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

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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. In Duchenne muscular dystrophy, 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 population[3] are reliant on upper limb function, which could be assessed using a wrist-worn inertial sensor, such as an accelerometer.

Use of acclerometers 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 pro-hormone of bone natriuretic peptide.[8]

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

Optimizing novel endpoint selection
1. Focus on measures that are meaningful to patients
2. Select the device after selecting an outcome assessment
3. Use a systematic approach to identify key novel endpoints
Practical approaches to the novel endpoint development process
1. Foster collaboration among key stakeholders
2. Create technical standards for mobile technology–derived assessments
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]

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

recommended by CTTI provide a framework to accelerate their collaborative development and adoption.

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