

How mHealth Technology Is REVOLUTIONIZING Clinical Research

By Michele Cleary

With the entry of technology giants
into the digital health market, big changes
are on the horizon for clinical research



This September, Apple once again dominated the world's daily news cycle with its latest product launch with not only its latest iPhone but also its newly enhanced Apple Watch—a connected device that includes an FDA-approved ECG. Apple's participation in this sector—the connected biosensor market—demonstrates the enormous appeal and profit potential these devices hold. As technology superpowers like Apple turn their innovation talents to developing connected biosensors, new products are changing clinical research, offering real opportunities to improve research data, enhance trial efficiency, and reduce costs.

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THE EVOLUTION OF mHEALTH

Over the past decade, digital health innovations have revolutionized healthcare delivery with solutions ranging from telemedicine services to electronic medical record software. Thanks to the innovation of mobile digital health services, commonly referred to as mHealth products, the clinical research environment now faces its own revolutionary moment with new challenges and opportunities.

Traditional clinical trials are being transformed into 'smart RCTs' by adding mHealth apps. Using tools such as Apple's Researchkit and the Google Study Kit, researchers can create custom mHealth apps specific to their clinical trials, which improve clinical trial operations by accelerating study recruitment, simplifying patient reporting, and enhancing participant engagement.

Now, connected mHealth biosensors are further revolutionizing clinical trials by allowing a real-time view of real world events.

Embedded within a wearable device, unobtrusive mHealth biosensors can continuously collect data throughout the patient's daily routine, objectively detecting disease-related physiological or behavioral biomarkers and relaying data back to researchers. These products represent a significant improvement over patient self-reported diaries and earlier monitoring devices.

Most importantly, mHealth innovation—through apps and biosensors—represent a patient-centric approach to clinical trial design. These products empower patients, allowing them the opportunity to participate fully in clinical research without shackling them to devices that impede their daily lives.

Currently, mHealth biosensors collect a wide range of physiological data, including blood pressure, posture, heart rate, electrodermal activity, pulse oximetry, and sleep patterns. As disease-specific algorithms embedded within these devices continue to improve, these sensors improve their ability to differentiate between disease-related bio-measures and normal variation, increasing their 'signal-to-noise' ratio, to better identify disease presence or disease progression.

SPECIFIC BENEFITS TO CLINICAL RESEARCH

The potential impact of mHealth biosensors on clinical research stems largely from their ability to provide more contextual, timely data with minimal burden on study participants. These products can improve clinical research in 3 key areas: data collection, analysis, and study operations.

DATA QUALITY BENEFITS

- *Collection of real-world data: mHealth biosensors fills the gaps between research assessments or episodes-of-care by providing contextual data on patients' daily lives. With such an enormous volume of real-world data, companies can refine their understanding of drug efficacy, enabling them to identify which types of patients are most receptive to the product and under which conditions. Such continuous measurement through an unobtrusive sensor can minimize the impact of the Hawthorne effect (changes in behavior stemming from observation), creating a more representative view of patient disease and treatment effects.*

- *More accurate data: mHealth biosensors' consistent, passive data collection mean that far more clinical events are captured, not just those that participants choose to report. These sensors also provide more objective data, eliminating patient interpretation as to whether a given clinical event is 'reportable,' thus minimizing the variability in outcome data.*

- *Deliver more timely data: Thanks to mobile data reporting, researchers can have near real-time access to patient data. More immediate access to data allows researchers to identify potential adverse events quickly. It can also help quickly identify subsets of patients for whom a product may be more effective. Rapid identification of emerging issues can empower companies with the information needed to respond quickly to unexpected outcomes, alleviating potentially dangerous patient events. Equipped with this information, companies can decide more quickly whether to restructure future studies or even whether to proceed with more trials.*

- *Identification of novel endpoints: The enormous volumes of data associated with mHealth studies may also help identify novel endpoints not previously observable in traditional clinical trials. These novel endpoints could, in turn, define better targets for early treatment intervention. As these novel endpoints undergo validation and as further research establishes their link to important health outcomes, these endpoints may even replace traditional in-clinic endpoints in future research and submissions.*

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Novel endpoints represent a critical step towards more patient-centric trials. mHealth biosensors collect more of the real-world outcomes most relevant to patients, as opposed to focusing solely on the biomarkers most relevant to clinical pharmacologists. The ability to capture these endpoints help drives clinical research towards more real-world investigations.

The identification of such novel endpoints is particularly important in conditions with a low signal-to-noise ratio. For instance, the study of some neurodegenerative diseases is limited given the difficulty in observing 'gold standard' metrics within a trial setting. Novel endpoints may advance clinical research for such conditions, improving treatment options and health outcomes in these patients. >

METHODOLOGICAL BENEFITS

By providing enormous volumes of research data cost-effectively, mHealth sensors can improve 2 significant methodological challenges often experienced with real-world data:

- Signal-to-noise ratio
- Variability across participants

Low signal-to-noise ratio is not uncommon, especially during early disease stages. With sporadic clinical assessments and standard patient diaries, traditional clinical trials struggle to collect sufficient data to clearly differentiate treatment effects (signal) from normal behavior (noise).

Deborah Kilpatrick, PhD, CEO at Evidation Health, a health and measurement company on the leading edge of mHealth biosensor use in clinical trials, recognizes an enormous opportunity to remedy these challenges through mHealth sensors. “These (challenges) are not new to clinical research. But the way we can now deal with them in the digital era is massively aided by faster, better, cheaper and bigger digital datasets that can be continuously and frictionlessly collected.”

According to Dr. Kilpatrick, as data sensors become more integrated into our daily lives, there is a risk of lowering the signal-to-noise ratio just due to the “noise” of so much variability outside clinic walls. However, the richness of continuously flowing datasets over time can mitigate this risk by finding disease signals that were simply not possible before to measure.

The second issue is the individual variability in the data—each patient is different, especially at early stages of a disease. In an ambulatory, real-world environment, there will be a great deal of variability in biomarkers from patient to patient as compared with a more severe population where the disease signal is much stronger and more concentrated.

Being able to collect large volumes of longitudinal, continuous data from very early state to advanced disease in the same set of patients allows for patients to effectively become their own control—which is enabled because the data are cheaper to obtain continuously over long periods of time.

OPERATIONAL BENEFITS

Finally, mHealth biosensors have the capacity to improve clinical trial operations by lessening the burden of trial participation and by making the trial process more cost effective.

- *Lessening the burden of trial participation: mHealth biosensors are inherently patient-centric, maximizing patient engagement by minimizing the burden of trial participation. Passive data collection causes minimal disruption to patients' daily routines as compared to the demands of traditional clinical trials, which often require frequent clinic visits and patient reports via daily diaries. And lessening the burden of study participation would likely improve participant retention rates, thereby improving both the quality and the quantity of study data.*

Finally, minimizing the burden of trial participation could potentially increase the participation rates of underrepresented groups. For some patients (eg rural, elderly, low income), trials requiring frequent clinic visits may be impossible due to the cost or complexity of

transportation. And for English language learners, patient diaries may be too complicated to consider study participation. Trials using mHealth sensors removes many of these barriers.

- *More cost-effective trials: With vast data resources accrued through mHealth biosensors, researchers can more readily identify patient subsets in whom treatment effects may be suboptimal, allowing companies to shorten certain clinical trials or refine future studies to target more appropriate subgroups. Adverse events could also be identified more readily than traditional methods, allowing for more rapid intervention and avoiding costs associated with widespread adverse events.*

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Finally, companies could benefit tremendously with additional data insight that could clarify their risk of failure in future trials. Traditional clinical data streams with traditional endpoints are often insufficient to predict the risk of failure in future trials, which may explain why nearly 60% of phase II clinical trials end in failure. [1] But equipped with more real-world data, perhaps even data on novel endpoints, companies can make more informed decisions regarding whether to proceed with further drug trials and avoid the enormous expense of failed trials.

CHALLENGES SURROUNDING MHEALTH BIOSENSORS IN RESEARCH

While mHealth biosensors allow researchers to better understand disease progression and treatment effects by using real-world, real-time data, their use in clinical research is not without challenges. Potential impediments include:

- *Infrastructure Requirements:* Continuous monitoring leads to enormous volumes of data, requiring significant information technology infrastructure. Some companies now support digital biosensor technology in clinical trials by collecting data remotely, and connecting data to other data attributes.
- *Data Security:* As with any connected devices, data security presents ongoing challenges. Necessary process and technical applications are integral to protecting data transmittals.
- *Accuracy and Reliability:* The accuracy and reliability of digital biomarker will need to be supported by evidence that demonstrates its specificity, sensitivity, and positive and negative predictive values.
- *Validation:* Perhaps the most challenging aspect of digital biosensors for clinical research is the question of validity—can these products perform a valid measure of the targeted biomarker as compared with the gold standard? Would comparisons even be appropriate? Are continuous measures of clinical attributes better than discrete measures? Do more novel measures better at identifying individuals at risk? Do they identify clinically meaningful events?

THE REGULATORY RESPONSE TO mHEALTH

Regulatory agencies in both the US and in Europe are scrambling to develop suitable regulations for digital health products.

In late 2017, the FDA introduced the Digital Health Innovation Action Plan as a way to spur digital health innovation, expanding opportunities for digital health tools to be incorporated into drug review. By April 2018, the FDA outlined its approach to digital health.

“If we want American patients to benefit from innovation, FDA itself must be as nimble and innovative as the technologies we’re regulating,” says FDA Commissioner Scott Gottlieb, MD. [2] Commissioner Gottlieb presented the FDA’s vision of a regulatory framework that would open a more efficient path to review and approval for digital health tools as part of drug review, thus ensuring that these tools reach their full potential to help us treat illness and disease, while meeting the FDA’s high standard for safety and effectiveness.

In September of this year, Commissioner Gottlieb announced that the agency’s FY2019 budget would include a Center of Excellence for Digital Health that would advance modernizing our regulatory approach to digital health, thus helping this industry grow, while protecting patients. Says Dr. Gottlieb, “This Center of Excellence would help establish more efficient regulatory paradigms, consider building new capacity to evaluate and recognize third-party certifiers and support a cybersecurity unit to complement the advances in software-based devices.” [3]

Meanwhile, the European Medicines Agency (EMA) has yet to issue general guidance on the subject. “At the present stage of knowledge and technology development, data collected in this manner are mainly envisaged to provide supportive evidence to clinical or functional claims, rather than constitute the main body of evidence to support regulatory approval,” says Francesca Cerrata, MSci, MPharm, Senior Scientific Officer, European Medicines Agency.

However, EMA has released several qualification advices on specific proposals, including the use of a novel methodology in the context of research and development, such as ingestible sensors. [4]

In both the United States and Europe, the regulatory landscape will continue to evolve in coming years.

WHAT MIGHT THE FUTURE HOLD FOR mHEALTH TRIALS

The era of mHealth-informed clinical trials is in its early stages.

Researchers are currently developing methods to contend with digital biomarker discovery. And they are developing ways to deal with the consumer-grade data streams, and not just clinical grade data streams. “We’re doing rigorous studies just like the molecular companies were doing with genomic data a decade ago to identify which biomarkers can be developed and validated and actually have relevance.” says Dr. Kilpatrick.

The regulatory world is still composing its guidelines for companies regarding how they will review mHealth data in their approval processes. It is unclear how technology companies, coming from a world that rewards bold designs and rapid innovation will thrive in the heavily regulated world of drug development. How will this change in corporate culture impact innovation?

And how will new sensor technology impact drug trials? mHealth sensors are becoming more resilient to environmental variations, expanding their potential for real-world data collection. Reductions in sensor size and power needs coupled with algorithm improvements will ease battery requirements, making biosensors less obtrusive and more easily integrated into patients’ daily life, allowing for even greater data. New sensor technologies, such as silicon-based microneedles, will continue to expand the potential for new types of clinical studies. [5]

Beyond clinical trials, mHealth sensors could be enormously beneficial to clinical practice. Additional real-world data could help providers better evaluate disease progression and treatment effects in their patients, equipping providers with the tools needed to deliver more personalized medicine. mHealth sensors could deliver the data needed to help providers identify optimal treatment at the best time for each patient, ISPOR is helping to facilitate the discussion regarding how these devices may improve research. Last May’s US ISPOR meeting, titled “Real-World Evidence, Digital Health, and the New Landscape for Health Decision Making,” provided a great opportunity for researchers and decision-makers to discuss digital health and its role in patient-centered outcomes research. [6]6 Workshops included discussions on how to better meet end-user needs, how to support the adoption of digital health, and how to communicate value.

Yet questions remain—will patients be willing to wear such devices? Will payers be willing to pay for them? Will providers be able to wade through the influx of data?

These are early days. But as we learn how best to integrate mHealth biosensors into research, these devices not only hold the promise to make trials faster, safer, and more cost-effective. They could help illuminate novel endpoints that may help deliver more individualized care to patients everywhere. ●

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