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THE mHEALTH CONNECTION TO ADVANCE CLINICAL RESEARCH:

EMERGING ROLE OF MOBILE HEALTH AND DIGITAL TECHNOLOGIES TO FOSTER PATIENT-CENTRIC TRIALS

August 2015

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The next revolution in clinical trial execution is taking shape in the rapid adoption of "mHealth" technologies — mobile devices ranging from smartphones to wearable health monitoring sensors. Mobile technologies have the potential to make the collection of clinical trial data more accurate, timely and convenient for study subjects. As mHealth devices are developed and deployed to collect data on multiple study endpoints, their adoption promises to improve research efficiencies and support the creation of vast health databases enabled by cloud computing. mHealth applications are expected to drive more patient-centric research models by increasing patient convenience and engagement, resulting in improved subject retention. This paper discusses emerging mHealth devices, their potential application in clinical trials and current PPD-conducted studies to assess the feasibility of wearable data collection devices in clinical trials to achieve focused endpoints and improve the patient experience.

DIGITAL TECHNOLOGIES ARE SHAPING CLINICAL TRIALS OF THE FUTURE

A new drug development paradigm is emerging, driven by technologies that use today's staggering computer power together with Internet connectivity to collect and analyze unprecedented amounts of health data. Databases of historical and current health data — from genetic profiles to electronic health records and health outcomes data — are providing information for modeling and simulations that improve clinical trial design. Real-time data management platforms underpin advances in study quality and efficiency with methodologies including adaptive trial design and risk-based monitoring.

In the past five years, clinical research models have evolved using these technologies to integrate and operationalize diverse sources of health data to:

+ Use simulation and predictive statistical models to improve the design of drug development plans and study protocols
+ Optimize clinical trial design using data-driven identification of study endpoints and patient populations
+ Access, recruit and enroll study subjects using social media
+ Conduct simulated trials using "virtual patients" to compare effectiveness of health interventions and predict long-term outcomes

In the next five years, these technologies will mature to enable research models that are expected to include:

+ mTrials that use mobile technologies — wearable devices, smartphone and tablet apps, Skype and other "face time" patient-physician interactions — to collect patient data and improve patient engagement by reducing site visits, delivering prompts and sharing information

+ Cloud health databases built from continuously uploaded patient data, analyzed in real time for drug sponsor and CRO operational use and scientific oversight

+ Remote trials managed by central sites in which study operations — recruitment, enrollment, informed consent, data collection — are conducted entirely on the Internet

+ Collaborative trial platforms in a precompetitive space that function based on shared investment; biopharma companies compete on the strength of the science rather than on speed and efficiency of duplicative development programs

This emerging research landscape is visible in initiatives such as I-Spy 2, the collaborative research platform to evaluate investigational breast cancer therapies,[1] and REMOTE, Pfizer's 2012 Internet-based pilot clinical trial.[2] Early simulated trials using virtual patients can be glimpsed in a 2015 study aimed at estimating the effectiveness of DPP-4 class antidiabetics in preventing major adverse cardiovascular events.[3]

The next step toward digital technology-driven advances in clinical trial execution has arrived in the rapid consumer adoption of wearable devices that monitor health data. From the growth of wearable devices like FitBit to the ubiquitous smartphone, diverse mobile technology applications are emerging to advance patient care, health services and health research — collectively known as "mHealth." Their benefits are based on improving operational efficiencies, increasing timeliness and access, and putting patients at the center of care and research interactions to provide greater control and engagement.[4]

This paper discusses evolving mHealth technologies, their potential to improve data collection and patient engagement in research, and PPD's current work in a collaborative project to implement and evaluate the use of mHealth wearable devices for data collection in a clinical trial.

THE NEXT ADVANCE IN DATA COLLECTION

Although clinical trials have used mobile communication devices like the Palm Pilot to collect patient-reported data since the 1990s, the new wave of mHealth sensor devices promises a paradigm shift in data collection. The use of low-cost wearable monitors to collect continuous, accurate health data in real time has the potential to transform the clinical research process.

The promise of mHealth research capabilities is evident in the current boom in consumer health devices as funding for and purchasing of health-centric wearables continues to increase. From 2011-2013, venture funding of biosensors and wearable monitors increased fivefold, more than double the growth of digital health technologies during the same period. According to ABI Research, of the 90 million wearable computing devices that were expected to ship in 2014, 74 million have biosensing capabilities.[5] In addition, according to a mobile health market report, more than 97,000 mHealth apps were available to consumers by 2013.[6]

Enabled by the smartphone-plus-GPS platform, devices like the FitBit wristband and the Misfit Wearables clothing tag conveniently track physical activity. Apple is developing a biometric headphone system to monitor vital signs, including heart rate and temperature, while the wearer listens to music. Google also recently developed a health-tracking wristband specifically for use in clinical trials capable of measuring pulse, heart rhythm, skin temperature and environmental factors such as light exposure and noise levels.

Medical grade monitoring devices are currently used to support patient care in gerontology and chronic disease conditions. For example, Equivital's EQ02 LifeMonitor belt collects metrics including ECG, respiratory rate, oxygen saturation, blood pressure, skin and core temperature and galvanic skin response.[8] Coupled with Bluetooth technology, monitoring devices like 9Solutions

IPCS and BodyTel transmit patient measurements directly to caregivers.[9] An ingestible monitoring device from Proteus Digital Health collects data on medication ingestion, dose timing and physiologic responses, which are transmitted to the patient's smartphone.[10]

The volume of health data being generated by mHealth devices will be transformative across the entire health care spectrum, from wellness and prevention to treatment and research. An example of this future is the IBM-Apple initiative to connect consumer fitness monitoring with wellness and prevention. IBM's Watson Health aims to create a "secure, cloud-based data sharing hub" to store and analyze data from smartphones and fitness trackers as a source of real-world health data to support diagnoses and disease alerts to individuals and caregivers.[11]

In the future, IBM hopes to evolve Watson's capabilities to include the ability to read and interpret medical images including brain scans and X-rays.[12] Examples from the biopharma industry include Novartis and GlaxoSmithKline. Novartis is partnering with both technology partners and a CRO in programs designed to use mHealth approaches that will improve the experience of clinical trial subjects[13]; GlaxoSmithKline is collaborating with Medidata Solutions on a method development project to explore the potential of linking mHealth data collection with cloud-based technologies to map patient-reported outcomes into clinical records.[14]

BENEFITS IN CLINICAL TRIALS: CURRENT APPLICATIONS AND ASSESSMENTS

Adoption of mHealth in clinical research is in its infancy but is likely to progress quickly based on compelling advantages demonstrated in early applications.

Wearable monitors measure vital endpoint data objectively and accurately with capability for continuous measurement and real-time reporting into clinical investigators and research databases. In clinical trials, mHealth devices offer the means to:

+ Generate real-world, continuous measurement of health status as subjects follow their daily routines; offer opportunities to build richer patient health profiles
+ Deliver accurate measurements that improve on patient-reported outcomes (PROs); deliver, time-marked data to compare and verify PROs
+ Deliver technology-driven data point analysis; facilitate actions in real time, based on the ability to assimilate patient data captured in an unsupervised environment
+ Reduce need for costly clinic visits
+ Increase convenience to encourage participation in trials
+ Improve subject retention by delivering prompts, encouraging compliance and sharing information

A 2015 search of ClinicalTrials.gov identified 95 clinical trials currently using mobile devices or applications in therapeutic areas ranging from asthma and cancer to schizophrenia and diabetes. Many of these investigations focus on mHealth feasibility in order to build a knowledge base that will guide wider use and support regulatory guidance.

For example, a Patient-Centered Outcomes Research Institute (PCORI) study is assessing mHealth benefits in implementing self-management interventions for mentally ill patients. The goal is to evaluate patient enrollment, engagement and satisfaction using mHealth-based operations compared to the traditional clinic-based approaches.[15]

Results of another comparative study demonstrated mHealth advantages in patient compliance. The Mobile Diabetes Intervention Study of 163 patients found that adding a mobile patient coaching application, together

with feedback on personalized analysis of blood glucose data and lifestyle behaviors via smartphones, substantially lowered glycated hemoglobin levels for over a year.[16]

In what may prove to be a groundbreaking cardiovascular study, the Healthy eHeart Study will combine use of social media, smartphones and wearable mHealth devices with clinic visits to "gather more data about heart health from more people than any research study has done before." The long-term study aims to develop more accurate ways to predict heart disease, identify causes and create personalized tools patients can use to forecast their risk and disease progression.[17]

OVERCOMING RESEARCH BARRIERS

A growing body of research is providing assessments of mHealth capabilities in overcoming widely recognized bottlenecks in traditional clinical trial practice: subject recruitment, subject retention and site management costs.

An estimated 70 percent of clinical studies suffer from delays in study startup, primarily due to site and patient recruitment issues.[18] The cost of managing a single active site can be has high as $2,500 per month; mHealth applications that could speed recruitment and reduce dependence on clinical sites would have a major impact on reducing research costs and time to market.[19] A 2015 audit of 14 major drug developers found that five are employing sophisticated and effective social media approaches in subject recruitment.[20] In other reports, companies including Sanofi, Pfizer and Novartis are said to be stepping up their social media applications.[21]

The high rate of patient dropout poses a number of serious challenges to today's clinical studies. A 2010 publication of the National Academies Press on issues surrounding missing data in clinical trials notes that trial dropout rate can exceed 30 percent.[22] The loss of subjects midstudy can waste valuable resources as well as jeopardize findings. Patient retention and compliance are essential for quality data and reliable results. mHealth applications have demonstrated value in improving patient engagement and compliance in care settings and promise to improve subject retention and compliance with study protocols in research.[23]

According to a 2015 SCORR/Applied Clinical Trials survey of CROs and other service providers, respondents viewed the greatest mHealth benefits as a means to improve data accuracy and patient experience. Of the half that reported using mHealth in a clinical trial, 60 percent considered mHealth applications important and said their primary objectives were to improve data quality (61 percent), patient retention (58 percent) and patient engagement (54 percent).[24]

As an emerging methodology, respondents cited four major challenges mHealth poses for implementation in clinical trials: data security and privacy, cost, data validation, and regulatory acceptance. Evolving regulation will be an important driver for adoption of mHealth solutions to advance data quality and study efficiencies.

REGULATORY CONSIDERATIONS

In the fast-moving mHealth environment, regulators are hard-pressed to keep guidance current and industry informed concerning the accepted use of these new technologies in the setting of regulatory submissions and product registration. At present, the U.S. Food and Drug Administration (FDA) may or may not categorize a given mHealth monitoring device as a medical device that is required to undergo regulatory review and approval. The FDA considers the intended use of the technology as the determining factor; depending on the use and claims made by the manufacturers, many mHealth technologies are not required to earn FDA approval.

In 2014, the FDA issued a draft guidance on its intent to exempt certain medical devices from premarket notification requirements with a list that includes a number of sensors and monitors considered mHealth technologies.[25] Further clarification is provided in the final 2015 FDA guidance, Mobile Medical Applications.[26] Sponsors now can use these guidelines, together with regulatory consultation, to determine regulatory acceptance of a given mHealth application in a trial setting.

PPD IS EVALUATING FEASIBILITY OF A WEARABLE DEVICE FOR DATA COLLECTION

A recognized innovator in clinical trial methodologies, PPD views mHealth as a transformative technology that offers a way forward in current efforts to improve data quality and eliminate bottlenecks wasting research time and investment. mHealth is also a disruptive technology that will demand leadership and research experience to design and implement clinical applications, together with a commitment to foster and promulgate best practices.

In this early stage of mHealth adoption, PPD will focus on applications aimed at improving real-time data capture and quality and increasing convenience for study subjects to support patient recruitment and engagement. We are championing the use of mHealth and developing our internal expertise and capabilities to offer effective, efficient mHealth platforms. Initial projects, like our current mHealth collaboration with Novartis, are laying foundations for future research models that will use global health databases for patient recruitment and site selection, and mHealth data collection platforms to build innovative new data resources to support future hypothesis testing and new, data-driven functions across the health care sector.

PPD is committed to implementing new methodologies with the potential to advance clinical trial execution. Central to that goal is support for patient-centric research in which health care technologies improve the experience of trial subjects as they improve research quality and efficiency. In an ongoing collaboration with a top-five pharmaceutical company, PPD is evaluating the use of mHealth devices in an observational study involving patients with chronic lung disease.

PPD is conducting a second, mHealth-enabled arm of a large study, in which a subset of patients will use two wearable monitors: one that measures blood pressure and one that measures patient activity. Some patients in the wearable device trial receive smartphones provided by the research team and other patients use their own smartphones. The research technical team created links between the smartphones and mHealth technology to automatically allow patients to report data collected by the mobile monitors.

Subjects were given trial medications and the wearable monitors, along with the trial-specific mobile application, developed by a technology vendor, installed either on their own phone or on a provided phone. In this study, the wearable monitor continuously transmits measurements to the smartphone via Bluetooth technology. At scheduled times, patients check their blood pressure and the measurement is automatically transmitted in real time to the clinical investigator and the research database. Measurements will be aggregated for use in the feasibility component of the study.

The most important objectives of the study are to evaluate mHealth usability, data quality and experience for patients. PPD will be focusing on the impact of this mHealth application on patient engagement, compliance and dropout rates. Results will provide insight into how well patient volunteers comply with instructions for using the devices. It will be important to understand how robust the devices are and how to manage possible failures. Higher-level issues include the scalability of mHealth-enabled trials and how

to identify and design mHealth technologies that earn regulatory approval for the collection of this type of data.

Researchers are now considering designs that might enroll patients and conduct some trial operations remotely, including informed consent. mHealth applications to support electronic patient reported outcomes (ePROs), which were not included in the initial study, are of particular interest.

PPD and a number of technology partners will continue joint efforts to develop customized mHealth technologies capable of collecting measurements for multiple trial endpoints. Long-term objectives include the integration of mHealth-collected trial data on PPD's real-time data management platform, Preclarus®, to enhance real-time data applications supporting adaptive trial design and risk-based monitoring practices.

CONCLUSION

Results from trials such as the one described above will become part of a growing body of mHealth research experience aimed at determining the benefits of mobile health and digital devices in clinical research. According to the U.S. National Institutes of Health, the implementation of mHealth in new models of clinical research and patient care will be transformative.

The recent proliferation of wireless and mobile technologies provides the opportunity to connect information in the real world via wearable sensors and, when coupled with fixed sensors embedded in the environment, to produce continuous streams of data on an individual's biology, psychology (attitudes, cognitions and emotions), behavior and daily environment. These data have the potential to be analyzed and used in real time to prompt changes in behaviors or environmental exposures that can reduce health risks or optimize health outcomes. mHealth has the potential to change when, where and how health care is provided; and to ensure that important social, behavioral and environmental data are used; to understand the determinants of health; and to improve health outcomes.

In clinical trial execution, mHealth access to real-word patient data — continuously and in real time — will underpin operational models that achieve the next giant step forward in improving data accuracy and research efficiencies.

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