(3)
Arthritis	1(5)	2(3)	3(3)
Psychology	0(0)	3(5)	3(3)
Cancer	2(9)	0(0)	2(2)
Nephrology	0(0)	2(3)	2(2)
Gastroenterology	1(5)	1(2)	2(2)
Nutrition	1(5)	1(2)	2(2)

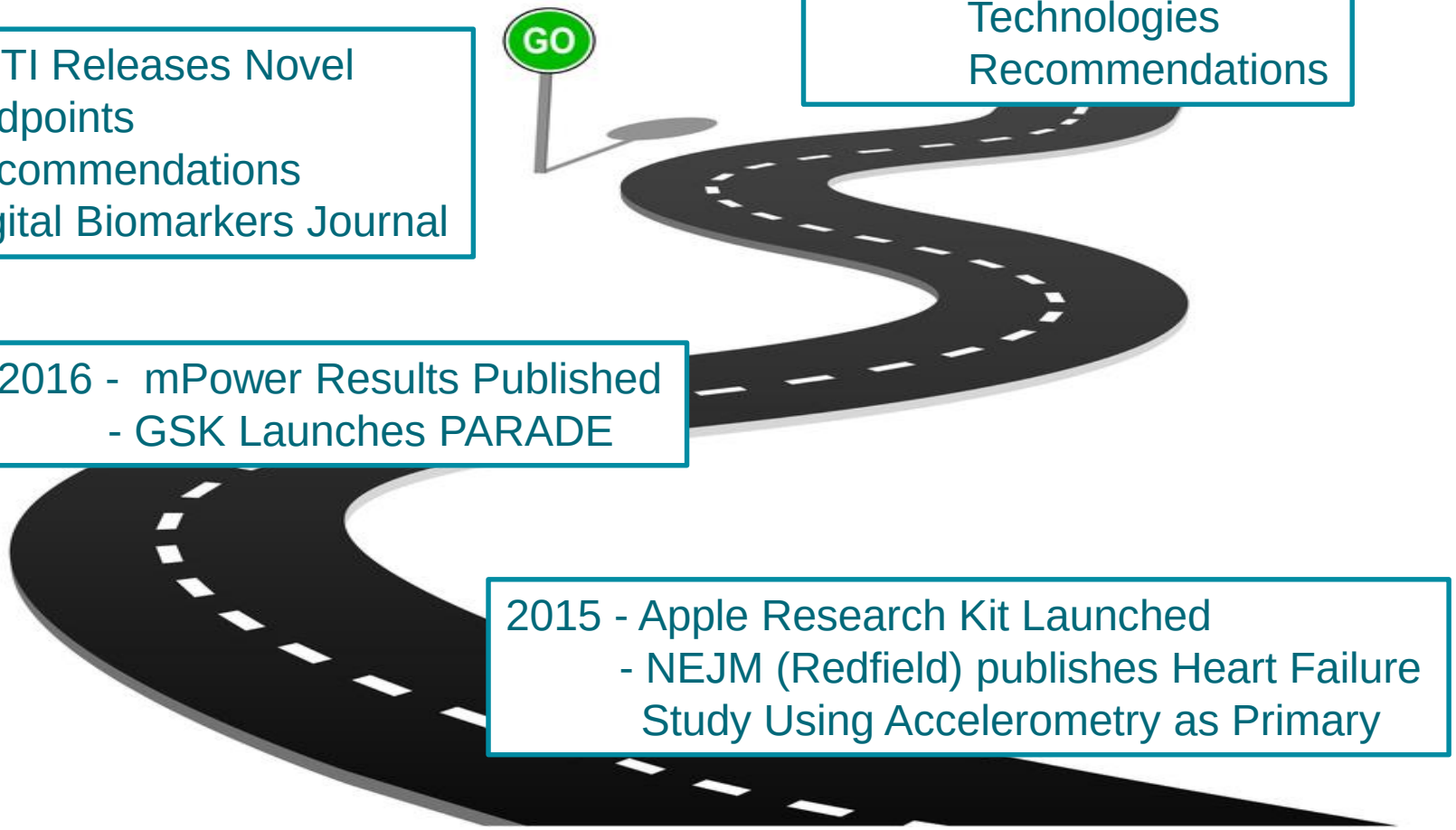
*Perry, Brian, et al. "Use of Mobile Devices to Measure Outcomes in Clinical Research, 2010–2016: A Systematic Literature Review." Digital Biomarkers 2.1 (2018): 11-30.

CTTI

Where Are We on the Journey?

2018 - CTTI Releases Mobile Technologies Recommendations

2017 - CTTI Releases Novel Endpoints Recommendations
- Digital Biomarkers Journal



2016 - mPower Results Published
- GSK Launches PARADE

2015 - Apple Research Kit Launched
- NEJM (Redfield) publishes Heart Failure Study Using Accelerometry as Primary

2011 - Pfizer Launches 1st Virtual Trial

CTTI

Moving From What the Device Measures to Clinically Meaningful Endpoints

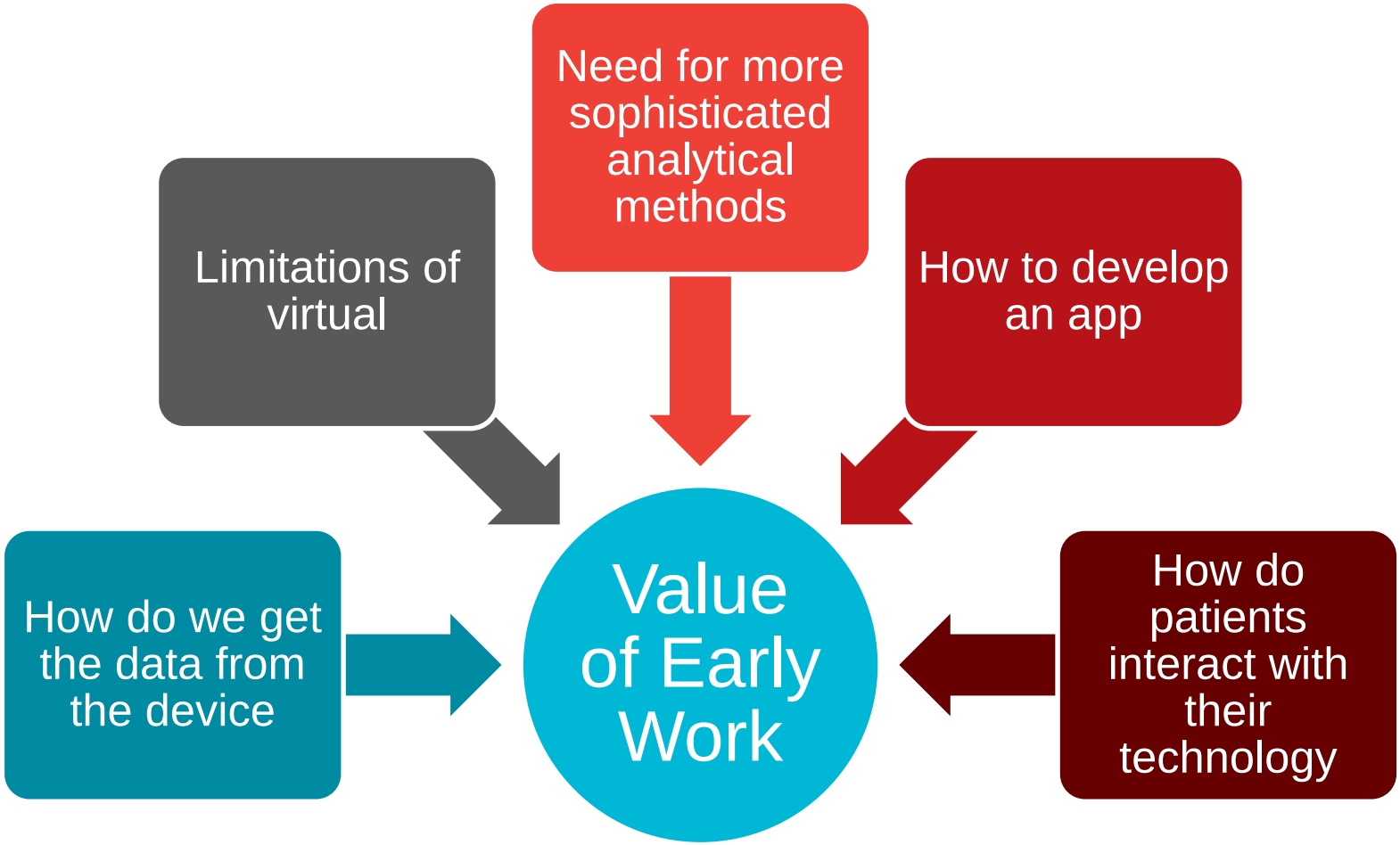
- CTTI describes 4 use cases
  - Heart failure
  - Parkinson's disease
  - Duchenne's Muscular Dystrophy
  - Hypoglycemia

- *Digital Biomarkers* Launched
  - Pilot study in patients with PD and Huntington's Disease
  - Significantly more time spent lying down
  - Differences in sleep patterns described
  - Data collected passively and actively
  - *Digit Biomark 2017;1:52–63*

https://www.karger.com/Article/FullText/479018

CTTI

What Are We Learning ?



The Way We Discover & Develop New Medicines is being Disrupted

Verily, Stanford and Duke kick off Project Baseline study to develop broad reference of human health

By **Heather Mack** | April 20, 2017

Alphabet-owned Verily has launched the **Project Baseline Study**, a collaborative effort with Stanford Medicine and Duke University School of Medicine to amass a large collection of broad phenotypic health data in hopes of developing a well-defined reference of human health.

Project Baseline aims to gather data from around 10,000 participants, each of whom will be followed for four years, and will use that data to develop a "baseline" map of human health as well as to gain insights about the transitions from health to disease. Data will come in a number of forms, including clinical, imaging, self-reported, behavioral, and that from sensors and biospecimen samples. The study's data repository will be built on Google computing infrastructure and hosted on Google Cloud Platform.

CTTI

How Can We Accelerate the Use of Mobile?

- Data sharing
  - MJF mobile tech advisory council, Vivli, TransCelerate ?
- Use existing paradigms for tissue biomarkers and patient reported outcomes
  - Engage regulators (and other stakeholders) early
- Define your mobile strategy along with the development plan for a medicine
  - What are the goals?
    - Facilitate enrolment, develop value evidence, measure disease burden, proof of principle, product labeling

CTTI's Commitment to Driving the Adoption of Technology-Derived Novel Endpoints in Clinical Trials

Jen Goldsack
Clinical Trials Transformation Initiative

Alzheimer's Disease

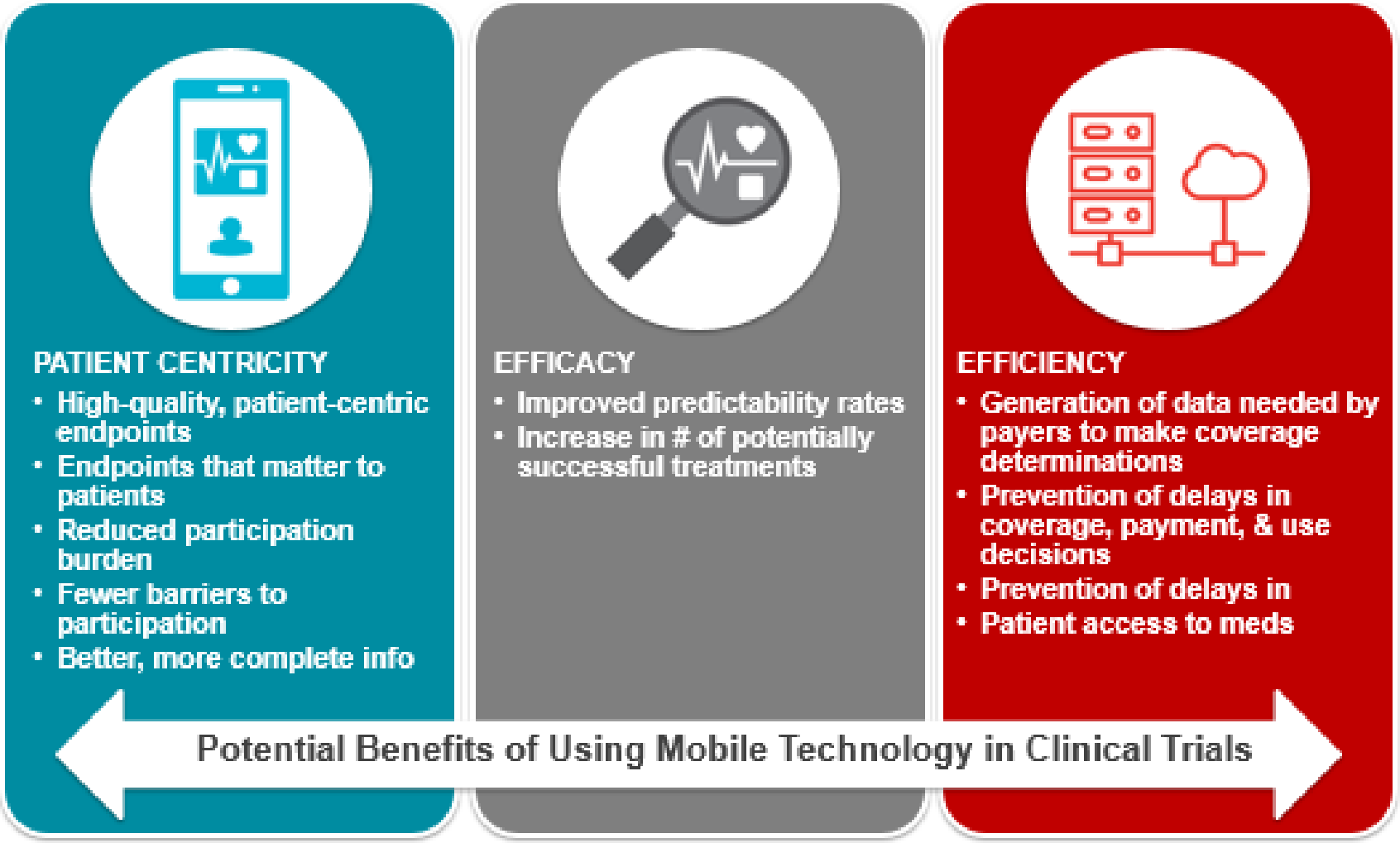
- Affects >5 million Americans today
- Projected to affect >16 million Americans by 2050
- Alzheimer's and other dementias cost $259 billion in the U.S. in 2017
- Projected to cost up to $1.1 trillion in 2050
- Symptomatic treatments offer little relief
- No disease modifying interventions
- "Gold standard" endpoint is ADAS-cog, first used in 1984

Parkinson's Disease

- Affects ~1 million Americans today
- Projected to affect >3.8 million Americans by 2050
- Direct and indirect costs were $25 billion in the U.S. in 2017
- Projected to cost up to $86.9 billion in 2050
- No disease modifying interventions
- UPDRS first used in 1987
  - Modified 2007 MDS-UPDRS
- PDQ-39 first used in 1995

Duchenne Muscular Dystrophy

Benefits of Technology-Derived Endpoints



CTTI

CTTI Mobile Clinical Trials (MCT) Program

PURPOSE:

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

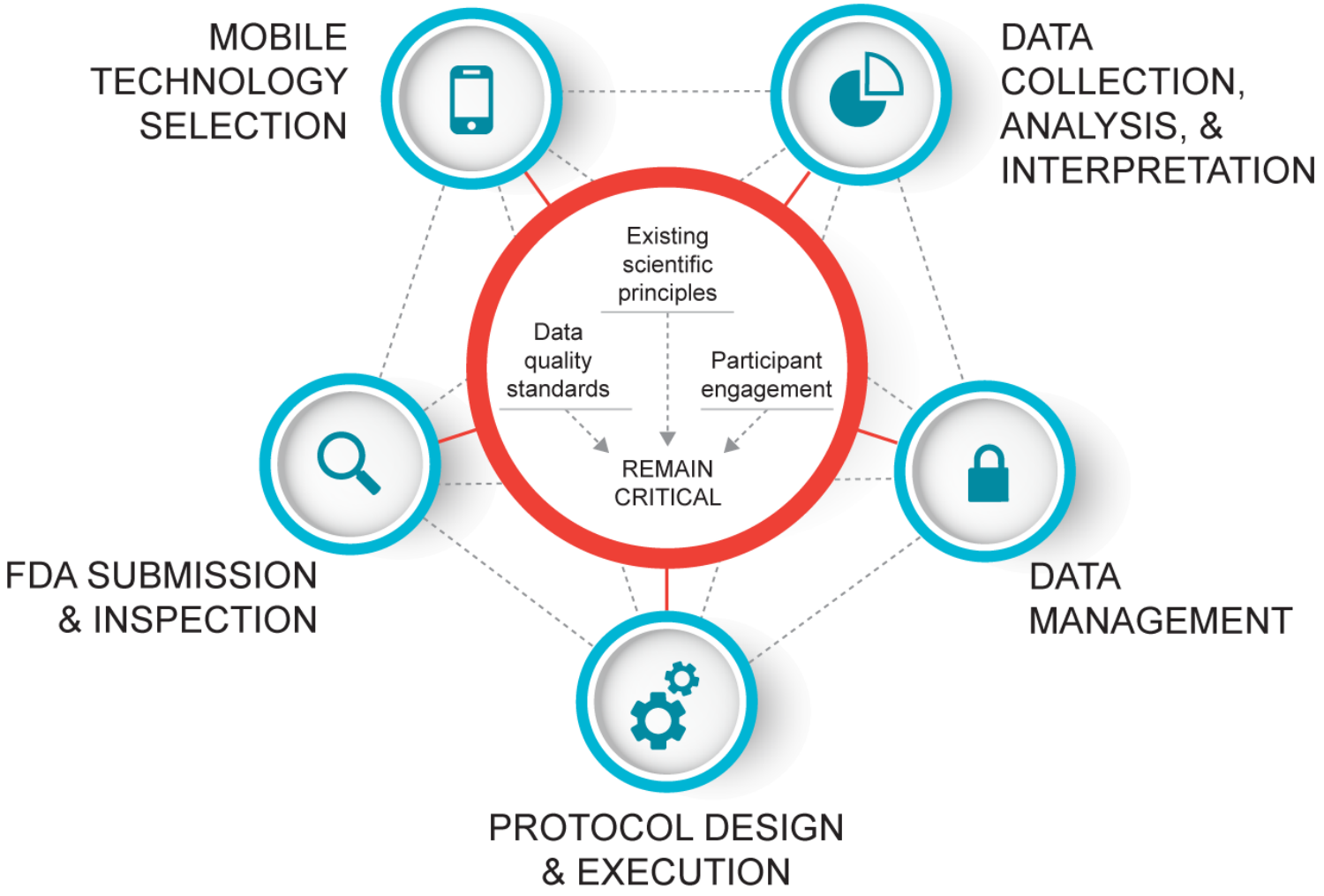
ANTICIPATED IMPACT:

Increased number of clinical trials leveraging mobile technologies

4 PROJECTS

**Scope: FDA-regulated clinical trials after the time of initial research volunteer consent*

CTTI MCT Mobile Technologies Project



CTTI MCT Decentralized Trials Project

- Focus is decentralized trials conducted through telemedicine and mobile healthcare providers in the U.S.
- Federal *and* local U.S. state laws, regulations, and considerations come into play
- The recommendations will target industry sponsors and CROs, addressing the following topics:
  - Protocol Design
  - Telemedicine State Licensing Issues
  - Drug Supply Chain
  - Mobile Practitioners
  - Considerations for Investigator Delegation and Oversight
  - Safety Monitoring

CTTI MCT Stakeholder Perceptions Project

Project recommendations and resources will address…

- Engaging patient and site perspectives for study planning
- Maximizing value and minimizing burden for study participants
- Addressing barriers for investigative sites

Creating a Comprehensive Toolkit

- **Developing an integrated, program-level offering**
  - A “one-stop shop” for mobile clinical trials
  - Coming in 2019!

Take Action

- **Download published recommendations and resources**
  - MCT Novel Endpoints https://www.ctti-clinicaltrials.org/briefing-room/recommendations/developing-novel-endpoints-generated-mobile-technology-use-clinical
  - MCT Mobile Technologies https://www.ctti-clinicaltrials.org/projects/mobile-technologies
- **Go to www.ctti-clinicaltrials.org to sign up to receive CTTI's monthly e-newsletter for updates on the rolling release of future recommendations**
  - Decentralized Trials, September 2018
  - Stakeholder Perceptions, January 2019
  - Additional Program level offerings
  - Related Driving Adoption Activities

CTTI

THANK YOU.

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Rob DiCicco dicicco.ra@gmail.com

Jen Goldsack jennifer.Goldsack@duke.edu

Will Herrington will.herrington@ndph.ox.ac.uk

www.ctti-clinicaltrials.org