Developing Novel Endpoints Generated by Mobile Technology for use in Clinical Trials

Multi-Stakeholder Expert Meeting

Summary of the Meeting held September 29-30, 2016

DoubleTree by Hilton
8727 Colesville Road | Silver Spring, MD

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

Meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: http://www.ctti-clinicaltrials.org/projects/novel-endpoints

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MEETING OBJECTIVES

Identify how to develop novel endpoints based on data generated by mobile technology for use in clinical trials by discussing the following use cases:

- Physical activity level and gait, measured using an accelerometer, as an endpoint for Parkinson's disease
- Physical activity level, measured using an accelerometer, as an endpoint for heart failure
- Blood sugar level, measured using a wearable continuous glucose monitor (CGM), as an endpoint for diabetes
- Physical activity level, measured using an accelerometer, as an endpoint for muscular dystrophy

MEETING BACKGROUND

Mobile technology offers a powerful tool to improve the quality and efficiency of clinical trials, yet it remains uncommon for endpoint data captured by mobile technology to be incorporated into clinical trials. Mobile technology-derived novel endpoints provide a number of advantages over traditional outcome assessments. Mobile technology offers the advantage that data can be acquired continuously, rather than at discrete time points, which should provide greater insight into disease progression. Moreover, as data are gathered in the "real world", they should more closely reflect patients' daily lives. By gathering data outside of the clinic, mobile technology can also decrease patient and investigator burden by reducing clinic visits, which may lead to increased patient recruitment and decreased loss to follow up. Finally, mobile technology offers a method to potentially reduce the overall costs of performing clinical trials.

The goal of the Clinical Trials Transformation Initiative (CTTI) Mobile Clinical Trials (MCT) Program is to increase the adoption and appropriate use of mobile technology in clinical trials. For the purposes of this project, we define novel endpoints as either new endpoints that are not currently used or existing endpoints that can now be measured in new ways, using mobile technology. The overall goal of the meeting was to write four use cases to generate new, empirical knowledge to support the development of recommendations to clarify the pathway for developing novel endpoints for use in clinical trials. Meeting participants discussed the following use cases: use of accelerometers to capture novel endpoints in clinical trials for heart failure, Parkinson's disease, and muscular dystrophy and use of continuous glucose monitors (CGM) to capture novel endpoints in diabetes trials.

MEETING EXECUTIVE SUMMARY

The MCT Novel Endpoints Project Team convened a meeting involving key stakeholders on September 29 and 30, 2016. The participants included investigators and patient representatives with expertise and experience in the disease states associated with each use case, engineers and mathematicians with expertise in the specified devices, regulators, nonprofit consortia, and statisticians. The majority of the discussion at the meeting occurred during four different breakout sessions where discrete teams were each tasked with developing one of four use cases, as outlined in the meeting objectives.

The meeting operated under the assumption that the device capturing the data for each proposed novel endpoint produces data that are reliable, valid, and sensitive, i.e. analytical validation was out of scope for this meeting. Developing data standards and proposed novel endpoints that focused on survival were also out of scope for this meeting. Work on the use cases focused on the treatment benefit these novel endpoints can demonstrate at the present time, and proposed novel endpoints were intended to demonstrate treatment benefit, not disease prevention.

Recurring themes throughout the meeting included the following:

- The starting point in developing novel endpoints must be patients and their needs.
- It is important to consider whether a particular device is optimal for a specific patient population or subpopulation.
- Novel endpoints must be considered and used in the context of established endpoints, e.g., mobile technology-derived endpoint data should still be used alongside measures such as survival and disease progression.
- Traditional endpoints, such as well-established clinical outcome assessments, provide a model for developing endpoints that can be recapitulated. We can look back at how these measures were developed and use insights to inform novel endpoint development.
- Traditional endpoints also provide a tool with which to correlate results from novel endpoints. This allows for validation that a change observed using a novel endpoint is relevant to the patient.
- An important step in the process is to establish the relationship of the mobile technology metric to disease severity and progression through, for example, observational or epidemiological studies. This provides a baseline for determining what is a meaningful change.

As a next step, the MCT Novel Endpoints project team will use the findings from this meeting to inform general recommendations to clarify the pathway for developing novel endpoints for use in clinical trials.

MEETING SUMMARY

The purpose of the meeting was to write four use cases to generate new, empirical knowledge to support the development of recommendations to clarify the pathway for developing novel endpoints for use in clinical trials. The intention is that ultimately this work, along with other efforts in the CTTI MCT Program, will increase the number of clinical trials appropriately leveraging mobile technology.

Session I: Developing Novel Endpoints

Session I focused on the process of developing novel endpoints. Outcome assessments (OAs) are the measures used in an endpoint that describe or reflect how an individual feels, functions, or survives. Outcome assessments provide an objective measure that can be used to demonstrate a clinically meaningful benefit of an intervention and can be broadly divided into biomarker-based outcomes and clinical outcome assessments (COAs). Biomarkers provide an objective, highly indirect measurement of patient health that is not affected by evaluator judgment and are typically molecular or physiological in nature. COAs are reliant on evaluator judgment and patient volition and may either directly or indirectly measure patient well-being. COAs can be divided into PROs, clinician-reported outcomes (ClinRos), observer-reported outcomes (ObsROs), and performance outcomes (PerfOs). COAs should be well-defined, reliable, and appropriate for the target population and indication.

Three important concepts in developing OAs are the meaningful health aspect (MHA), concept of interest (COI), and the context of use (COU). The MHA is an aspect of a patient's life that is negatively affected by a disease. MHAs are often relatively "abstract" and might encompass multiple activities relevant to patients' daily lives, such as cognitive decline associated with Alzheimer's disease. The COI is the concept that an OA is meant to measure. COIs effectively provide a simpler, more measurable element of an MHA. For example, if an investigator wanted to assess a patient's ambulatory abilities (the MHA), they might measure the patient's walking capacity (the COI) by having them perform a 6-minute walk test (the COA). COU specifies how an OA fits into the overall study design, which can include factors such as the disease of interest, patient subpopulations, concomitant care, endpoint positioning, etc. The overall COU must be factored into development of OAs, as no single OA is sufficient to characterize and assess a disease state on its own. Rather, different classes of outcome measures should be used in combination to provide complementary information.

Some of the key steps in designing a new outcome measure are identifying the aspect of the disease that is meaningful to patients (MHA), developing assessment tools that can measure the COI in a valid and reliable way, and determining the amount of change that reflects a meaningful benefit to the patient. Important factors to consider in the process include:

- Content validity – does the OA actually represent the COI?
- Interpretability – does the COI reflect the MHA?
- Reliability – is the measure consistent within and between patients, observers, and over time?

- Responsiveness – does the measure change when COI changes?
- Quantitative interpretation – what is a meaningful amount of change?

Session II: The Use Case Approach

Session II began with some background on the approach for creating the proposed use cases. The main goal in developing the use cases was to identify steps necessary to successfully develop a novel endpoint based on data generated by a mobile device. As steps were identified it was important to recognize requirements to complete each step in the process. Finally, it was necessary to identify any challenges that exist in the process of developing novel endpoints and to propose solutions to those challenges. The meeting then broke up into two different sessions offering a review of the technologies of interest in the use cases, with one session focusing on accelerometers and one session focusing on CGM.

Nirav Sheth from MC10, a company developing wearable sensor systems, provided an overview of accelerometer-based data capture. Accelerometers are able to detect acceleration through micro-electromechanical systems (MEMS). MEMS are capable of measuring minute accelerations in relation to gravity. Specifically, linear accelerometers provide a measure of acceleration along three axes (x, y, and z) and these three outputs are plotted against time. The raw data itself can be further processed using data science approaches to connect the signals to discernible patterns of movement. One of the strengths of accelerometers is their versatility. Modern sensors can be placed on a variety of bodily locations in order to measure a variety of movements, over time, and in different environmental contexts. Accelerometers are able to break down different levels of activity across a day, for example differentiating lying versus sitting versus walking. Some specifications to consider in choosing a particular accelerometer include the power and memory requirements, size and weight of the wearable system, and the desired resolution of the data.

Courtney Lias from the Food and Drug Administration (FDA) provided an overview of CGMs. Type 1 diabetes patients use regular Blood Glucose (BG) monitoring to help determine needed insulin doses to stay within a safe BG range. Traditionally this is accomplished with finger-stick blood samples, test strips, and glucometers. Alternatively, CGMs measure interstitial glucose levels on a continuous basis, enabling the detection of glycemic variability, excursions, and trends that would not be evident using only traditional finger-stick BG measures. CGM measures glucose concentration frequently (e.g. every 1 to 5 minutes) via a subcutaneous sensor in the interstitial fluid. The sensor is physically connected to a small transmitter which sends the data via Bluetooth to a receiver. Receivers can be a CGM-dedicated receiver, an insulin pump, or a smart phone and have alarms that alert patients to both high and low BG values/trends. CGM technology extrapolates interstitial glucose measures back to arterial blood glucose levels, however interstitial measures are less accurate than BG measures and also lag about 15 minutes behind them.

Breakout Sessions and Use Cases

Following the technology review sessions, the meeting attendees split into four different breakout sessions, each focused on one of the use cases. Each use case team successfully selected a potential novel endpoint and determined the steps necessary to develop it for use in a clinical trial. As these steps were identified, each use case team noted the requirements to complete each step in the process and identified any challenges that exist. Finally, each use case team proposed solutions to those challenges as identified opportunities for reducing friction in the process. At the end of each day, the breakout groups reconvened in a general session so that the facilitators of each use case team could share updates on progress and considerations across all use case teams.

The four use cases written during this meeting are currently being used by the CTTI MCT Novel Endpoints project team, along with findings from a systematic review and data extraction tool, to inform the development of recommendations to clarify the pathway for developing novel endpoints for use in clinical trials. The use cases will be published shortly and recommendations are expected in 2017.

FUNDING STATEMENT

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact the MCT Novel Endpoints Project Manager Jennifer Goldsack at Jennifer.goldack@duke.edu or visit http://www.ctti-clinicaltrials.org.

Appendix A. Multi-Stakeholder Expert Meeting Agenda

THURSDAY, SEPTEMBER 29, 2016

8:30AM — Welcoming Remarks

8:30AM — Welcome and Background
Jen Goldsack, Clinical Trials Transformation Initiative (CTTI)
- Brief overview of CTTI and the Mobile in Clinical Trials Program
- Review of Novel Endpoints Project, meeting goals and agenda

8:50AM — Introductions

9:05-10:20 — Session I: Developing Novel Endpoints

Session I Facilitator: Martin Landray, University of Oxford
Session I Objectives:
- Provide a high level overview of the general pathway to qualifying objective study endpoints.
- Review the difference between developing clinical outcome assessments and biomarker outcomes.
- Describe lessons learned from investigators' experience developing new outcome assessments.

9:05AM — Clinical Trial Endpoints from Mobile Technology: Regulatory Considerations
Elektra Papadopoulos; FDA, CDER

9:25AM — Developing Objective Study Endpoints
Marc K. Walton, Janssen

9:40AM — Performance Outcome Assessments: Identifying Endpoints that are Meaningful and Measurable
Stephen Coons, Critical Path Institute

9: 55AM — Developing Performance Outcome Measures for Use with Regulatory Agencies: The Aging in Motion (AIM) Coalition Experience
Cynthia Bens, Alliance for Aging Research

10:10AM — Discussion

10:40-11:05 — Session II: The Use Case Approach

Session II Facilitator: Jen Goldsack
Session II Objective:
10:40AM — Review:
- Approach to writing use cases
- Framework and definitions
- Target deliverables
- Group & room assignments for technology review sessions and breakouts

11:05-11:40 Session III: Technology Review Sessions

Session III Objective:

- Explain How the Mobile Device Makes Measurements and Generates Data

11:00AM Move to Technology Review Sessions

Accelerometer Review Session, Pinnacle Grand Ballroom

Muscular Dystrophy, Parkinson's Disease, and Heart Failure Groups
Session Facilitator: Jen Goldsack, CTTI

11:05AM Accelerometer-Based Data Capture
Nirav Sheth, MC10

11:25AM Discussion

Continuous Glucose Monitor Review Session; Council Room, Mezzanine Level

Diabetes Group
Session Facilitator: Amy Corneli, CTTI

11:05AM Use of Continuous Glucose Monitors in Clinical Trials
Courtney Lias; FDA, CDRH

11:25AM Discussion

12:30PM Convene in Breakout Group Rooms *(Assigned)*

Parkinson's Disease
Facilitator: Jen Goldsack, CTTI

Heart Failure
Facilitator: Brian Perry, CTTI

Diabetes
Facilitator: Amy Corneli, CTTI

Muscular Dystrophy
Facilitator: Annemarie Forrest, CTTI

12:30-4:00 Session IV: Breakout Sessions

12:30PM Breakout Session Member Introductions

12:40PM Introductory Comments

- Parkinson's Disease; *Diane Stephenson, Critical Path Institute*
- Heart Failure; *John Alexander, Duke University School of Medicine*
- Diabetes; *Steve Griffen, JDRF*
- Muscular Dystrophy; *Pat Furlong, PPMD*

1:00PM Facilitator-led Breakout Discussions

3:00PM Facilitator-led Breakout Discussions (Continued)

THURSDAY, SEPTEMBER 29, 2016

4:00-4:45 Session V: Use Case Progress Reports and Cross-Team Learning

4:00PM Review and Discussion of Progress in Each Use Case
Return to General Session, Pinnacle Grand Ballroom (Level 2)

- **Parkinson's Disease:** Physical activity level and gait, measured using an accelerometer, as an endpoint for Parkinson's disease
- **Heart Failure:** Physical activity level, measured using an accelerometer, as an endpoint for heart failure
- **Diabetes:** Blood sugar level, measured using a wearable continuous glucose monitor, as an endpoint for diabetes
- **Muscular Dystrophy:** Physical activity level, measured using an accelerometer, as an endpoint for muscular dystrophy

4:45PM Adjourn Day 1

FRIDAY, SEPTEMBER 30, 2016

8:30-11:45 Session VI: Breakout Sessions *(Continued)*

8:30AM Facilitator-led Breakout Discussions

10:30AM Facilitator-led Breakout Discussions *(Continued)*

12:30-1:45 Session VII: Highlights and Review of Next Steps

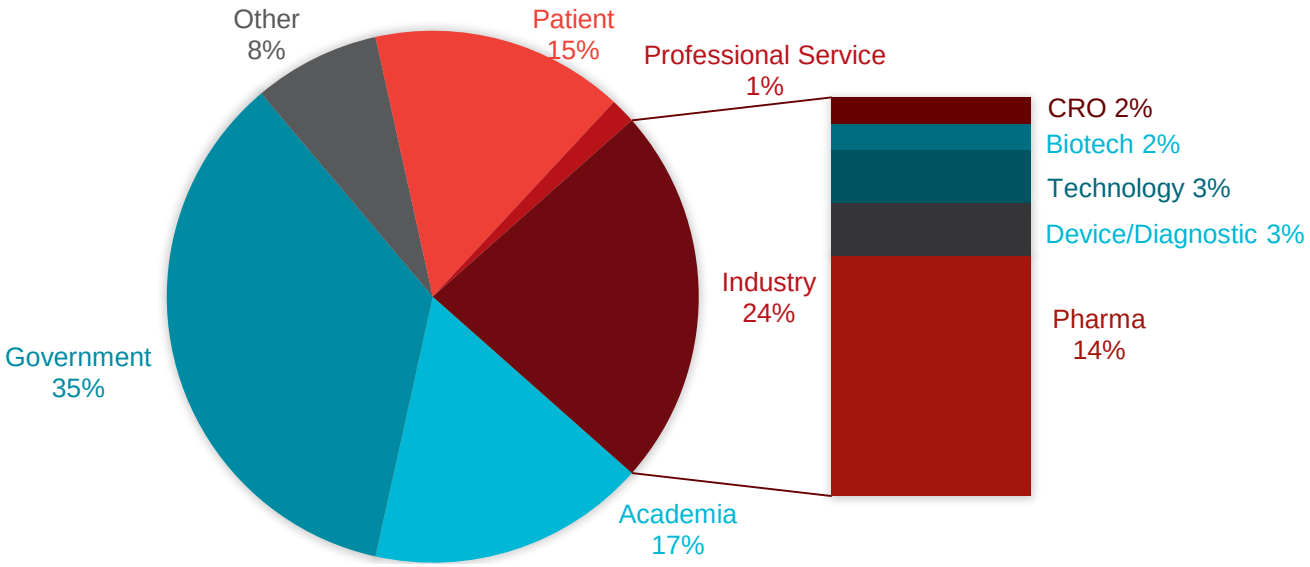
12:30PM Review of Highlights from Each Use Case
Return to General Session, Pinnacle Grand Ballroom

1:30PM Review of Next Steps
Jen Goldsack, CTTI

1:45PM Adjourn and Departures

Appendix B. Multi-Stakeholder Expert Meeting Participants

Our multi-stakeholder expert meeting participants include representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants are expected to be actively engaged in dialogue both days.



MULTI-STAKEHOLDER EXPERT MEETING PARTICIPANTS

Participant Name	Affiliation
Chul Ahn	Food and Drug Administration, CDER
John H. Alexander	Duke University, Duke Clinical Research Institute
Shashi Amur	Food and Drug Administration, CDER
Adem Aten	Duke University, Margolis Center for Health
Lauren Bataille	Michael J. Fox Foundation
Cynthia Bens	Alliance for Aging Research
Tracy Bergemann	Medtronic
Michael Binks	Worldwide Research and Development, Pfizer Inc
Thomas Birkner	Food and Drug Administration, CDER
Abby Bronson	Parent Project Muscular Dystrophy (PPMD)
Michelle Campbell	Food and Drug Administration, CDER
Stephen Carlson	Whitsell Innovations
William Chong	Food and Drug Administration, CDER
Jennifer Clark	Food and Drug Administration, CDER
Stephen Joel Coons	Critical Path Institute (C-Path)
Selena Daniels	Food and Drug Administration, CDER
Amy DeLozier	Eli Lilly & Company
Robert DiCicco	GlaxoSmithKline (GSK)
Ray Dorsey	University of Rochester
Billy Dunn	Food and Drug Administration, CDER
Sonya Eremenco	Critical Path Institute (C-Path)
Annemarie Forrest	Clinical Trials Transformation Initiative
Patricia Furlong	Parent Project Muscular Dystrophy (PPMD)
Jennifer Goldsack	Clinical Trials Transformation Initiative (CTTI)
Cheryl Grandinetti	Food and Drug Administration, CDER
Steve Griffen	JDRF
Matthew Heasley	GlaxoSmithKline (GSK)
William Herrington	CTSU, University of Oxford
Campbell Hutton	JDRF
Leslie Jacobsen	Bristol-Myers Squibb
Nicole Jelesoff	Duke University Medical Center
Kun Jin	Food and Drug Administration, CDER
Daniel Karlin	Pfizer, Inc.
Kathi Kinnett	Parent Project Muscular Dystrophy (PPMD)
Paul Kluetz	Food and Drug Administration, CDER
Craig Kollman	Jaeb Center for Health Research
Scott Komo	Food and Drug Administration, CDER
Nicholas Kozauer	Food and Drug Administration, CDER
Martin Landray	University of Oxford
Mary Jane Lapinski	Women's Heart Alliance
Courtney Lias	Food and Drug Administration, CDRH
Walter Maetzler	UKSH, Campus Kiel
Tristan Massie	Food and Drug Administration, CDER

Participant Name	Affiliation
Anna McCollister-Slipp	Scripps Translational Science Institute
Aristide Merola	University of Cincinnati
Christopher Miller	AstraZeneca
Evan Muse	Scripps Translational Science Institute
Ashish Narayan	Northwell Health
Gary Ostroff	UMass Medical School
Elektra Papadopoulos	Food and Drug Administration, CDER
Dharmesh Patel	Food and Drug Administration, CDRH
Nikunj Patel	Food and Drug Administration, CDER
Brian Perry	Clinical Trials Transformation Initiative
Gerald Podskalny	Food and Drug Administration, CDER
Miriam Rafferty	Northwestern University
Leonard Sacks	Food and Drug Administration, CDER
Julie Schulman	Duke Clinical Research Institute
Jonathan Seltzer	ACI Clinical
Ravi Shankar	Merck
Nirav Sheth	MC10
John Shin	Medtronic
Ken Skodacek	Food and Drug Administration, CDRH
L Mary Smith	Bamboo Therapeutics
Komathi Stem	ReThynk Consulting
Diane Stephenson	Critical Path Institute (C-Path)
Theresa Strong	Foundation for Prader-Willi Research
H. Lee Sweeney	University of Florida, Myology Institute
Robert Temple	Food and Drug Administration, CDER
Pamela Tenaerts	Clinical Trials Transformation Initiative
Kaveeta Vasisht	Food and Drug Administration, CDER
Marc K. Walton	Janssen Research & Development
Jeremy Wyatt	ActiGraph