The Value of Predictive Analytical Applications as Digital Health Tools

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Summary

The pace of wearable sensor device deployment in decentralized clinical trials is increasing significantly. These devices capture enormous amounts of data from patients in real-world settings, providing measured and quantifiable insights for a variety of populations across different therapeutic areas.

This article will describe the emerging benefits and capabilities of predictive analytic applications that are enabled by high-resolution data originating from wearable sensor devices deployed in real-world settings. Retrospective detection of statistically significant biomarker measurements across a population of patients in a clinical trial can signal prospective clinical events, offering opportunities for the development of accompanying novel digital health apps to support both patients and caregivers in optimizing treatment for a specific condition. These digital health applications also stand to offer passive and continuous objective data attesting to therapy efficacy, supporting the interests and decisions of health care providers, researchers and regulators that constitute emerging connected digital health care ecosystems.

Introduction

Imagine wearing a sensor device on your wrist or chest that captures and communicates physiological measurements such as sleep, heart rate (HR), heart rate variability (HRV) and electrodermal activity (EDA) to a mobile application capable of predicting and alerting to the onset of clinical events with increasing probability. Patients suffering from migraines or other conditions that prove to indicate foretelling symptoms or clinical events may use such a device and application as a "digital accessory" to administer therapy at the time of alert, rather than onset. Efficacy of therapy intervention across populations of patients could be improved by empowering the patient with real-time decision capabilities in support of deciding the optimal time to administer treatment.

While this may sound like clinical science fiction, connected wearable sensor device platforms, mHealth applications, smartphones, ubiquitous connectivity, cloud architectures and machine learning algorithms have emerged to enable these predictive analytic models across diverse patient populations. The enormity and scale of the COVID-19 pandemic highlighted long-standing problems with care delivery in traditional settings. Mobile health technologies deployed within digital health ecosystems offer integrated and connected care delivery systems that are poised to accelerate clinical research while improving the efficacy and safety of therapeutic interventions by leveraging remote patient monitoring technologies. Within this context of emerging digital health ecosystems, some sponsors and clinical research organizations (CROs) are evaluating the feasibility of wearable sensor device technologies with respect to endpoint measurement feasibility and subsequent development of applications for patients to use in real-world settings.

Device Validation

Wearable sensor devices generate physiological measurements continuously at a sample rate that is measured in hertz (Hz). It is not uncommon for measures to range from 32 ~ 256 Hz. When considering the volume and amount of patient data that this generates over time, it is imperative that the device measurement outputs be compared to those of a validated clinical predicate device to ensure that accurate data can be used as verifiable inputs to upstream statistical and analytical processing algorithms.

Toward that end, novel digital device validation is typically performed within an observational study to confirm validity, consistency and reliability of sensor measurement within a specific patient population.

One of the more well-known examples of such a device validation study is the Apple Heart Study, which validated the capability of the photoplethysmography (PPG) sensor on an Apple Watch to detect arrythmias as a possible precursor to atrial fibrillation. The arrythmia detection capabilities of the Apple Watch were compared to an ambulatory ECG monitor. The PPG sensor on the Apple Watch and accompanying algorithmic detection analyzed the pulse rate at the wrist, while the ambulatory ECG measured electrical characteristics of the heart. Outcome measures for the novel clinical event detection method of the Apple Watch were validated "side by side" using the ambulatory ECG monitoring device. A significant percentage of the patients in the study who registered arrythmia detections on the Apple Watch subsequently recorded atrial fibrillation events on the ambulatory ECG, attesting to the ability of the Apple Watch arrythmia detection feature to reasonably anticipate a higher incidence of atrial fibrillation within a population exhibiting irregular heart rhythms

Published results from device validations can be used for peer review and reference for future studies on the same patient population.

Event Detection

As the device automatically generates measurements passively and continuously, there needs to be a mechanism for the patient to record a clinical event, such as the onset of a migraine. Some wrist worn wearable sensor devices are designed to include a simple event detection button. As the trial participant experiences the onset of a clinical event, the individual squeezes the button to record the date and time of the event alongside the continuous physiological monitoring data values. Alternatively, ePROs or electronic patient diaries can be deployed on an mHealth app to support the capture of the clinical event.

N=?

Study protocol design for predictive analytical models is primarily concerned with determining the appropriate number of diverse trial participants to enroll and equip with wearable sensor devices, along with the duration of time required to monitor and collect physiological data. The designated size of this sample population and "wear time" will support the generation and curation of the data set to be consumed by processing algorithms. Necessary support for patients during the trial is typically structured around upfront training and ongoing support throughout the trial to optimize device power management, connectivity, and wear time according to protocol.

Biomarker Detection

If we now envision n=500 patients in a disease cohort wearing passive sensor devices continuously generating clinically validated physiological measurements such as sleep, HR, HRV and EDA over a period of time and within a remote patient monitoring or ePRO platform supporting patient reported record of clinical events, we have architected the population health foundation for a real-world data (RWD) set. Subsequent algorithmic design will aim to detect statistically relevant physiological signal patterns relative to baseline measurements that may present across a patient population in advance of the clinical event.

If such patterns are detected and identified by the algorithm across a significant percentage of the study population, the resulting signal can serve as a probabilistic predictor of the clinical event within that patient cohort.

Digital Health Ecosystem and Connected Applications

Patient

Now that we have identified a wearable sensor device that is fit for purpose to passively measure continuous patient physiological signals and identified a pattern of measurement deviations from the baseline that constitute clinically proven evidence of a probabilistic forthcoming clinical event, we need a means to notify a patient wearing the device that their body just "signaled a possible warning."

Validated native mobile applications that run on iOS or Android mobile operating systems offer secure wired or wireless connectivity to both the wearable sensor devices connected to the patient and carrier/Wi-Fi connections to machine learning algorithms hosted in cloud operating environments central to cohorts of patients who share a disease or condition. This allows for both the downloading of algorithms to detect the target physiological signal pattern on the patient, as well as the uploading of de-identified sensor and event data to the cloud to support ongoing curation of data used to train the machine learning algorithm(s).

Population health

As more patients suffering from specific conditions adopt wearable sensor devices and applications, there has been a growing "crowdsourcing effect" of clinically relevant data sourced from that population in a real-world setting to support statistical and quantitative analysis. Subsequent iterations of trained machine learning algorithms stand to become "smarter" in their ability to predict the onset of clinical events with higher probability and lower error rate.

Secure web or native mobile applications connected to these platforms provide a means for patients to consent to authorized sharing of their real-world wearable sensor device data with their health care providers, sponsors, CROs, device technology vendors and regulatory authorities. Each stakeholder group has various interests and uses for data processing. Data access, privacy and compliance concerns are governed according to the patient's country- and region- specific authorities and institutional organizations.

Challenges

Although the industry offers a number of success stories and proof points across various areas of digital health and real-time

data analytics, several challenges emerge when looking toward mainstream market adoption of the use case previously described.

Consumer grade devices and measuring clinical validation across condition-specific patient populations

As stated at the outset of this article, clinical evidence attesting to the measurement validation of the novel wearable sensor device to perform accurate, reliable and consistent physiological measurements is required to be generated in support of predictive analytical processing. For novel digital devices intended for use in non-clinical settings, this validation is often performed via comparison studies against existing "predicate" devices offering the same physiological measurement in clinical settings.

In the device validation study of the Apple Heart Study described earlier, scale is significant in terms of investments in time, money, resources and coordination between the technology device vendor and clinical research apparatus. Market opportunity and benefit to public health in deploying affordable, consumer-grade wearable sensors as de facto population health early warning systems for conditions like atrial fibrillation justified Apple's investment in the device validation and research.

Many consumer-grade device vendors market their products toward health and wellness, but stop short of similar device and clinical measure validation for specific patient conditions that would allow for the device to support integration into digital health application ecosystems. The Apple strategy and approach set an example for others to follow by creating enough clinical evidence for the Apple Watch to support "informing" the patient of the detection of arrythmias, and advised the patient to use that information to schedule a consult with a specialist to clinically diagnose atrial fibrillation.

The prospect of empowering a patient with a digital companion app that offers decision support on when and how frequently to take a medication would effectively transfer some of the medication's instructions from the sole direction of the physician to the device and algorithm. A corresponding amount of supporting clinical evidence would need to be generated and offered to regulators to ensure the efficacy of therapeutic intervention is maintained or improved while attesting to any risks to patient safety.

Vendor validation

Regulation, risk and liability are some of the reasons that many consumer device companies avoid moving into the "medical/clinical grade" distinction. Devices and data that will be integrated for use in clinical decision-making can stratify the vendor device and indication for use into a risk category that warrants regulatory oversight and accompanying burdens, including filing, reporting, audit, quality systems and compliance.

Regulatory position notwithstanding, consumer-grade wearable sensor vendors and devices being considered for integration into predictive analytic applications need to generate and offer supporting evidence of clinical and analytical validation for the patient populations featured in the use case. With so many patient disease populations to explore, vendor determination and selection of patient population and condition to explore for study validation and clinical evidence generation is complex and risky. There is no assurance or guarantee that the clinical and analytical evidence generated in the validation study will be sufficient to justify integration of the vendor device into the application or algorithm.

Device and technology obsolescence

Consumer purchasing patterns and behaviors with respect to consumer electronic devices are much more dynamic than the methodical, deliberate device and measurement validation processes described here. A patient's consumer-driven interest to upgrade or replace a clinically validated wearable sensor device model may lead them to part company with the support for predictive analytics, punctuating any long-term RWD contribution to training algorithms.

Global regulatory, privacy and compliance

Most countries have controls and protections in place to protect the privacy and security of their citizens. Passive, continuous measurement of physiological measurements from country-specific patient populations for the purpose of centralized analytical processing external to country borders are met with regulations that may range from restrictions and limitations on the type of data that can be exported to outright prohibition of any patient data. This may require localization of cloud infrastructures and applications to operate within the host country itself.

Conclusion

Wearable sensors and the real-world data generated from these devices continue to proliferate, providing valuable insights into the health of global patient populations. Clinical and analytical validation of the data from these devices is a necessary step in determining whether the device measurements can support development of predictive analytic algorithms and applications. As clinical trials integrate these novel devices and measurements to study designs, the predictive capabilities enabled by the combination of passive, continuous monitoring of measurement data and patient-recorded clinical events offer an opportunity for the development of digital health applications and algorithms to support both pre-market therapy development during clinical trials and post-market real-world surveillance. Consumer wearable device vendors and global regulators are working to adapt to corresponding market and compliance realities as sponsors and CROs navigate the global patient populations and countries where predictive analytics can be implemented toward improving therapy development and patient outcomes using novel digital technologies.