Increasing the use of mobile technology–derived endpoints in clinical trials

William G Herrington¹, Jennifer C Goldsack² and Martin J Landray¹,³

Mobile technology can be used in clinical trials to generate novel endpoints that provide information that was previously difficult or impossible to obtain. Technology-derived novel endpoints could also make clinical trials more efficient and less burdensome to trial participants while contributing to a meaningful and real-world understanding about patient experiences beyond the brief data “snapshots” typically gathered in clinical care or research settings. This research letter summarizes the recommendations provided by the Clinical Trials Transformation Initiative (CTTI) which are intended to support the selection, development and inclusion of such technology-derived novel endpoints in future clinical trials.

The need for recommendations

The functional capabilities of mobile technologies, such as smartphones, wearables and other remote sensor devices, and the ease with which devices transmit data has driven a remarkable increase in their use. It is estimated that globally in 2015, 25 billion devices were connected to the Internet, equating to about 3.5 devices/person.¹ Use of such technology in routine healthcare (referred to as mHealth) offers opportunities for improved care outcomes as well as more effective, convenient, patient-centric and lower cost healthcare delivery.²

Incorporating electronic technology into the design and conduct of clinical trials may also offer quality and efficiency improvements.³ However, it is currently uncommon for mobile technology to be used to ascertain trial endpoints. The paucity of technology-derived novel assessments is potentially a missed opportunity to realize more scalable, objective and patient-centric clinical trial endpoints. As mobile technology can be used with minimal interference to participants’ daily lives, such endpoints may prove preferable to the current practice of lengthy and costly study visits. Using mobile technology could reduce the barriers to, and burden of, participation in clinical trials and inform measurements that better reflect how patients feel and function in the real world.

Mobile technology additionally has the potential to record completely novel, patient-centric endpoints in areas of unmet need. For example, a 6-min walk test is the commonly used and accepted outcome, but more than half of people with this disease, particularly those who have lived the longest with the disease, cannot walk well enough to perform the test and are therefore excluded from trial participation. Many activities identified by this patient population³ are reliant on upper limb function, which could be assessed using a wrist-worn inertial sensor, such as an accelerometer.

Use of accelerometers is not without challenges,⁴ but they could facilitate the collection of commonly used trial endpoints. For example, combining them with large capacity memory and long-life batteries into small devices allows continuous measurements of activity over weeks. The resultant raw accelerometry data can be processed to derive meaningful measurements of physical activity (and also sleep, gait and tremor)⁵,⁶ and has been successfully used to measure physical activity in 100,000 participants in UK Biobank.⁷ In one example, a difference in physical activity with a heart failure intervention compared to placebo was identified by accelerometry measures, but not by the traditional regulatory-accepted patient-reported outcomes, the 6-min walk test or lab assessment of N-terminal prohormone of bone natriuretic peptide.⁸

¹Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK
²Clinical Trials Transformation Initiative (CTTI), Durham, NC, USA
³Big Data Institute and Oxford National Institute for Health Research Biomedical Research Centre, University of Oxford, Oxford, UK

Corresponding author:
Jennifer C Goldsack, Clinical Trials Transformation Initiative (CTTI), 300 W Morgan St, Durham, NC 27701, USA.
Email: jennifer.goldsack@duke.edu
The opportunities for mobile technology–derived trial endpoints to enhance trials are not limited to accelerometer-based assessments of movement. There are now wireless wearable remote sensors which can measure heart rate, rhythm and blood pressure, skin patches which can conveniently estimate sweat glucose concentration, injectable tissue oxygenation monitors for use in peripheral arterial disease and contact lenses which measure intraocular pressure. To develop data captured from such technologies into valid endpoints which can be used in regulatory submission trials, collaborative efforts are required. To accelerate such work, CTTI—a multi-stakeholder organization co-founded by Duke University and the US Food and Drug Administration (FDA) in 2007—convened a project team to issue recommendations on how to select and develop such endpoints and include them in clinical trials. The recommendations are summarized in Table 1 above, and the full resources are all available online at the CTTI website.9

### Recommendations

Accelerating the use of mobile technology in trials will likely be best achieved by sponsors, patients, clinicians, technology companies and regulators collaborating in a precompetitive environment. Regulators should be engaged early in the process of developing novel endpoints for use in clinical trials for regulatory submission. CTTI has developed a quick reference guide to interacting with the FDA to support this engagement.9

Development of clinical endpoints should be based on an understanding of the disease and its impact on health, and conceptualize the treatment benefit. The FDA has published in this area.10 This process should include patients and clinicians familiar with the disorder to ensure that novel endpoints address an aspect of the disease that, if improved or prevented, would be clinically meaningful.

Technology-derived measures should only be developed if they offer a real advantage over existing endpoints and methods of assessment. Specifically, technical feasibility alone should not provide a rationale for accepting a new measurement. A systematic approach is recommended when deciding if such endpoints are potentially useful. To support this approach, CTTI has developed an interactive selection tool.9

The minimum criteria to select a device should include establishing: (a) tolerability and acceptability of the device by participants and (b) analytic validity of the device (i.e. the device should have known and acceptable performance characteristics). Since the technical performance requirements of the device are driven by the outcome assessment, selection of the mobile device should occur after the specific measurement the device is required to capture is identified.

Currently, there are few technical standards in the field of technology-derived assessments. Such standards are required for the efficient development and rapid adoption of any technology, and to promote efficient exchange of information derived from different studies. Standards allow investigators and device manufacturers to invest resources with assurance of end-user confidence. Industry-wide standards are needed to foster consistent use of terminology, common data (and metadata) storage and transparent use of analytic algorithms to convert raw data into clinically meaningful values.

The process of developing novel endpoints generated by data captured using mobile technologies for regulatory acceptance does not differ substantially from developing any other kind of outcome assessment. Notwithstanding the need for thoughtful selection and standards across measures, sponsors and academic investigators should consider adding technology-derived measures to existing studies and trials. CTTI has created a flowchart of the steps required for this iterative process, a tool detailing each step, and example use cases in a range of conditions, including Duchenne muscular dystrophy, Parkinson’s disease, heart failure and diabetes.9

In conclusion, there are real opportunities for technology-derived endpoints to address unmet clinical need, make endpoints more patient-centric and/or enhance existing trial endpoints. The approaches

---

**Table 1.** Summary of Clinical Trial Transformation Initiative recommendations for developing novel endpoints generated by mobile technology for use in clinical trials.

| Optimizing novel endpoint selection | Practical approaches to the novel endpoint development process |
|------------------------------------|------------------------------------------------------------|
| 1. Focus on measures that are meaningful to patients | 1. Foster collaboration among key stakeholders |
| 2. Select the device after selecting an outcome assessment | 2. Create technical standards for mobile technology–derived assessments |
| 3. Use a systematic approach to identify key novel endpoints | 3. Engage with regulators |
| 4. Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies | 5. Think critically about how to optimally position novel endpoints in interventional trials |

*a*Full details available online at the Clinical Trial Transformation Initiative (CTTI) website.9
recommended by CTTI provide a framework to accelerate their collaborative development and adoption.

Acknowledgements

The Clinical Trials Transformation Initiative’s (CTTI) Developing Novel Endpoints Generated by Mobile Technology in Clinical Trials Project Group included the following people: Jennifer C Goldsack, CTTI; Lauren Battaille, The Michael J Fox Foundation for Parkinson’s Research; Rob DiCicco, GlaxoSmithKline; Cheryl Grandinetti, U.S. Food and Drug Administration (US FDA); William G Herrington, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), and Medical Research Council-Population Health Research Unit (MRC-PHRU); Martin Landray, CTSU, MRC-PHRU, Oxford National Institute for Health Research Biomedical Research Centre, and Big Data Institute, University of Oxford; Kaveeta Vasisht, US FDA; Ashish Narayan, Mount Sinai Health System; Elektra Papodopoulos, US FDA; Nirav Sheth, MicroMedicine, Inc.; Ken Skodacek, US FDA; Komathi Stem, monARC Bionetworks, Inc.; Theresa Strong, Foundation for Prader-Willi Research; Marc K Walton, Janssen Research & Development; and Brian Perry, CTTI.

Declaration of conflicting interests

All authors have completed and submitted ICMJE Form for Disclosure of Potential Conflicts of Interest.

Funding

Funding for this article was made possible, in part, by the U.S. Food and Drug Administration through grant R18FD005292 and cooperative agreement U19FD003800. Views expressed in publications do not necessarily reflect the official policies of the U.S. Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the U.S. Government. Partial funding was also provided by pooled membership fees and in-kind contributions from the Clinical Trials Transformation Initiative’s member organizations.

ORCID iD

Martin J Landray https://orcid.org/0000-0001-6646-827X

References

1. Topol EJ, Steinhubl SR and Torkamani A. Digital medical tools and sensors. JAMA 2015; 313: 353–354.
2. Roess A. The promise, growth, and reality of mobile health—another data-free zone. N Engl J Med 2017; 377: 2010–2011.
3. Rosa C, Campbell AN, Miele GM, et al. Using e-technologies in clinical trials. Contemp Clin Trials 2015; 45(Pt A): 41–54.
4. Murphy SL. Review of physical activity measurement using accelerometers in older adults: considerations for research design and conduct. Prev Med 2009; 48: 108–114.
5. Van Hees VT, Sabia S, Anderson KN, et al. A novel, open access method to assess sleep duration using a wrist-worn accelerometer. PLoS ONE 2015; 10: e0142533.
6. Elble RJ and McNames J. Using portable transducers to measure tremor severity. Tremor Other Hyperkinet Mov 2016; 6: 375.
7. Doherty A, Jackson D, Hammerla N, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank study. PLoS ONE 2017; 12: e0169649.
8. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015; 373: 2314–2324.
9. Clinical Trials Transformation Initiative—Official Recommendations. Developing novel endpoints generated by mobile technology for use in clinical trials, https://www.ctti-clinicaltrials.org/briefing-room/recommendations/developing-novel-endpoints-generated-mobile-technology-use-clinical (2017, accessed 28 November 2017).
10. US Food and Drug Administration. Roadmap to patient-focused outcome measurement in clinical trials, https://www.fda.gov/downloads/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm370174.pdf (accessed 17 March 2017).