Gaps in Accelerating Digital Endpoint Development and Adoption

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Abstract

A “digital endpoint” is a novel classification defined by an endpoint’s use of sensor-generated data often collected outside of a clinical setting such as in a patient’s free-living environment. Applicable sensors exist in an array of devices and can be applied in a diverse set of contexts. For example, a smartphone’s microphone might be used to diagnose or predict mild cognitive impairment due to Alzheimer’s Disease or a wrist-worn activity monitor (such as those found in smartwatches) may be used to measure a drug’s effect on the nocturnal activity of patients with sickle cell disease[1,2].

Digital endpoints are generating considerable excitement because they permit a more authentic and objective assessment of the patient’s experience, reveal formerly untold realities of disease burden, and can cut drug discovery costs in half[3–5]. However, before these benefits can be realized, effort must be applied not only to the technical creation of digital endpoints, but also to the environment that allows for their development and application. The future of digital endpoints rests on meaningful interdisciplinary collaboration, sufficient evidence that digital endpoints can realize their promise, and the development of an ecosystem in which the vast quantities of data digital endpoints generate can be analyzed.

The fundamental nature of healthcare is changing. With coronavirus disease 2019 serving as a catalyst, patient adoption of telehealth has risen sharply. Between March and April 2020, New York University Langone Health’s telemedicine urgent care visits rose 683%[6]. While a sustained shift in the importance of telemedicine is not assured, there is reason to suspect that telehealth will become more entrenched in the healthcare ecosystem[7]. With the ubiquity of relatively

inexpensive sensors, digital endpoints are positioned to impel consequential change to drug discovery. It is therefore not surprising that regulators, physicians, researchers, and consultants have each offered their assessment of these novel tools. However, as we further describe below, the broad adoption of digital endpoints will require a unified effort. In this paper we consolidate the typically divided exploration of digital endpoints and conclude with an interdependent list of challenges that must be collaboratively addressed before these endpoints are widely adopted.

Contextualizing the Benefits of Digital Endpoints

To understand the potential of digital endpoints, we must first examine the deficiencies of traditional endpoints. Consider heart failure. The traditional primary clinical endpoints for heart failure are cardiovascular death and hospitalization with heart failure[8]. These endpoints are coarse and only allow physicians to assess pathophysiology as discrete variables.

Moreover, because clinical evaluation of a patient's health requires a visit to an office or lab, data arrives in a series of snapshots. Consequently, traditional endpoints only allow the assessment of the patient's disease in a clinical setting; they do not offer insight into the patient's daily burden. This is particularly problematic for diseases with persistent and limiting symptoms. It is perhaps predictable that patients with advanced heart failure often emphasize quality of life over duration of life[9]. Surrogate endpoints such as The Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire attempt to elucidate the disease's effect on a patient's daily life, however these patient reported data are typically sensitive to extreme developments in symptom severity, but are often insufficient to indicate more subtle shifts to a patient's quality of life[10].

Deficiencies in traditional endpoints are not unique to heart failure. Historic trends in drug discovery suggest that a fundamental change is necessary: from 1950 to 2010, the number of new FDA-approved drugs per billion dollars spent on research and development has halved every nine years; this trend is referred to as Eroom's Law (Moore's Law backward)[11]. The authors of Eroom's law, Scannell *et al.*, asserted that simply reorganizing research and development efforts is not sufficient change to reverse these grim economic realities. Instead, they suggest that there is a fundamental problem of productivity.

Recently, however, optimism that Eroom's Law might be broken has surfaced; between the periods of 2010 (when Eroom's Law was published) and 2018 there was an increase of 0.7 new molecular entities per billion dollars spent on research[12]. Understanding the drivers of Eroom's Law and its potential subsequent reversal is a speculative exercise, however much of the analysis credits the quality of newly available data, which is a demonstrably relevant variable in predictive validity, and therefore, drug discovery[13].

Importantly, utility cannot be derived from all data; the evidence must be of high quality and relevance[13]. To be considered clinically meaningful by the FDA, an endpoint must directly measure how a patient feels, functions, or survives[14]. Thus, data used to improve drug trial success rates should measure the patient's experience in one of these respects. This is not a contemporary position. In fact, since 1990 – when the FDA required the first Pulmonary Hypertension randomized clinical trial to use a primary endpoint that measured participant symptoms, fitness, or survival – the 6-Minute Walk Test has served as the primary endpoint for

nearly every clinical trial evaluating pulmonary vasodilators in Pulmonary Hypertension[15]. The FDA continues to fortify its guidance that patient experience must be primarily considered in drug discovery[16]. The 21st Century Cures Act, signed into law on December 13, 2016 and the Prescription Drug User Fee Act Reauthorization explicitly describe efforts to elevate the patient's voice in drug development[17,18].

While the FDA's position on this matter has been unchanged, the availability of data that elucidates the way a patient feels functions and survives is novel. As described above, traditional efforts have required patient evaluation in a clinical setting, outside a patient's free-living environment. Lab data, however, can only serve as a proxy for a genuine representation of the way a patient feels, functions, or survives. A bona fide examination of these variables requires the context of a patient's typical day. By continuously collecting data, sensors and other widely available technology permit this sort of analysis; thus, digital endpoints can offer previously unavailable insights about disease.

For example, multiple sclerosis's heterogeneity has encumbered traditional clinical assessment of disease state[19]. For decades, the primary clinical endpoints – the Expanded Disability Status Scale and relapse rate – have remained unchanged despite their considerable deficiencies[20]. In recent explorations, however, digital endpoints have used an array of sensors, from infra-red cameras[19] to commonly accessible accelerometers[21], for the purpose of demonstrating the burden of a patient's disability. There is reason for optimism beyond multiple sclerosis. Similar efforts have been undertaken for Huntington's disease, autism spectrum disorder, Parkinson's disease, diabetes management, Duchenne muscular dystrophy, and heart failure with preserved ejection

fraction[22–28]. The Clinical Trials Transformation Initiative, a public-private partnership organized to improve the quality and efficacy of clinical trials, have presented a convincing argument that several of these diseases – heart failure, Parkinson's disease, diabetes mellitus, and Duchenne muscular dystrophy – are particularly well-suited for innovation by means of mobile technology[29–32]. The Digital Medicine Society maintains an ever-evolving library of digital endpoints employed in industry-sponsored studies[33]. An abbreviated list of recent efforts is available at the end of this paper.

Regulators across the world recognize the benefits of employing non-clinical data to better design and conduct clinical trials and have thus established guidance for real-world data. As defined by the FDA, real-world data are "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources[34]." These real-world data are typically generated by the sensors digital endpoints rely upon for their assessment of disease state[35]. The introduction of these guidelines as law in 2016 and their subsequent expansion in 2018 is an indication of the FDA's willingness to facilitate the introduction of innovative approaches to disease measurement[36]. European regulators have similarly identified the utility of real-world data and have thus formulated a consortium to enable the development of novel solutions that leverage this class of data[37].

The value of objective real-world data will continue to develop in a post-COVID environment. The pandemic has changed the nature of patient-physician interaction. Telehealth trends suggest the number of patients who will digitally interact with their physician will only grow. Eleven percent of patients in the United States used a telehealth platform in 2019, in April 2020 a

reported 46% of patients used telehealth as a replacement for canceled office visits[7]. Moreover, before the pandemic there were positive trends in telemedicine adoption and patients reported high levels of satisfaction with telehealth[38,39]. It is reasonable to assume an increasing proportion of patients will prefer to have some degree of interaction with their physicians via a telemedicine platform, thereby making in-clinic data more difficult to obtain.

The potential for these data is not limited to the virtualization of current clinical practices. For example, the utilization of machine learning models to diagnose and measure disease is a particularly compelling use for these real-world data. Initial efforts are already underway. For example, an algorithm was designed to identify non-diagnosed prodromal Alzheimer's disease[40]. Separately, a machine learning approach was applied to smartphone data to quantify Parkinson's disease motor symptom severity[41]. Both of these studies produced promising results relative to their respective standard measures. The utilization of these sophisticated techniques in the analysis immense library of data generated by sensors will likely be a driver of innovation offered by digital endpoints.

Impediments to Digital Endpoint Adoption

The enthusiasm for digital endpoints has swelled as the continuously-collected and objective data these endpoints apply to their assessment of disease state offer previously inaccessible accuracy and precision, expose previously unobtainable insights about disease burden and can markedly reduce the cost of drug development[3–5]. It is therefore natural to wonder why digital endpoints are not more frequently applied. There are several reasons.

1. Disjointed Efforts

A review of published government initiatives indicates a global consensus regarding the opportunity to apply digital tools to healthcare: in the United States, the FDA has established a Digital Health Innovation Action Plan to imagine the application of digital technologies at all levels of healthcare, Health Canada has established a division within their Therapeutic Products Directorate's Medical Devices Bureau with the intention of improving their digital health review analysis, an inter-council European Union group offered a statement in strong support of digital tools for building a healthier society, the United Kingdom's Medicines and Healthcare Products Regulatory Agency is actively seeking to engage with those working on digital health technologies, Swissmedic is broadly applying digital tools to increase efficiency and effectiveness, and Japan's Health Care 2035 initiative emphasizes the use of digital tools[42–47].

Despite a unified vision, little international cooperation exists. Perhaps it is ambitious to suggest nations should be more collaborative in their efforts, however, there is precedent. For example, the International Medical Device Regulators Forum is a consortium of medical device regulators from around the globe that attempt to coordinate regulatory requirements for medical products[48]. Continued international participation will be important to acceleration of digital endpoint acceptance; in fact, the Innovative Medicines Initiative, a public-private partnership between the European Union and the European pharmaceutical industry, has identified international collaboration as a critical variable to success to the adoption of digital endpoints[49].

In addition to collaboration across regulatory agencies, interdisciplinary participation is necessary for the successful development of digital endpoints. While all endpoints demand cross-

functional cooperation, it is especially true for digital endpoints because these novel endpoints require software, hardware, and clinical validation[50].

In assessing the sensors and other hardware upon which digital endpoints rely for data generation, the FDA may consider every component of the device. If, for example, the accelerometer changes from one generation of a phone to the next, the device may have to be re-evaluated before its data can be collected[51].

Software in the form of machine learning algorithms, mobile applications, and other types of device software are subject to the same scrutiny as physical devices, however, the assessment of software is often more complex[52,53]. For example, while changes to hardware are characterized by long lead times, software changes rapidly and may be updated between time of submission and time of regulatory report rendering[54].

Of course, even if regulators deem a digital endpoint's associated hardware and software to be valid, the endpoint must meet the same high standards for clinical validation as any traditional endpoint.

Compelling progress continues to be made across disciplines. For example, as noted above, efforts in computer science have used machine learning algorithms to identify non-diagnosed prodromal Alzheimer's disease and to quantify Parkinson's disease motor severity[40,41]. Unfortunately, the application of machine learning models such as in the previous examples occur far too infrequently relative the number of available algorithms; it is often the case that

progress is halted for a lack of the domain knowledge requisite for applying machine learning models in a clinical setting[55]. Efforts to facilitate collaboration have been initiated such as by The Digital Medicine Society and even the FDA itself[56]. However, moving healthcare forward to a meaningful degree requires further unification of disjointed efforts.

2. Unproven Value

Even if collaborative efforts are established to develop digital endpoints that have a well-defined use case and gain regulatory approval, digital endpoints, as a category, must also allay any risk-averse participants; most notably pharmaceutical companies. While digital endpoints offer a promise of cheaper and more effective clinical trials, because these endpoints have been applied so sparsely, this potential remains hypothetical[57,58]. Given the cost of a clinical trial failure is immense, pharmaceutical executives exercise caution when presented an opportunity to significantly reshape their drug discovery processes[59,60]. Notably, it has been suggested that, without a drug discovery paradigm shift, digital endpoints will only further complicate the pharmaceutical model thereby contributing costs and complexity[60].

There is, however, some reason for optimism. In a 2018 Health Research Institute Survey, 42% of pharmaceutical executives stated they were investing in digital therapies in earnest. Of the 58% of respondents who had yet to invest in digital products, 42% suggested they would in the next one to two years and the other 58% planned to work on this type of therapy within three to six years[61].

3. Nature of Healthcare Data

Finally, the very nature of health data is an impediment to the implementation of digital endpoints. In fact, healthcare data has become so difficult to manage, interpret, and reuse that a set of principles known as the FAIR (Findable, Accessible, Interoperable and Reusable) Guiding Principles for scientific data management and stewardship were published as a protocol for improving the experience of working with health data[62]. These guidelines have received authoritative advocates: the European Commission issued an action plan for "turning FAIR data into reality" and the G7 have offered its endorsement[63,64]. Despite this enthusiasm, the implications of adhering to FAIR principles in the context of digital tools in pharmaceutical therapy discovery must be considered carefully. For example, the adherence to these guidelines will require a shift in perspective from both pharmaceutical executives and researchers – executives will need to be convinced of FAIR's economic benefit while researchers will need to unburden themselves of the often tightly held belief that data generated in their lab should be accessible only to them[65]. Moreover, there are technical challenges that must be overcome to unlock the benefits of FAIR data[65]. Generally, the acceptance of FAIR principles will require work, much of it significant, and any point of friction will only serve to suspend the application of digital endpoints.

Conclusion

The collective confidence requisite for the broad adoption of digital endpoints continues to build. Across the globe regulators, researchers in and out of healthcare, and physicians are applying their expertise to the exploration of these novel tools. There is tremendous optimism that digital endpoints will provide a platform to abate the cost of therapeutic discovery while offering a more accurate and authentic portrayal of disease burden.

However, before digital endpoints can build appreciable popularity, genuine collaborative efforts are required. International regulators must continue to harmonize their guidance for digital tools and, more importantly, researchers and practitioners must offer their respective expertise so that the technical and regulatory ecosystems in which these endpoints will be employed can be appropriately cultivated.

Abbreviated List of Digital Endpoints[33]

Date Listed	Study Phase	Endpoint	Technology	Measurement	Indication
8/4/20	Four	Change in total physical activity from baseline to weeks 10-12 and 22-24	Activity monitor	Activity Count	Sickle cell anemia
8/4/20	Four	Change in mean nocturnal hemoglobin oxygen saturation percentage from baseline, week 10-12, and week 22-24	Pulse oximeter	Overnight pulse oximetry	Sickle cell anemia
7/20/20	One	Change in Wake after sleep onset from beginning of study to weeks 4, 8, 12, and 16	Activity monitor	Wake time after sleep onset (WASO)	Menopause, depression, anxiety
5/8/20	Three	Change in PD symptoms as assessed by the Parkinson's KinetiGraph/Personal KinetiGraph (PKG) wearable device from baseline to Week 12	Activity monitor	Tremor, bradykinesia, dyskinesia, and daytime somnolence	Parkinson's disease
6/1/20	Four	Percent time in euglycemia (BG 70 to 180 mg/dl) by CGM during the final 14 days of each treatment	Continuous glucose monitor	Glycemic variability	Diabetes mellitus
1/30/19	Two	Change in physiological stress response	Heart rate monitor	Heart rate variability	Diabetic foot ulcer
1/20/19	Two	Change in speech features from baseline to week 48	Microphone (audio recordings)	Acoustic and linguistic language features	Alzheimer's disease
6/6/18	Two	Average change in pre-bronchodilator FEV1 from Week 16 to Week 24	Home spirometer	FEV1	COPD
2/28/18	Three	Percentage of participants with a ≥30% reduction from baseline in 24-hour coughs per hour at week 24	Chest contact sensor with audio recording	Cough count	Chronic cough
12/21/17	Four	Percentage of rescue free days between month 4 and month 6 as determined by the rescue medication sensor	Ingestible sensor	Medication adherence	Asthma

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