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The Case for Wearable Devices in Clinical Trials

Niklas Morton and David Blackman

With growing availability and use, wearable devices are an increasingly viable option for research.

The rapid consumer adoption of wearable devices for the collection of health data is laying the foundation for the next revolution in clinical trial operations. The integration of wearable health monitors with smartphones offers capabilities to collect continuous, accurate health data in real time. This emerging digital research platform has the potential to increased data accuracy and timeliness, improve operational efficiencies, and achieve greater patient engagement in the clinical trial process[1]

In the burgeoning consumer market, more than 97,000 mHealth apps were available to consumers by 2013.[2] Health and wellness devices like the FitBit wristband and the Misfit Wearables clothing tag conveniently track physical activity based on smartphone and GPS technology. Apple is developing a biometric headphone system to monitor vital signs while the wearer listens to music.[3]

Broad consumer use of such devices is building familiarity and will facilitate the implementation of similar medical grade devices in clinical studies. Anticipating this future, major technology companies are entering the clinical research space. Google recently developed a health-tracking wristband for use in clinical trials capable of measuring pulse, heart rhythm, skin temperature, light exposure, and noise levels.[4] The new Apple ResearchKit offers a software platform that allows researchers to create apps to manage data collected via wearable devices and smartphones.[5]

Medical grade monitoring devices now support patient care in most therapeutic areas including gerontology and chronic disease. Devices are available that monitor respiration, oxygen saturation, ECG, blood pressure, skin and core temperature, and galvanic skin response. Other devices transmit patient measurements directly to caregivers using Bluetooth technology. A number of technologies are available to monitor drug adherence. For example, ingestible monitors are available that collect data on medication ingestion, dose timing and physiologic responses, then transmit measurements to the patient's smartphone. In our experience, we are seeing more and more biopharma and technology companies partnering to launch mHealth apps that monitor conditions ranging from diabetes to heart attacks.

In clinical trial applications, electronic patient-reported outcome (ePRO) companies are integrating wearable devices to advance data collection by adding objective data points to subjective PROs. For example, one company offers ePRO software for mobile devices with apps on Android, Windows 8, and iOS. Another company offers dedicated mobile devices for use in clinical trials, including site-based devices and "bring-your-own-device" options that allow patients to use their own smartphone apps.

mHealth in clinical trials: benefits and challenges

Clinical trial models based on the integration of wearable devices and smartphones are in their infancy, but early applications demonstrate compelling benefits, including:

Increased Use of mHealth Devices

The mHealth boom: Wearable devices + smartphones

+ Fivefold increase in venture funding for wearable monitors since 2011
+ 97,000 mHealth apps available in 2013
+ Wearable vendors estimate shipment of 46 million units in 2015; 126 million in 2019
+ 4 million patients expected to use remote monitoring technologies by 2020
+ 2.1 billion global smartphone subscriptions in 2015; 6.1 billion expected by 2020

Source: Ericsson Mobility Report, June 2015

- Real-world, continuous measurement of health status as subjects follow their daily routines; opportunities to build richer patient health profiles
- Accurate measurements to improve patient-reported outcomes (PRO); deliver time-marked data to compare and verify PROs
- Improvement in subject retention by delivering prompts, encouraging compliance, sharing information; more convenience to encourage research participation
- Reduced costs by decreasing the need for clinic visits

An increasing number of trials use mobile devices or applications in therapeutic areas ranging from asthma and cancer to schizophrenia and diabetes. Results from the comparative 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 more than a year.[6] The long-term Healthy eHeart Study will combine use of social media, smartphones and wearable mHealth devices with clinic visits to develop more accurate predictions of heart disease, while creating personalized tools to forecast patients' risk and disease progression.[7]

According to a 2015 SCORR/*Applied Clinical Trials* survey of CROs and other service providers, mHealth's greatest benefits will come from improving data accuracy and patient experience.[8] A growing body of research is evaluating mHealth capabilities to improve subject retention and reduce site management costs. With dropout rates as high as 30%[9] and site management costs as high as $2,500 per month,[10] data collection based on integrated wearable devices and smartphones could reduce site dependence and deliver significant cost reductions.

Drug developers identify five major challenges in the adoption of mHealth technologies in clinical trials:[11]

- Data security and privacy
- Data qualification and validation
- Regulatory acceptance
- Adoption costs and demonstration of return on investment
- Implementing mHealth technology on a global scale

Evolving regulation will help drive adoption of mHealth-based research models. In this fast-moving environment, however, regulators are hard-pressed to keep guidance current and industry informed regarding the accepted use of these new technologies in the setting of regulatory submissions and product registration. The U.S. Food and Drug Administration has issued two sets of guidance (in 2014 and 2015, respectively) presenting regulatory views on use of mHealth technologies in clinical trials.[11,12] These evolving guidelines, together with regulatory consultation, can help sponsors determine regulatory acceptance of a given mHealth application in a specific trial setting.

Pilot study: evaluating feasibility of a wearable device in data collection

The ultimate goal of this transformative technology is to exceed standards for data quality and study efficiencies delivered by the current "gold standard" operational models. The application of wearable devices in clinical trials is beginning with feasibility evaluations to determine how mHealth technologies can be deployed effectively.

PPD participated in a collaborative, early-stage feasibility study of a wearable device-plus-smartphone application. Its goal was to evaluate the usability of the interface in data collection; training requirements for appropriate use of the mHealth technologies; and the impact of the model on data quality and patient engagement.

The feasibility study was conducted as a second, mHealth-enabled arm of a large observational study. In this arm, a subset of patients used two wearable monitors: one mea-

sured blood pressure, while the second measured patient activity. Smartphones equipped with Bluetooth-enabled links transmitted and tracked the data from the wearable devices to an investigator portal. Patients received medications, the wearable device-plus-smartphone technologies, and training to use the devices and smartphones correctly.

The goal was to test as many hypotheses surrounding the uses and types of wearable technologies as possible. For example, some patients received smartphones provided by the research team with the study mobile app installed; others downloaded the study mobile app to their own smartphones. Patients were instructed to wear the activity monitor at all times and to take their blood pressure from the wearable device at scheduled times. This allowed for the analysis of data consistency, reliability and compliance from patients on data that is transmitted constantly and automatically—without any action by the patient—with data that needed patient interaction at scheduled times. Measurements were aggregated for use in feasibility and operational future studies.

Conclusion

The volume of health data generated by mHealth devices will be transformative across the entire health care spectrum, from wellness and prevention to treatment and research. During the next five years, mHealth technologies will mature to enable advanced research models, including cloud-based health databases of continuously uploaded patient data and Internet-based trials conducted remotely. This future envisions "mTrials" that use wearable devices, smartphone and tablet apps, and patient-physician interactions via telemedicine to collect accurate data in real time. The immediate challenge is to integrate mHealth technologies into global research processes, and to learn how best to apply and interpret the data tsunami they are about to deliver.

Niklas Morton is Senior Vice President of Site and Patient Access, and David Blackman is Business Innovations Director, both with PPD.

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Where Technology and Human Behavior Intersect

Three habits can help bring patients and researchers closer together.

It's true. Bad habits can be tough to break. And it can be just as hard to adopt good ones. This is especially true in highly regulated sectors such as clinical research where changing from what's worked in the past can be seen as too risky.

But change often can improve outcomes by reducing many of the risks inherent in the process. Sometimes those changes stem from technology alone. And other times they're achieved by implementing innovative solutions where technology and human behavior intersect.

Habit #1: Leverage ePRO

The Digital Era has introduced a host of tools to streamline trials and enhance patient safety and compliance. Electronic patient reported outcomes (ePRO) help researchers collect more accurate data from patients quickly and efficiently. ePRO provides a secure method for subjects to enter diary information in the way that best suits their needs. By helping patients fulfill their responsibilities more easily, we increase the likelihood of their complying with information gathering requirements so more reliable data is collected across therapies, populations and geographies.

Habit #2: Adopt an RBM Approach

ePRO brings patients closer to researchers by incorporating their preferences into the data collection process. Other tools can bring researchers closer to subjects and help them keep closer watch on how each patient is faring during the study. For example, a risk-based monitoring (RBM) platform empowers researchers to focus resources around clearly identified risks that could compromise patient safety or study integrity.

The latest RBM tools are integrated with EDC platforms and offer end-to-end study management in an audit-trailed environment with real-time data exchange. When data indicate an established risk threshold has been crossed, the RBM software prompts you to take immediate corrective action such as unblinding a patient whose health could be in danger. In addition to improving trial safety and quality, RBM can reduce overall study costs by up to 25 percent (e.g., RBM decreases the need for onsite source data verification).

Habit #3: Practice Safe Social Media

The rapid expansion of social media has presented researchers with a proverbial double-edged sword. On the one hand, leveraging social media like Facebook and Twitter can bring researchers and patients closer together and support safer and faster trials. On the other hand, though, the use (or misuse) of social media can expose sites, CROs and sponsors to huge regulatory, financial and reputational risks.

Many organizations have learned they can tap social media to communicate more effectively and build trust with current and potential patients. By answering questions and disseminating factual information before, during and after a trial, researchers can alleviate misconceptions, strengthen compliance, increase retention and identify prospects for future studies.

But the social media sword cuts both ways. Online posts in forums, Facebook groups, blogs, etc. can compromise a trial by accidentally (or purposefully) revealing how one subject is responding (e.g., an increase or decrease in symptoms or an adverse reaction).

Subject consent forms and information materials should include strict guidelines about what patients can and cannot share online during a trial. Researchers also should monitor patients' feeds for unsuitable posts. Finally, an organization should develop a crisis communications plan to help manage its public response in the wake of a problem.

More than ever, success in clinical research depends on effectively integrating humans and technology in common pursuit of answers that will help people live healthier, more fulfilling lives. By incorporating innovative tools and habits that bring researchers and patients closer together, we can accelerate the trial process while enhancing the safety, accuracy and integrity of our work.

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mHealth Clinical Trial Measures Sleep Outcomes

Moe Alsumidaie

Study app used to scale and broaden Sleep Apnea Association's message to patients.

Adam Amdur, Chief Patient Officer of the Sleep Apnea Association launched the SleepHealth mobile app study, the first large-scale observational sleep study that leverages mobile health to collect real world data. The SleepHealth Study is available on the App Store.

Moe Alsumidaie: What inspired you to launch the SleepHealth mobile app study?

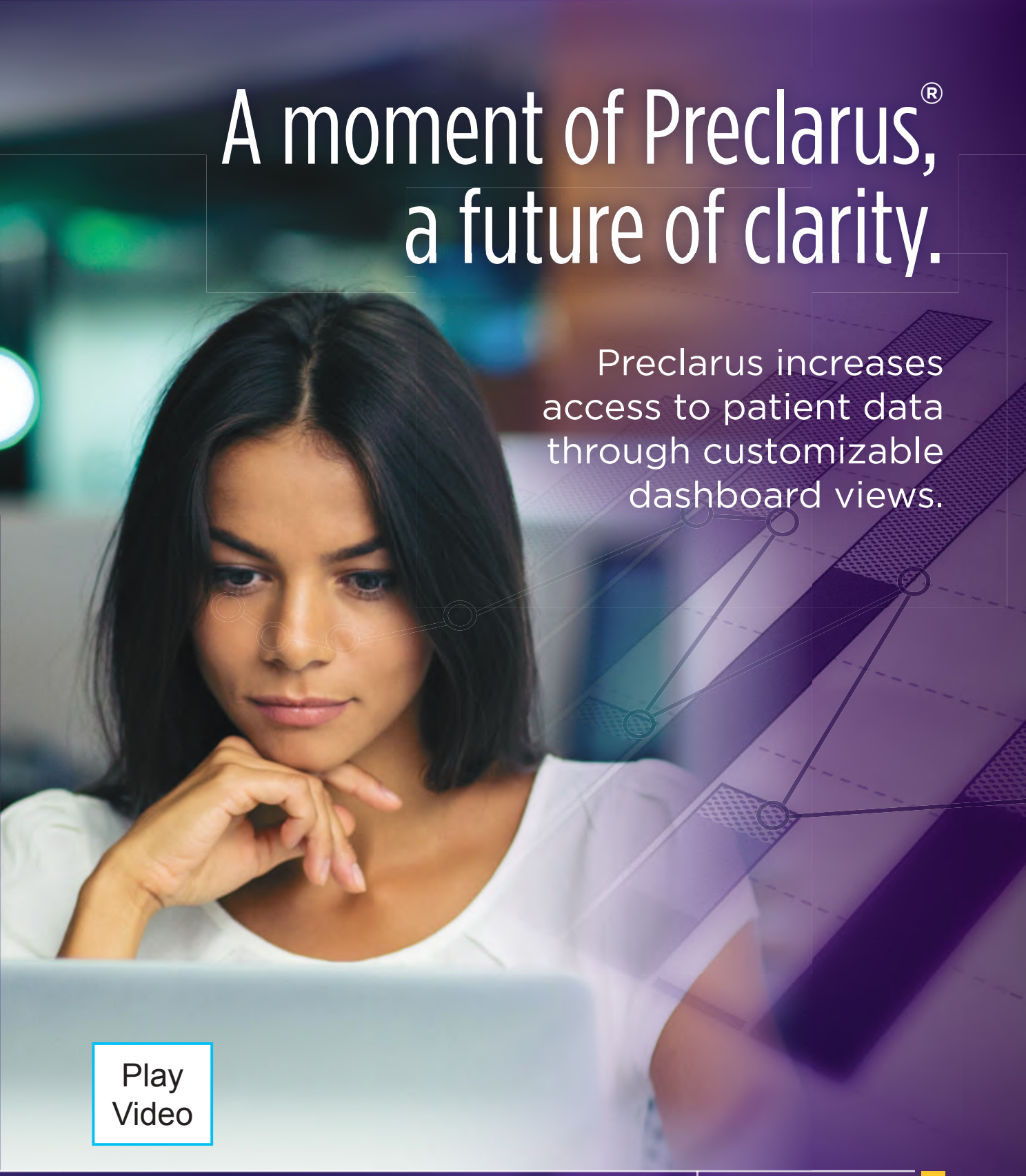
Adam Amdur: I am a big believer in technology and embracing the real-time bidirectional, connected world. As a patient advocacy association, we decided it was essential for us to adapt the SleepHealth platform for our community. We want to use technology to scale and broaden our message to patients.

We saw that Apple's Research Kit had tremendous enrollment outcomes by reinventing the recruiting/consenting mechanism to enroll a large amount of patients into clinical trials overnight, and we wanted to leverage our patient access to collect sleep apnea patient centered outcomes. We have reach to more than 350,000 patients through our online and social channels, including our website (www.sleepapnea.org), Facebook page, Linkedin Group, and active professionals including sleep specialists, dentists, cardiologists, endocrinologists, and diabetes experts, mental health experts, oncologists, neurologists, pediatricians, and even autism specialists in early childhood development.

MA: Why was the SleepHealth App developed?

AA: There is a sleep component that we all do in every day of our lives; in fact, it's something that we do for a third of our lives. Sleep deprivation was overlooked in the medical world for far too long, and it is changing. That behavior change is what led us towards coming up with a research kit that is not only sleep-disease focused but contains a sleep preventative health focus. Everyone is up to speed on exercise and nutrition and in movement. We want sleep to become the third pillar in the health and prevention world.

We feel that by launching our research kit, we not only want to look at all the unhealthy sleepers in the world, but we



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also want to look at the healthy sleepers so that we can finally show what good healthy sleep does for an average everyday person and what happens when you do not get sleep, even if you don't have the disease, how it's affecting your life. Sleep affects your cognitive alertness, mood, productivity, performance on the playing field, classroom and work. It affects the quality of your relationships at home, your marriage, children and parents. We now have a society that is dependent on caffeine and energy drinks that are constantly trying to fix the shortcomings of poor quality sleep or some sort of deprivation. I always tell people, it's not only how many hours of sleep you need, but what kind of hours. It needs to be good sleep. It can't be interrupted. You can't be on your phone. The temperature in the room needs to be cooled down, it can't be polluted. We have to try to do everything in our power to get back to the world that was pre-electricity where our bodies biologically reacted and knew when to go to sleep and when to wake up. We do not have that anymore, so we need to learn to adapt to that.

MA: Who is eligible for the SleepHealth Study? Can you describe the study's design and ultimate objectives?

AA: The SleepHealth Study is a prospective observational study. Everybody in the world is encouraged to participate. Right now it is available for ages 18 and older. Our next version is to target a younger age, because we feel that younger kids, especially teenagers, are more adept to participating on iPhones and mobile devices. By conducting long term measurements, we can change their behavior pattern in their teen years when their biological clock and their circadian rhythms are really changing. We can help educate them now. We believe that in the long-term we will wipe out most of the comorbidities that are plaguing our society today. So these millennials are important and generations coming after these millennials is even more important because technology is all they know.

We are collecting passive data from the iPhone, and heart data from the iWatch. In the future, we plan on using the iWatch in the workout mode, so that patients can wear the watch at night during sleep and collect heart rate data every five seconds.

We have self reported questions we are asking, and are looking at the passive data coming in from their iPhone and iWatch. We have not brought in any other devices because we feel that it's really important to start to educate the public about all the sleep data that they think they are getting, which we know is not necessarily accurate or objective. We have given people the opportunity to participate with their sleep diaries for seven days and will reissue those quarterly.

MA: What are subjects' experience with taking Patient Reported Outcomes surveys via mobile platforms?

AA: We have an alertness measurement everyday when subjects receive random notifications if they want to participate, and have a PVT (Psychomotor Vigilance Test) that tests your alertness. However, people have complained that this 3 minute questionnaire takes too long); Apple iWatches are designed and programmed to enable people to glance at it for a few seconds, not fill our surveys for three minutes. So there's a behavioral shift going on in society that is mixed with the changes in technology, and we are embracing it.

MA: How will you be able to detect sleep patterns through limited wearables functionality, such as heart rate?

AA: We are working with a group called Cardiogram that is doing research for atrial fibrillation by looking at major data with the Healthy Heart Alliance at UCSF. We are in the early stages of figuring out what the data is going to show us, but basically if we get heart rate data every five seconds on participants, 24x7x365, that is more heart data in a public health study than we've ever had in the history of time, and that can certainly contribute towards detecting sleep patterns, such as apnea, and sleep cycles. We think we can find an algorithm that will help us, at least as an early detection or as an early warning; not necessarily as a diagnosis, but more as a risk prevention measure. As the Apple watch opens up, we think we can potentially take other sensors and other features of the watch like the heart rate, skin temperature, and oximeter

We can now take measurements with three variables; if we have four variables, oxygen, heart, skin temperature and actigraphy that would give us four out of the five major variables to match up to what will be considered the gold standard of objective sleep measure, which is a full PSG (Polysomnographic study) inside a lab. There are some start-ups that are work on wearable innovations; there are wireless EEG leads on the forehead that measure brain activity which is the other way of really confirming what stages of sleep patients are getting.

MA: Can the 'Mobile App' sleep measurement system be used in clinical trials to measure sleep outcomes?

AA: Absolutely, The last thing people do before they go to bed is to look at their phone and the first thing they do when they wake up is to look at their phone. Moving forward, there is no doubt that this should be right in the middle of the heart of every clinical trial that goes on traditionally or non-traditionally, as sponsors can collect very detailed sleep outcomes data from patients.

The BYOD approach has been very successful with adoption, since it is so easy and diffusible with patients. While many argue that not everyone has an Apple phone, we disagree; we have been able to access and enroll patients so rapidly. You can look at our demographic data and see how many people across the globe are using Apple phones. We plan to also deploy the SleepHealth Study app on Android devices to further expand our reach.

Moe Alsumidaie is a regular contributor and member of *Applied Clinical Trials* Editorial Advisory Board.

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Bring Your Own Device for Trial Outcome Assessment

Bill Byrom, Jeff Lee, Kara Dennis, Matthew Noble, Marie McCarthy, Willie Muehlhausen

Survey uncovers the challenges, myths, and potential useful strategies associated with BYOD adoption.

Using patients' own mobile devices to collect self-reported outcomes data (referred to as electronic patient-reported outcome [ePRO] or electronic clinical outcome assessment [eCOA]) is an industry hot topic. Limited use of "Bring Your Own Device," or BYOD, in regulatory studies to date is mainly due to industry concerns spanning two areas. The first is a concern that different device sizes and operating systems might affect the measurement properties of a PRO instrument. When employing eCOA on a single device type, the measurement properties can be assessed fully by usability testing, cognitive debrief, or quantitative equivalence studies. In a BYOD setting, performing validation studies to cover all possible device types and sizes would be impossible. The second area is concern around the technical and practical aspects of using a patient's own hardware. Concerns, for example, include the effect of a subject changing their device mid-study, upgrading their operating system, or having insufficient storage space available to store eCOA data due to other apps, data, pictures, and music.

Between August and October 2015, we conducted a research survey to identify and assess the perceived barriers and challenges with the use of BYOD for eCOA in clinical trials. Our aim is to provide information helpful in devising future strategies for BYOD adoption, and to help identify popular perceived challenges that perhaps are more myth than reality. In preparing the survey questions, we supplemented our own knowledge of commonly considered challenges and issues with information gathered during telephone interviews of five respected industry eCOA experts.

Survey respondents

Ninety-eight individuals accessed our survey which was promoted primarily through LinkedIn connections and groups. Of these, 19 individuals answered only the first question, a mandatory question measuring employment type, but did not answer any of the BYOD-specific questions. We excluded these respondents, leaving a sample of 79 respondents, and assume that the individuals answering only the initial question did so to proceed but then realized that they would be unable or unwilling to answer the technical questions that followed.

Of the 79 respondents, 14 (18%) were employed at biopharmaceutical companies, 18 (23%) at contract research organizations (CROs), and 27 at eCOA vendors (34%) (see Figure 1). For confidentiality reasons we do not report the individual organizations represented, but note that in all categories companies ranged from large to small organizations, and each contained a number of household names. The four respondents in the "Other" category included a patient advocate employed by a number of charities, a psychometrics expert, and two individuals from research institutions.

In all cases, responses collected represented personal views and not necessarily those of the respondents' employing organizations.

Attitudes toward equivalence requirements

While the challenge of proving equivalence across multiple device types seems to dominate the public discussion regarding BYOD, our respondents seemed significantly less deterred by the equivalence challenge:

- Overall, 44% agreed or strongly agreed that equivalence should be demonstrated on all possible devices used in a BYOD study (see Figure 2).
- Only 30% of respondents disagreed or strongly disagreed that demonstration of equivalence on a single device was acceptable if access using devices of a smaller screen size or resolution could be prevented.
- In addition, 68% of respondents agreed or strongly agreed that showing equivalence only on a single device would be acceptable if the strategy was agreed a priori with the regulatory bodies.
- Few saw distinction between primary and secondary data—only 22% agreeing or strongly agreeing that demonstrating equivalence on a single device was necessary only if the data represented secondary endpoints.
- Seventeen percent of the respondents disagreed or strongly disagreed that no further equivalence testing would be needed if a similar equivalence study had already been conducted and reported.

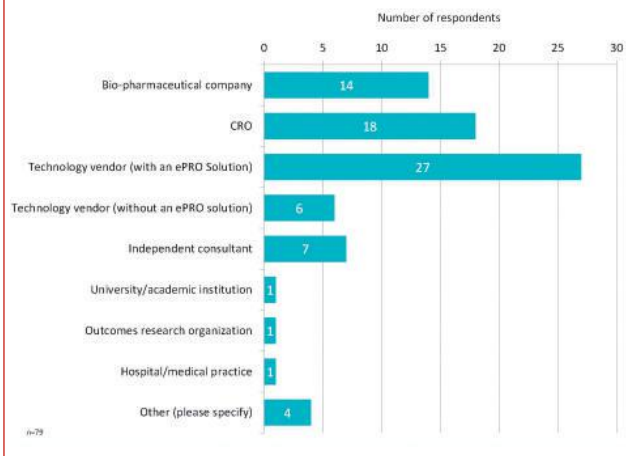
Few respondents disagreed that scale author agreement would be necessary if using an existing instrument in a BYOD setting—only 17% and 5% disagreeing and strongly disagreeing, respectively (Figure 2B). The majority of respondents agreed or strongly agreed that ensuring minimum screen size would be sufficient for valid implementation of a visual analogue scale (41% and 27%, respectively), and that differences in font sizes between devices was unimportant (44% and 26%, respectively).

There was some evidence of trends indicating differing strength of agreement based on the employment type of the respondents, although the sample was not considered large enough to assess this formally. In comparison to CROs and eCOA vendors, biopharmaceutical company respondents generally saw a greater need for equivalence demonstration across all device types, with 72% agreeing or strongly agreeing, compared to 48% among CRO respondents and 34% among eCOA vendor respondents. That said, these sponsor respondents were supportive that equivalence demonstration on a single device was acceptable if usage could be limited to devices of at least that screen resolution and size (79% of sponsor respondents agreed or strongly agreed, compared to 67% and 35% for eCOA vendors and CROs, respectively).

Concern over perceived BYOD practical or technical challenges or issues

Of the 21 perceived practical/technical challenges and issues associated with BYOD use for eCOA that we con-

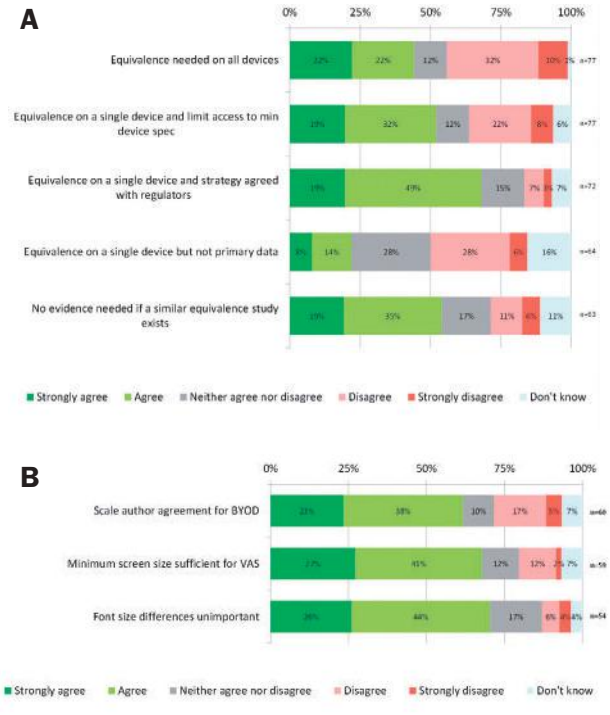
Range of Respondents



Source: Byrom et al.

Figure 1. The breakdown of survey respondents by discipline/classification.

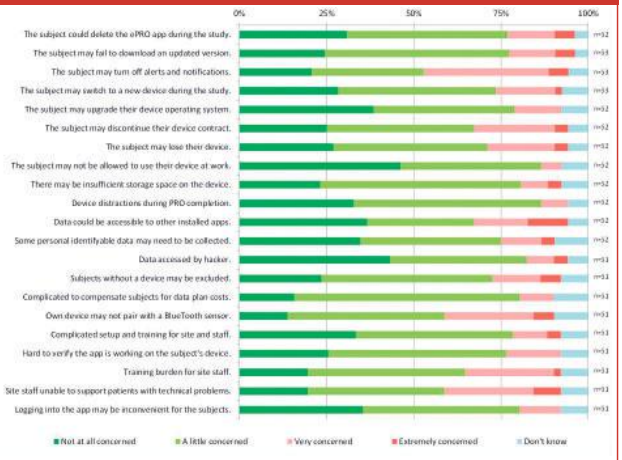
Device Equivalence Views



Source: Byrom et al.

Figure 2. Respondents attitudes toward various device equivalence requirements (A) and other measures in the BYOD setting (B).

BYOD Concerns



Source: Byrom et al.

Figure 3. The concern levels of 21 perceived practical/technical challenges and issues associated with BYOD use for electronic clinical outcome assessment.

sidered, few appeared of significant concern to the respondents in this survey (see Figure 3). Over 75% of respondents identified they were "not at all concerned" or "a little concerned" about the following perceived challenges:

- The subject could delete the app during the study.
- The subject may fail to download an updated version.
- The subject may upgrade their device operating system.
- The subject may not be permitted to use their device at work.
- There may be insufficient free storage capacity on the device.
- The subject may become distracted by other things on the device during ePRO completion.
- Some personal identifiable data may need to be collected
- Data on the device could be accessed by a hacker.
- It may be complicated to compensate subjects due to differences in individual data plans.
- Patient setup and training may be more complicated for site staff.
- It may be more difficult to identify that the app is working correctly on the subject's own device.
- Logging into the app in addition to their device may be inconvenient for the subject.

Fifty-three percent of respondents were "not at all concerned" or "a little concerned" that the subject may be able to turn off in-app notifications, such as diary reminders, using their phone settings.

There was little concern about subjects changing their phone during a study. Seventy-four percent of respondents were "not at all concerned" or "a little concerned" about subjects changing device mid-study, 67% that subjects may discontinue their contract, and 71% that subjects may lose their device during the study.

Respondents were generally not greatly concerned about perceived security issues with using subjects' own devices. Sixty-seven percent (67%) were "not at all concerned" or "a little concerned" that eCOA data could be accessed by other apps on the subject's device, and 83% that data could be accessed by a hacker.

Almost 20% of respondents were very concerned or extremely concerned that subjects without a suitable device would be ineligible to participate in the study. Thirty-two percent of respondents indicated they were very concerned or extremely concerned that a subject's device may not pair with a Bluetooth device if used in the study, with 59% "not at all concerned" or "a little concerned."

There was moderate concern around training and support of study participants. Twenty-seven percent were very concerned or extremely concerned about the potential training burden on sites in a BYOD study, with 33% of respondents expressing the same degree of concern that site staff may be unable to troubleshoot more technical problems associated with using an eCOA app over multiple device types.

Again, while the numbers per group prohibited formal analysis, we noted some possible trends that may indicate differing strength of concern over certain perceived issues based on the employment type of the respondents. In comparison to CROs and eCOA vendors, biopharmaceutical company respondents generally appeared more concerned about subjects deleting their ePRO app during the study, subjects discontinuing their device contract during the study, subjects losing their device, data being accessible to other apps on the subject's device or being accessed by a hacker, and the subject's device being unable to be paired with a provided Bluetooth device.

Discussion

When it comes to demonstrating measurement equivalence across all devices in BYOD settings, over half of the respondents in our survey neither agreed nor strongly agreed that testing was required on all possible devices; and over half agreed or strongly agreed that demonstrating equivalence on a single device was acceptable if all subjects could be guaranteed to use a device of at least that minimum screen resolution and size. Would that strength of feeling translate into the use of BYOD to deliver eCOA instruments in a regulatory study today? Perhaps, but maybe that's unlikely. However, as we see more and more evidence that electronic devices of all shapes and sizes do not adversely affect the measurement properties of eCOA instruments across different study contexts and patient populations, this position may relax.

REVEALING NEW POSSIBILITIES IN MOBILE HEALTH TRIALS.

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There are already positive signals that measurement equivalence across modalities is less problematic than previously thought, especially if ePRO design best practices are employed (see the C-Path institute's ePRO consortium white paper for example).[1] One of these signals is the growing evidence of paper and electronic equivalence. One might argue that the magnitude of change is far greater from paper to an electronic device, than from device to device. A recent meta-analysis by Muehlhausen and colleagues provides strong evidence of the equivalence of paper and electronic over multiple instruments, patient populations and electronic media.[2] This study also included two studies in which the equivalence of two electronic formats was assessed. If patients respond consistently with PRO instruments, whether in paper or electronic form, then it seems a reasonable inference that the subtle changes across different mobile phones should not present an equivalence challenge.

This isn't the first meta-analysis we've seen exploring this topic. Gwaltney and colleagues published a meta-analysis of 46 equivalence studies conducted up to 2006.[3] This analysis reported a pooled correlation of paper to electronic scores of 0.90 with a 95% confidence interval from 0.87 to 0.92. This is above the correlation threshold of 0.75 or 0.8 considered to represent acceptable reliability.

Muehlhausen et al.'s meta-analysis considered new equivalence studies published from 2007 to 2013. Significantly, these studies were reported after the publication of the ISPOR ePRO Task Force recommendations on the design and analysis of equivalence studies and many, therefore, adhered to the task force recommendations. This new meta-analysis included 72 equivalence studies from 23 different patient groups and included a wide range of electronic modalities including PC, tablet, handheld device/smartphone, and interactive voice response system (IVRS). Their conclusions were in line with Gwaltney and colleagues—a pooled correlation of 0.875 (CI: 0.867-0.884).

These two important studies provide extensive evidence that paper and electronically administered PROs are equivalent—across many different PRO instruments, patient populations, and electronic modes of administration. While none of these studies were conducted in a BYOD setting, it seems that device type does not affect equivalence to paper—so we might gain encouragement that device-to-device differences are likely to be similarly insignificant in affecting the way in which patients respond to ePRO instruments if the design of the questionnaire follows the ePRO Consortium white paper design guidelines.[1]

Should measurement equivalence concerns be assigned to the category of myth? We argue that the body of evidence collected to date strongly suggests this. The above pieces of work, and others actively being conducted, provide a positive signal on the way to greater acceptance of BYOD as a valid approach that protects eCOA instruments' measurement properties when applied appropriately.

As we have seen in our survey, however, perceived issues and challenges with BYOD for eCOA are not confined to considerations of measurement equivalence. There are perceived practical and technical concerns with the use of a subject's own mobile device to collect submission data.

Some perceived issues and challenges can likely be dismissed as myth—at least in the sense that they do not apply specially to BYOD, but apply equally to other approaches to PRO collection.

Some of these concerns are tangible situations that could happen in a clinical trial. Subjects, with full control over the contents and operation of their mobile device, could indeed delete the eCOA app, prevent notifications appearing on their home screen outside the app, may upgrade their operating system during a study or change their device or mobile contract during a trial. Can these risks be mitigated and what is their potential impact on the measurement of the PRO? Certainly some could be limited through training, and additional information from system-based monitoring of the app can help to present issues for patient follow-up by sites. This might include regular receipt of information on the device operating system and version of the app being used to identify when changes have occurred, and flagging when push notification tokens indicate that notifications have been disabled on the patient's device.

However, eliminating the possibility of the user upgrading his or her device or turning off notifications in a BYOD setting will be hard to eliminate completely. Do these risks outweigh the potential advantages of BYOD? We argue the potential benefits of BYOD are greater than these concerns. While the cost of provisioning mobile devices in current trials is high, we do not believe that BYOD will necessarily result in significant cost savings. Some provisioning may be needed to enable inclusion of patients without compatible hardware, and provisioning savings may be balanced by a higher support cost when patients use their own mobile devices to operate study eCOA solutions.

It is hoped, however, that BYOD brings with it greater patient convenience and centricity—enabling subjects to utilize their own smartphone to maintain their symptom diaries and instrument entries using the device they already carry with them and refer to over the course of each day. With BYOD, subjects will use a device they are

familiar with and know how to use. They will also not be required to carry and keep charged a separate device solely for the purposes of their eCOA entries. Previous patient preference studies have shown that the majority of patients prefer to have a single device, and this can only benefit PRO convenience, completion, and compliance.

Some perceived issues and challenges, however, can likely be dismissed as myth—at least in the sense that they do not apply specially to BYOD and in fact apply equally to other approaches to PRO collection. Subjects can equally lose a provisioned device or paper diary as opposed to their own mobile device, and subjects may be equally unable to use a study device as opposed to a personal device in a working environment. In an unsupervised setting, subjects may be equally distracted by their own smartphone while completing a paper diary or a diary on a dedicated study device; and the same requirements for collection of personal identifiable data apply to both BYOD and provisioned device studies.

Other issues fall into the category of surmountable technical considerations, which should be addressed by good mobile app design. Security, for example, while an important concern, has not limited the prevalence of online and mobile banking services. There is no reason why we cannot learn from the application of technology solutions in other industries to gain confidence and develop solutions that are appropriate for healthcare and clinical trials. While the banking industry has the benefit of large investment, leveraging their R&D may be less expensive, and online banking has already had an impact on user behavior and acceptance of online solutions to manage sensitive information.

Conclusion

We believe that the time for BYOD is upon us. With that we see greater potential to apply eCOA to study protocols where paper data collection remains quite popular despite its well-known limitations. As an industry, we should continue to investigate the use of BYOD and share our findings, positive and negative, so that as a collective we can provide sufficient evidence to turn the tide.

FDA recently requested public input from a broad group of stakeholders on the scope and direction of the use of technologies and innovative methods in the conduct of clinical investigations.[4] This docket includes a specific question for comment: "What are the challenges presented when data are collected using the Bring Your Own Device (BYOD) model?" This is a positive signal from the regulators that we welcome and one that can only help to ultimately provide better understanding of FDAs position and any gaps in evidence required to make BYOD a fully endorsed approach.

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How to Collect eCOA and Give Patients What They Want

Study uncovers differences between current eCOA practice and what would greatly improve the process for patients.

The scientific, operational and regulatory implications of using electronic Clinical Outcome Assessments (eCOA) in clinical development have been reviewed in literature for over a decade. And the benefits of eCOA have been repeatedly proven in terms of improved patient protocol compliance, greater study power and regulatory acceptance of data collected. Despite these advances, industry has provided little insight as to how patients prefer to interact with COA. Most research has only approached patients' preferences for eCOA over the traditional pen-and-paper approach.

To address this gap, ERT scientists set out to understand what patients want when completing eCOA assessments during clinical trials. Data from 408 patients in the US with osteoarthritis, chronic obstructive pulmonary disease (COPD), depression, or type II diabetes were collected in the following categories: patient preference, engagement, compliance, ease of use, human factor impact, and useful function extensions. In total, 132 different questions were asked, revealing considerable learnings across categories, therapies and patient demographics. Following are some of the findings that provide greater insight into patient preferences, intended to influence study design to improve patient compliance and engagement during clinical trials.

Improving Screen Design

Is there an optimal screen design for collecting patient data? Questions on fundamental layout structures were asked, including wording emphasis (bold, underline, caps, italics), question placement (top to bottom or left to right), and preference for viewing one question per screen or a matrix layout. Overall, patients preferred underlining and a question/answer placement of top to bottom. They preferred having one question per screen, as this format enabled them to focus on the question and answer without becoming distracted by multiple questions at once. While seemingly simple, this finding counters an established practice in eCOA. Prior to these results, it had long been surmised that in order to optimize patient compliance and reduce burden, an eCOA design should minimize the number of clicks on the data collection device, and require a shorter time interval.

Improving Study Design

How does the designated data collection time period affect patient protocol compliance? Questions about patient preferences were asked regarding: time of daily diary completion, trial participation duration, modality and the use of alarms for electronic diary completion and medication reminders. Overall, the learnings indicate that patients slightly prefer evening rather than morning completion, but rate both windows of the day quite favorably. Shorter windows of completion are preferable. Patients were willing to engage in trials for considerable periods of time, including several years; but overwhelmingly preferred studies of one year or less in duration. Patients indicated the strongest preference for having an electronic device provided to them, rather than using their own smartphone device for participation in a clinical trial, which runs counter to the popular bring your own device (BYOD) trend. The majority found device alarms not only necessary, but very helpful in prompting them to complete a diary or take their medication, confirming best practices.

Susan M. Dallabrida, PhD
Vice President, Clinical Science and Consulting, ERT
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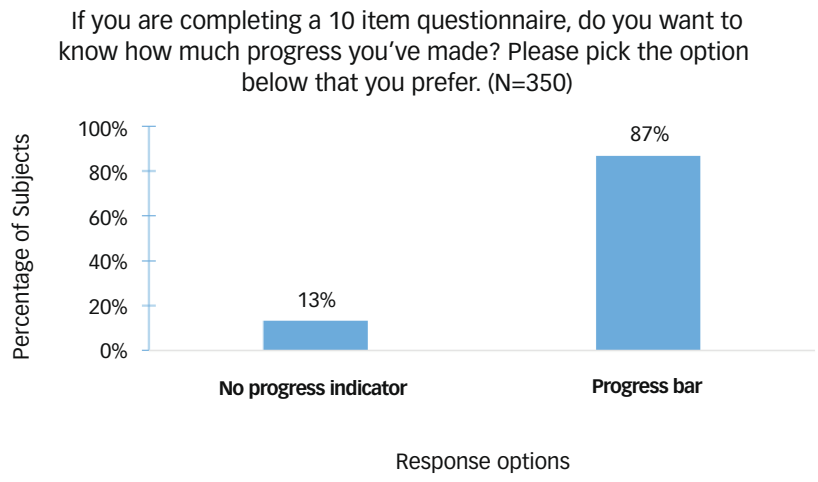
Improving Patient Engagement

Many discoveries around how patients interact with the eCOA device rebuked existing practice in diary design. Contrary to existing beliefs, this study found the majority of patients preferred to spend more time interacting with the device as long as it had a more useful and engaging interface. Specifically, patients strongly favored having a screen at the beginning that shows the number of questions in the diary and the estimated time to completion, as well as progress bars as they move between screens. Patients also resoundingly expressed a desire for a 'Thank you'

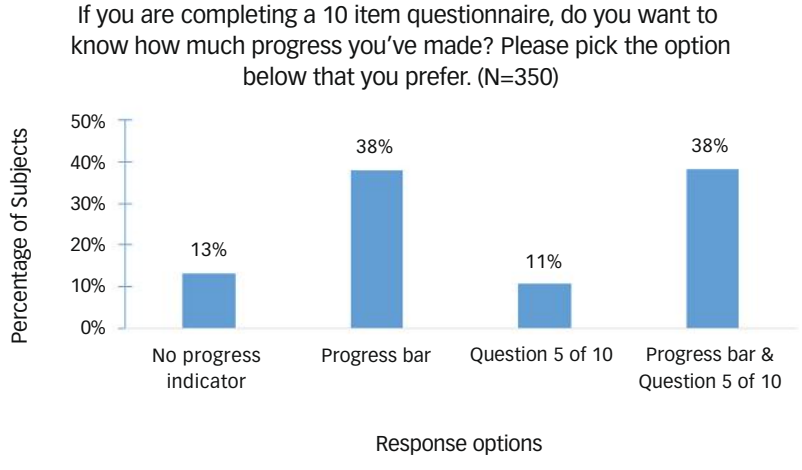
Progress Bar vs. No Progress Bar in Questionnaires



Source: ERT

Figure 1. Patient preference for progress indicator bar throughout eCOA assessment.

Type of Time Stamp for Progress Preference



Source: ERT

Figure 2. Patient preference for progress indicator options.

screen at the end of a diary and were interested in gaining access to their data either during or at the end of a study. The key learning was that simple changes in a user interface can improve patient engagement. (See Figures 1 and 2)

Optimal wording was tested to reveal best practices for eCOA compliance. It is beneficial to provide patients with a comparison of their data to that of the group and the overall trial target. Patients confirmed that a smiley face drives engagement and compliance. Negative imagery such as a frowning face had the opposite effect.

Improving Patient Communication

How do patients prefer to communicate with their physicians? Most patients expressed interest for additional technologies as a means of better care and communication with their health care providers. Phone calls, text messages, emails, and reminders for clinic visits and medication were cited. In addition, there were strong preferences for information about new treatments and how to better manage their disease. Overall, the majority of subjects cited being very interested in using electronic methods to interact more with their physician between visits and to better monitor their disease.

Improving Clinical Trials with eCOA Science

This study's findings reveal the value of listening to clinical trial patients in order to better understand their preferences. As a result, patient compliance and engagement have been optimized with improved user interfaces, additional content and detailed eCOA design strategies. The combination of collecting data electronically in the manner preferred by patients results in improved data collection during clinical development. Ongoing research enables this advantage.

ERT's patient reported outcomes (PRO) and eCOA Clinical Science and Consulting team is continuing to advance the science behind eCOA use in clinical development. The team of scientific and regulatory experts is committed to improving the patient experience and to ensuring their compliance with and engagement in clinical research. Pharmaceutical researchers and clinicians regularly work with ERT's PRO and eCOA Clinical Science and Consultants to implement optimal PRO/eCOA trial design strategies that ensure the success of clinical development programs.

For additional information, visit https://www.ert.com/ecoa/pro-ecoa-scientific-services.

Pilot Proves eConsent Better Than Paper

Hilde Vanaken, PhD

Post-survey results show extremely high overall satisfaction levels from sites and patients.

The drawbacks of today's paper-based informed consent methods for clinical trials are well understood, but the industry has yet to perfect the process and tools to best ensure human subject protection while at the same time achieving a streamlined electronic consent process.

Janssen is working to change that, releasing the findings from the company's multi-country pilot study of electronic consent technology to guide the development of industrywide practices. The eConsent study was conducted at 13 sites—10 in the U.S. and three in Hungary—in a Phase III clinical trial of INVOKANA™ (canagliflozin) in subjects with Type II diabetes.

Each participating site received an iPad device loaded with the patient eConsent app, as well as a training app and a training webinar for site staff.

The eConsent app first informed patients that their name and all data would be time-stamped and securely stored in a database. After patients provided their approval, the app played an animated video explaining the full study and key aspects of procedures. Next came the actual informed consent e-document, along with an app-based dictionary and the ability to indicate when a word was not understood. Finally, patients took an eight-question multiple-choice quiz that highlighted key aspects of the study. Both the patient and site staff signed the document electronically, using a stylus. The study's sponsor had real-time access to all eConsent activities per patient via a web portal.

A total of 76 patients participated, each completing a detailed satisfaction survey immediately after the initial eConsent. Sites responded to a brief survey every two months and then completed a comprehensive survey after the study was completed.

Overall, satisfaction levels were extremely high from both patients and sites, indicating a broad willingness to transition to an electronic process for consent. As a whole, the eConsent functionalities and features received a "satisfactory" rating of greater than 85%. (Other possible response options were "neutral," "unsatisfied," or "not used.")

Highlights included the video (96% of patients rated it satisfactory), content review quiz (94%) and a feature that allowed patients to mark unfamiliar words (90%). Meanwhile, 77% of sites said eConsent improved the entire consent process.

Diving deeper into the survey results, here are some of the key takeaways:

- Older participants adapted well to new technology. Of patients 60 or older, only 27% had experience with a tablet device. While that could prompt cause for concern, older users universally reported high satisfaction on each eConsent feature. As a whole, all age groups rated the process "easy" or "very easy" to use and no one with experience using paper forms said they thought the traditional process was better.
- More time to focus on what's important. When site staff were asked about the length of time

Paper vs. Electronic Informed Consent

	PAPER INFORMED CONSENT	ELECTRONIC INFORMED CONSENT
Patient-site interaction	Patient is given a form to sign and site personnel are responsible for ensuring that patient understands the ICF and answers all questions	Patient engages in an interactive process with videos, retention questions, and dictionary definitions. Site personnel answer questions that are prompted by the patient within the software application. Patient's retention of information is documented
Patient comprehension	Limited due to extent of documents and medical and legal terminology	Enhanced due to video assistance in native language and layman's terms
Multiple languages	Studies show that many paper translations are not up to par	Video augmentation of the process with high quality translations
Fraud protection	Complete reliance on the paper document	Complete audit trail showing when all parties signed the document
IRB and EC review	Multiple circulating paper copies varying by IRB/EC and by country	Standardized process with web portal for review
Site consistency	Process varies considerably from site to site	Standardized process at all sites
Storage, access, and site monitoring	Cumbersome review of charts and paper	All forms and data are easily accessible via a secure web portal
Version control and new signatures for protocol amendments	Poorly done with paper, with a significant number of patients not receiving updated safety information	Strict version control with notifications to sites and patients when a form is updated and requires a signature

Source: Jeffrey Litwin, MD, from "Engagement Shift: Informed Consent in the Digital Era," *Applied Clinical Trials*, June 2016. http://bit.ly/2cbJQn5

Comparing the advantages of electronic informed consent approaches over paper across several categories.

it takes to use eConsent versus paper forms, 46% reported it was about the same. Twenty-three percent said it was faster, and 23% said it was more time-consuming. Sites could more quickly address items patients didn't understand or missed on the form—which didn't always result in a workload reduction, but was certainly a process enhancement.

- Improved patient understanding and engagement seen. Most (69%) of the sites reported eConsent as a helpful tool for improving subjects' engagement during the consenting process and in boosting their initial understanding of material (also a key advantage reported by patients). In addition, 38% of sites said that eConsent improved patients' desire to enroll or stay in the trial.
- Valuable insights into the patient's mind. The sites and sponsor were able to see which app features the patients used and how much time was spent on each section, as well as which words were marked as unfamiliar or looked up in the dictionary. This feedback is a promising feature as the industry seeks to make clinical trials easier for patients to understand.
- Plan for local differences. All of the app's content must be translated into native languages. In addition, country-specific requirements will have to be incorporated. For example, Hungary requires patients to provide date of birth and place of birth.

Janssen is sharing these and other findings while leading TransCelerate's eConsent work stream. In parallel, Janssen is preparing a new eConsent study with visually impaired patients in the U.S. and Canada. The 15-site study will include five different consent forms and additional audiovisual features. Three more studies will kick off within the next year to broaden the global perspective and assess other eConsent functionalities and patient populations.

The benefits of eConsent are clear, but now it's up to the industry's many players to come together to share their learnings and remove barriers to implementation. This also requires close collaboration with patients, trial sites, health authorities and ethics committees.

As with many new digital technologies for clinical trials, eConsent is a tool to enhance the site-patient relationship, not replace it. A positive experience at the onset of a trial is a gateway to better engagement throughout the study and afterwards, bringing our industry closer to patients—our most important allies.

Hilde Vanaken, PhD, is director of the R&D Operations Innovation Department at Janssen Research & Development and is the TransCelerate eConsent Workstream Leader

Matching Patients to Trials

Lisa Henderson

Using EHR, personalized medicine and physician knowledge to enhance patient recruitment.

Two years ago, Applied Clinical Trials looked at the technologies intending to close the ever-elusive patient recruitment gap. Since that time, other innovative approaches have emerged, and while there are no hard and fast numbers that any have in fact sped up the recruitment process, many have re-imagined electronic health records (EHRs), and offer insight into the future of personalized medicine, as well as the physician's role in clinical trials.

Patient iP

At HIMSS16 in March, Microsoft announced the winners of its Health Innovation Award. Among them was West Ridge Obstetrics & Gynecology and Patient identification Platform, or Patient iP, which won in the category of Building the Intelligent Cloud. The Platform securely de-identifies and aggregates EHR data so that clinical trial protocols can be automatically processed to more quickly identify where and how many patients match the inclusion/exclusion criteria requirements.

Michael J. Margiotta, CEO, said the inspiration for Patient iP came from his long history in healthcare IT, close familiarity with the strengths and limitations of EHRs/EMRs, and observing that the clinical trial recruitment system was broken because of manual processes.

Margiotta says, "EMRs are just a repository of patient data. Those systems don't capture data in a way that can be aggregated or analyzed and perform data mining on the patient populations." According to Margiotta, even the top three EHR vendors—Epic, Cerner and Allscripts—still face significant challenges in the markets they serve. "65% of all larger institutions, your typical study sites, can't get data usage rates or analytics, even in a de-identified manner, to do anything with the information they have in their EHRs."

As the healthcare industry moves into Meaningful Use 3, significant changes around the use of EHR and the disconnect between its use and promise are expected to be addressed. Most of that is out of scope to this article, suffice to say that EHR interoperability and data sharing potential are considered a limitation. And that is where Margiotta stepped in—to provide a platform that would be able to leverage EMR data in a way the software currently can't. In 2014, he launched his company to be able to match patients to specific criteria based on aggregated information including genetic markers, blood values, medications, and more to find those exact patients very quickly. Think of it as an EMR booster. For CROs and sponsors, they can use Patient iP for protocol modeling—making sure patients actually exist for the protocol they have designed; as well as site feasibility—are there patients in their sites that are applicable to the study.

For sites, it works two ways. If the site is already conducting clinical trials, they can quickly know how many patients in their networks are potential participants through the EHR. And, as in the case with the West Ridge Obstetrics & Gynecology, find out how many patients in their practice were eligible for a current protocol and then decide if they wanted to join the world of clinical research. They could pursue a study to offer cutting edge therapies to their patients, expand their revenue potential with clinical studies

and/or ensure that current patients weren't referred out of their care into a clinical trial.

The application for Patient iP spans clinical trials. For example, Margiotta says, an accountable care organization could use the platform to identify an at-risk population with the potential of going to the next stage of disease, or a healthy population at-risk to a condition, and intervene by applying patient matching and inclusion/exclusion criteria. Others that receive grants, would be able to show actual successes from the aggregated data in the population. And also the ability to share clinical outcomes and aggregate successful clinical care options within a network.

But for now, Margiotta says they will prove their platform in the clinical trials world. "It seems the pre-process of the clinical trial is the toughest part and the steps leading to success are manual," explained Margiotta. "We have bridged the gaps between pharma, CRO and sites and automated it for success."

ePatientFinder

Another solution that incorporates EHRs in the mix is ePatientfinder. ePatientfinder crossed our radar [3] later in 2014 and Tom Dorsett, President and CEO, explained the history of the company that he founded in 2010. Since that interview, the company has experienced growth among both its clients in the life sciences world and its network of EHR partners, which provides the access to physicians and patients. Dorsett believes that though many solutions for patient recruitment in clinical trials have emerged, there exists a lack of actionable models for getting those patients into clinical trials. And here is where his solution comes in—to provide what Dorsett calls "the last mile solution"—the puzzle piece missing between pharma, CRO, medical device sponsor, the EHR, the physician, and the patient.

That last mile, as explained in the previous article, is ePatientfinder's three-tier funnel or level of screening to find the highest quality of referrals. The funnel includes ePatientfinder sending potential trials with patients to a physician through the EHR. If the physician opts in, ePatientFinder reaches out to patients initially to see if they are interested, then provides an IVR pre-screen survey to uncover any subjective issues that may not be in an EHR. Those patients are then referred to the opted-in physician for a consultation to see if they can go into the clinical trial.

According to Dorsett, the platform builds on the trust inherently found between patient and doctor, and is a process that keeps the physician in the drivers' seat, which Dorsett says they appreciate. In addition, the company has been achieving the best quality referrals to sites, and has feedback from the sites themselves that the three-tier screening provides very high conversion rates.

Recently, Tufts CSDD released results of a survey it conducted on the attitudes and practices of physicians and nurses and clinical trials. The top three reasons these healthcare providers gave for not referring patients into trials were "lack access to the information," "unsure of where to refer" and "not enough time to learn."

Dorsett explained that their solution hits each of these points, and more, through its business model. "We are an information delivery platform, we educate physicians on trials, and then they decide whether they want to refer their patients or not." Dorsett's team curates information, including geographical site locations, so the information given to physicians on the clinical trials is concise, specific, available to their patients, and is tailored to that physician's proclivities. "We do all the heavy lifting on their behalf." Which also hits on the remaining four reasons why HCPs don't refer patients into trials: "trials are not 'appropriate,'" "lack of time to discuss," "proximity to research center" and "fear of losing a patient."

The company recently raised $8.2 million in Series B funding for its future growth plans, increasing the company's total funding to $11 million. Dorsett said that it's taken three years to build the partnerships and technology together to make it work for them and their clients. Future plans include other data services such as site selection, and protocol design and refinement, an expansion into Europe in early 2017, and an extension of therapeutic areas.

Dorsett says the platform, which focused on chronic diseases initially, has perfected its processes enough so the technology can now address oncology. He explained, "Oncology is nuanced. You have to get the patient when they present with the disease, when they've been diagnosed. So it wasn't a large pivot for us, but we did need to make a few technological adjustments." Many of ePatientfinder's clients, as well as numerous cancer centers, have been asking for the service, and Dorsett confirms they very excited to be undertaking oncology in Q4 2016.

MolecularMatch

While getting patients matched and into all clinical trials is a challenge, it's been shown that recruitment for oncology studies is very low. In March 2016, MolecularMatch, a cloud-based, clinical informatics company that works with labs, hospitals, genomic cores and physicians to connect cancer patients to treatment options, launched its MM LAB software [4] This software allows pathology labs and others to match patients' test results to personalized cancer treatments, including clinical trials and experimental drugs.

MolecularMatch offers a public-facing web site for people looking for oncology treatments, searchable by diagnosis, specific gene mutation, comorbidities and more. The data behind the search is culled from web-based information sources including clinicaltrials.gov, registries, insti-

tutions, PubMed abstracts, COSMIC and more. It is fully automated to create structured data from unstructured sources.

According to Xuan Shirley Li, PhD, Chief Scientific Officer of Molecular Match, the MM LAB software was a natural next step for the company's offerings. MM LAB generates a customized report based on the specific markets that come from tumor testing. "The variant data is quite important for all patients and that comes from diagnostic labs. Labs using our software can offer physicians and patients a tailored report with more information on specific trials and treatments that is culled from our data." She continued, "We can align what labs generate to what physicians can offer their patients." Basically, for labs, the software can be used to generate a value-add service for those physicians or health networks.

Li told *Applied Clinical Trials*, "Diagnostics traditionally found only what you were looking for. But now with Next-Generation Sequencing (NGS), it also comes with discovery." She explained that the need for information management in the lab is a direct result of NGS testing. "For patients that relapse or have an aggressive cancer, they are looking at NGS testing and larger work-ups on the lab side. Targeted treatments for gene mutations are mostly in the pipeline, which is where we see clinical trials as the best option. Physicians need to consider clinical trials in complex cancer cases or patients looking for new options if the Standard of Care pathways are not compatible with their life or lifestyle."

Quintiles' precision enrollment

Also in the realm of oncology is Quintiles' precision enrollment model, which is comprised of a network of more than 80 U.S.-based oncology centers, designed to speed up recruitment using pre-identified patients based on study and biomarker criteria, across broad geographic areas, using electronic health records (EHRs) and other data sources. In this newly-launched model, patients upon entering the network have their tumors tested. The genomic analysis and alterations of these tumors are reported back to the patient and site and can be matched to protocols using the genomic alteration criteria for the protocol. It isn't until a patient is identified that the site is activated. In this article, Jeff Ventimiglia, Director, Site & Patient Networks, Quintiles, explains that study start-up is reduced because the site previously joins the Quintiles network and fills out all the documentation and service agreements and joins the Quintiles Infosario Site Gateway. A site is activated once the patient is identified and the remaining start-up activities take 21 days.

Ventimiglia shared in the article the results of a small-scale pilot study targeting 50 metastatic colorectal cancer (mCRC) patients, sponsored by Quintiles, suggests that genomic profiling may increase clinical trial participation among cancer patients from the current level of 3-5% to as much as 35%. This was due to treating physicians recommending a clinical trial in 35% of cases that reported actionable mutations. This pilot suggests that there is potential to increase screening rates and shorten timelines for clinical trials by providing a broad genomic panel rather than using a single biomarker.

WIRB-Copernicus ReferralPlus. In April 2014, ePharmaSolutions announced [6] positive results of studies using its patient matching and triaging solution, ReferralPlus, its tool to match patients who disqualify for one study with other studies they might qualify for using a geo-therapeutic matching algorithm listed on its technology. The pilot data came from three pharmaceutical companies who listed their studies on the CenterWatch web listing service and used the ReferralPlus screening and matching solution.

- The positive results included 33% of the total patients who screened for one study were eligible for and referred to a study site
- 18% of patients who disqualified from the first study, pre-qualified and were referred to another study
- 50% of patients who disqualified for any of the studies listed, registered to be contacted about future studies

In September 2014, ePharmaSolutions was acquired by WIRB-Copernicus. As of this writing, the company does not have an update on the pilot, but will be a focus in 2017.

ICON/IBM Watson. In September 2015, ICON announced that it would be using IBM's Watson Clinical Trial Matching in its breast, lung, colon and rectal cancer trials. In the initial six-month pilot, ICON was using the matching in 25 studies in those four oncologic areas. The ICON sites would have access to Watson and Watson has access to the inclusion/exclusion criteria for those studies and access to the records at the sites. Watson will use the records and inclusion/exclusion criteria to match the up with the EMRs in its database. The pilot is concentrated in the Midwest, primarily because of Watson's access the Mayo Clinic and Cleveland Clinic's records. Initial feedback on the pilot was expected by end of first-quarter 2016, however, at the writing of this article, the company reported that the pilot program was still underway, and then ICON and IBM will review the results and discuss next steps.

Lisa Henderson is the Editorial Director of *Applied Clinical Trials*.

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Virtual Clinical Trials: Design of the Future

Sujay Jadhav

How technology and regulatory advances are paving the way to a new future for clinical trials.

Virtual trials represent a relatively new method of collecting safety and efficacy data from clinical trial participants, from study start-up through execution to follow-up. These trials take full advantage of technologies (apps, monitoring devices, etc.) and online social engagement platforms to conduct each stage of the trial from the comfort of the patients home--including recruitment, informed consent, patient counseling, through to measuring clinical endpoints and adverse reactions. By relying on electronic processes, many argue that virtually conducted clinical trials offer opportunities for a more patient-centered approach.

There are a number of advantages that virtual trials have over the traditional model, which uses multiple study sites and requires multiple patient visits to the site in order to conduct the study protocol. The most obvious advantage is that the virtual trial design maximizes patient availability and enrollment in the study. Patient recruitment and enrollment is often the longest stage of a clinical trial with almost 80% of trials failing to meet initial targets.[1] Unlike site-based clinical trials, which require frequent visits to a designated research facility, remote clinical trials are based from the patient's home so those with mobility issues--such as the elderly or patients who live in rural areas--are also able to participate in the trial. The convenience of a virtual methodology alone will increase numbers of patients willing and able to enroll. Also, electronic health records can help identify increasingly targeted trial subjects and online patient support networks which could be used more to raise awareness of trials and directly recruit subjects. While virtual trials still require the study site to house support staff and invest in data collection and analysis platforms, they are potentially significantly more cost effective because they don't require the traditional brick-and-mortar set-up of multiple study sites.

Another advantage to virtual trials is their potential to keep subjects engaged with the study. As many as 40% of Phase III trial subjects become disengaged and drop out of the study.[2] Some of the causes of this attrition are related to convenience--due to issues like the inconvenience of traveling to study sites, or the complexity of the trial design and data collection. Virtual clinical trials could remove the need for frequent travel to study sites and automate data collection, increasing patient engagement and retention.

Virtual trials also offer the ability to reduce risk in the drug development process. Data from remote monitoring devices could be accessed by trial investigators in real time, opening up possible efficiencies in data cleaning, which could move to an on-going process rather than cyclical. Remote monitoring capabilities could thus facilitate an adaptive clinical trial approach, allowing improvements in trial design based on the accumulating data. Decisions to terminate a drug's development could also be made faster, improving patient safety and reducing expenditure on failed trials that have unfortunately become the norm in the drug discovery process.

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Finally, the virtual trial design may allow groups who have a vested interest in the success of the trial (including investors, physicians, government agencies, patient advocacy groups and even the patients themselves) to have more opportunities to play an active role in the study, potentially leading to better data quality and shorter timelines.

Early pioneers in virtual trials

In 2011, Pfizer pioneered the virtual clinical trial model with its Research On Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial.[3] The REMOTE trial was the first randomized clinical trial using web- and smartphone-based patient recruitment, enrollment and collection of study data without requiring patients to visit a physical study site. One of the main goals was to compare the virtual approach to a conventional Phase IV clinical study in order to determine if the virtual trial design would be a feasible way to conduct future trials. Unfortunately, Pfizer's REMOTE trial faced a host of challenges, not least of which was the issue of patient recruitment (most members of the target patient group were older, so the use of a technology-based trial was an unknown.)

Early this year, Sanofi announced its intention to support a virtual diabetes trail (VERKKO) to be conducted remotely in Europe.[4] This virtual clinical trial has one key difference compared to Pfizer's REMOTE study in that no drug is being tested. Instead, Sanofi has teamed up with three other organizations to test a 3G-capable, wireless glucose meter. This trial represents significant advancement in the clinical trial community, as it is the first clinical trial using an electronic informed consent approved by European regulatory agencies.

What does the FDA say?

Though the FDA has stated that they see benefits in the appropriate use of technology in clinical trials, they are still in the process of learning about virtual clinical trials, the bring-your-own-device (BYOD) model of provisioning and other aspects of today's tech-enabled research environment.[5] A docket has been established to gather feedback on how researchers are using technology and what barriers are stopping more widespread adoption.[6] The agency is seeking input on four specific issues:

- How the FDA could encourage adoption of such tools.
- What barriers are seen as blocking uptake today.
- How new models of research will affect patients.
- Whether the need to comply with regulatory requirements is seen as an impediment to the application of virtual technology in trials, as well as whether gaining clearance from institutional review boards is an issue.

The fact that the FDA is seeking input is no surprise, as it is part of the FDA's role to support, and even encourage, innovation. In fact, the FDA's recently published new draft guidance document "Use of Electronic Informed Consent in Clinical Investigations"[7] explains how federal regulators will permit companies to use electronic media (like interactive websites) to help facilitate the informed consent process. This will certainly serve to help companies conduct virtual clinical trials. Most companies are finding the FDA to be very supportive of virtual trials. Transparency Life Sciences, a Boston-based biotechnology startup, for example, recently secured FDA approval for an entirely tele-monitored trial protocol in a mere 30 days, and was encouraged to do more innovation in the direction of virtual trials.

Looking to the future, several scenarios seem plausible. Perhaps virtual studies will augment rather than replace traditional study practices and workflows. Virtualizing aspects of the study may be leveraged when the circumstances call for it--similar to how remote monitoring workflows are being adopted by study oversight teams today. Or perhaps virtual clinical trials are used in rescue studies. Perhaps virtual studies will lend themselves well to sensors and diagnostics, which will continue to increase in importance as the technology evolves. And hybrid models are likely to emerge as sponsors increasingly step forward to test the new model.

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