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How soon will digital endpoints become a cornerstone for future drug development?

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Digital technologies are transforming healthcare and will provide the basis for more patient-centric innovation in the pharmaceutical industry. Digital endpoints in clinical studies have the potential to drive innovation and reduce costly late-stage failures. This is also currently under consideration by regulatory agencies, such as the US Food and Drug Administration (FDA). The academic–industrial collaboration MOBILISED-D aims to implement and validate real-world walking speed (RWS) as a digital endpoint accepted by regulatory authorities as a first of its class. Previous work has shown that loss of mobility driven by chronic illness and frailty in older patients can be a relevant readout or effect of different diseases and various organ systems.

Introduction

Pharmaceutical innovation needs to become more patient centric, and digital applications are set to revolutionize clinical research, delivering a wealth of individual patient data. This is at least the way recent industry and consultancy publications frame it [1]. In a similar recent statement, the FDA commissioner sees a role of wearables to better understand a patient's well-being and needs [2]. Typically, endpoints accepted by the FDA include how a patient feels or functions and/or if they live longer. In selected cases, surrogate endpoints [e.g., validated biomarkers, such as blood pressure or low-density lipoprotein (LDL) cholesterol concentration] can replace relevant clinical endpoints, such as mortality [3]. The approvals granted based on surrogate medical evidence are often subject to post-approval Phase 4 studies to confirm and/or strengthen the evidence. Furthermore, health technology assessment (HTA) agencies want to evaluate evidence regarding clinical and cost effectiveness, safety, and overall patient benefit of the pharmaceutical intervention. Currently, the pharmaceutical industry is challenged by declining research and development (R&D) productivity, with the return on investment (ROI) in the industry at an all-time low of 3.7% in 2016 [4]. Scannell and co-workers named this phenomenon 'Eroom's law', in reverse to the widely known Moore's law on computational processor power, in that pharmaceutical R&D becomes slower and more expensive over time, despite advances in biomedical sciences [5]. One distinct problem that can be identified is the increasing number of so-called 'late-stage failures'. These are mostly Phase 3 studies in which primary efficacy endpoints were not met or safety signals emerged. Hwang and co-workers, using public sources, showed that, between 1998 and 2015, out of 640 novel therapeutics, 57% failed because of inadequate efficacy and not meeting the studied endpoints [6]. A recent publication from MIT, using two large data sets, showed a success rate of only 40% for Phase 3 studies [7]. Of course, at the time point at which these late-stage failures occur, large investments have already been made. This translates into a diminishing pipeline and portfolio value and reduced ROI of the overall pharma R&D activities. A question that needs to be asked is whether preclinical scenarios are disconnected from real clinical outcomes If

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yes, no new endpoint could help to reduce the number of late-stage failures. If no, the reason for Eroom's law could be a failure to translate meaningful changes in disease state in currently used endpoints.

Clinical endpoints hardly reflecting patient burden

In general, clinical endpoints, such as mortality, might only reflect one aspect of a disease burden because mortality can be rather low because of the benign nature of the disease and, therefore, not applicable as a clinical endpoint. Nevertheless, through its impacting signs and symptoms, the disease can significantly limit the patient's quality of life. Furthermore, current clinical study designs, where only intermittent evaluations occur, often only allow for snapshot assessments of enrolled patient, with long periods during which important data points are not collected. This all contributes to late-stage failure, which technology has the potential to change. A good example is heart failure with a preserved ejection fraction (HFpEF), which has a huge disease burden with a reduced quality of life but a low rate of events (e.g., mortality) that lend themselves for regulatory approval. This is especially true for early stages of the disease, which can show impaired functional capacity. However, studies in this patient population are prone to fail, because the sample size needs to be very large to reach statistical significance when traditional endpoints are used. For this reason, some industry players even refuse to develop drugs for this patient population, which stifles innovation for this population in need. The overall topic is further explored by Butler *et al.* [8].

Digital endpoints as new armamentarium for clinical development reflecting patient burden

A hypothesis that recently gained more traction across industry in different disease areas is the use of technology to gain new endpoints to quantify disease improvement by measuring physical parameters in a quality that is acceptable from a regulatory point of view. Recently, the Prescription Drug User Fee Act (PDUFA VI) was implemented. FDA is now required to consider the 'patient's experience' to be an integral part of the benefit versus risk of new drugs to facilitate successful product development. To measure these patient benefits, new methods, including wearable devices, medical applications (apps), and even machine-learning programs, will be needed. Furthermore, tools for capturing the patient's experience, be they quantitative or qualitative, can transform many aspects of medical product development [2].

Although a clinical assessment can currently be supplemented by several digital phenotypes, one key integrating concept is physical activity: Loss of mobility is a growing unmet medical need, driven by chronic illness and frailty in older patients, a key morbid effect of diseases of various organ systems, such as lung [e.g., chronic obstructive pulmonary disease (COPD)], heart (e.g., heart failure) or neurological and/or neurodegenerative [e.g., multiple sclerosis (MS)] diseases. Physical activity can be assessed in various ways. One major relevant component of physical activity is mobility. Mobility can be measured using the number of steps over time or using elements such as gait speed, also known as walking speed. In clinical research, the 6-min walking test is a surrogate mobility test that is a widely used measure and regulatory endpoint. It has been shown that gait speed is associated with survival in community-dwelling older patients [9,10].

Various lessons learned can be drawn from Parkinson's disease (PD). Activity and gait have been extensively studied in patients with PD and are in use to assess disease progression in practice. Espay and co-workers provide an excellent overview in their 2016 review of technology challenges and opportunities in this devastating disease [11]. Although much progress has been made, including latest technological developments, issues remain even in this well-researched area. Del Din identified three focus areas to work on to foster free-living (activity) monitoring in PD: (i) clear definitions of the clinical feature to be studied; (ii) validation using real-world data compared with better-controlled studies; and (iii) consensus on relevant outcomes [12]. In another publication, Lord and co-workers demanded a more structured approach to assess gait in contrast to inconsistent application, reporting, and interpretation. We think that the points made by Del Din and Lord *et al.* are not only applicable to PD [13] but might also be expanded to other indication areas. However, there is a large gap between assessing activity parameters for the use in observational studies and the potential use thereof as a validated outcome parameter accepted by regulatory authorities.

In a comprehensive review of relevant literature, Bohannon *et al.* showed that a minimal change in a patient's gait speed of 0.10–0.20 m s^{-1} can be clinically relevant across multiple patient groups [14]. It is also well known that, in general, gait is a characteristic of the functional status in older patients [10,15]. However, studies that currently assess activity and mobility as primary endpoints are often based on patient's self-reported outcome or performance testing (e.g., 6-min walking distance), both of which have significant shortcomings and vary among different classes of disease and clinical setting. Self-reported outcomes in particular have shown to be biased and, thus, need further development. Promising results in that direction have been generated by Godfrey and co-workers [16]. Furthermore, emerging digital technologies can now measure many aspects of mobility in the 'real world' on a continuous and long-term basis. Rispens and co-workers showed that the real-world gait pattern differs significantly in real life compared with on a treadmill [17]. Preliminary results suggest that those real-life approaches have the potential to fundamentally change clinical trials across different indications.

Newer technologies for the assessment of mobility, or the loss thereof, have advanced over the past few decades. These digital trackers and wearables allow for continuous mobility endpoint detection via remote or telemetric sensors. Moon *et al.* used a novel wireless skin-mounted sensor to examine gait characteristics in patients with MS under controlled conditions. Step number and temporal gait parameters were recorded and compared with those of healthy controls. The authors showed a high accuracy and a difference compared with controls that also enabled them to discern different disease states [18]. Mobility pattern can also be combined with machine-learning applications to characterize individuals based on their age and health status. In a recent study, machine-learning algorithms could classify younger and older adults with high accuracy. 'Fallers' of the older adults could be also identified, which resulted overall in better predictions compared with traditional methods [19]. In addition, mobility assessment through the use of smartphone apps can be used to track mobility patterns: Bondaronek and co-workers reported that there are over 400 apps available with various different functions, such as mobility tracking, and collection of data, education, and remote monitoring of patients are also feasible [20]. Merilathi *et al.* also demonstrated an association of daily mobility with a patient's well-being and functional status using a smartphone app [21]. Cheong *et al.* used a mobile health app in combination with wearable devices to assess the association of improved physical performance of patients with cancer with patient-reported outcomes and nutritional status [22]. However, the sole application of activity parameters in an observational study does not provide the necessary information for its use a

digital biomarker in a regulatory sense. Instead, this could serve as the starting point for its later validation in a randomized controlled interventional study against accepted traditional endpoints (e.g., activity trackers versus 6-min walking distance). For example, in a recent study, Wang and co-workers compared frequently used wrist-worn heart rate monitors to standard electrocardiography under exercise. The results showed variable accuracy [23].

In the end, it will be necessary to provide sufficient evidence that an improvement in a 'digital' endpoint (e.g., gait speed) translates into improved quality of life by showing increased social interaction. For cross-validation, credit card use could be measured to validate geographical location and social activities. Furthermore, there is no uniform guideline on how to record, sort, analyze, or report data gathered using activity endpoints. Traditional clinical storage tools used to collect and process data in clinical studies in the past might easily be overwhelmed by new digital data sources (e.g., with high sampling rates). Furthermore, data security and privacy need to be addressed, with regulatory uncertainty remaining. Moreover, clinical studies using digital technologies and digital endpoints can only become successful and sustainable when taking individual needs and preferences of patients into consideration. Current studies mainly focus on new innovative devices and neglect the problem that users of apps and wearables can quickly lose motivation to use them [24].

If digital assessments are to impact drug development, it will be necessary to convince health authorities that these digital assessments are sufficiently robust and accurate to reflect medically important endpoints that regulators can respond to. Also, one may need to convince health authorities that data cannot be easily manipulated. Activity monitoring is the most advanced use case for digital assessment in the 'real world'. At the same time, aspects of physical activity, especially gait speed, are known to be strong predictors of clinical outcomes, such as falls, hospitalization rates, disability, and death [9,15].

Pioneering work of the MOBILISED-D consortium

To address the current gap between consumer use of activity monitors and regulatory requirements, a group of pharmaceutical and technology companies recently sponsored an Innovative Medicines Initiative (IMI) program called MOBILISED-D in the EU [25]. MOBILISED-D is designed to establish a robust, device-agnostic, publically available algorithm to detect RWS and test its predictive power for endpoints of regulatory interest in three populations of frail or chronically ill patients. If successful, this effort will result in regulatory recognition of digital mobility assessment as a key secondary or primary endpoint for clinical trials, which would enable both digital assessment and drug development to progress.

In general, studies with digital technology might also show higher recruitment rates if they require less travel or shorter treatment duration and, therefore, more data points could be evaluated [26]. Currently, most digital endpoints refer to activity and mobility, but this might only represent the beginning. Given that medical device and technology companies offer a range of digital devices, the potential of digital endpoints is limitless and could someday include implantable biosensors that can sense blood glucose or digital imaging biomarkers [27]. The success of Apple's HealthKit has already shown that there is both a need and a market to support digital clinical research, especially in connection with the Internet of Medical Things (IoMT) connectivity [26]. The IoMT is defined as wireless devices connected to each other via the internet to improve healthcare delivery [28]. It is estimated that, by 2020, there will be 50 billion connected devices on the globe, of which 40% would be found in the IoMT space, which means an average of two to three connected medical devices per person worldwide [28,29].

Digital endpoints are not limited to clincal development

Going forward, the use of digital endpoints is not limited to clinical studies. Whereas it was not previously possible to measure clinical outcomes continuously and assessments were instead done by retrospective analysis of large clinical studies, this setting is changing through the advent of the IoMT. Now, outcomes can be measured on an individual level continuously in real-time together with a new medical intervention before (i.e., in clinical studies as outlined above) or after its market launch. Thus, in the frame of value-based care, which according to Michael Porter defines value as outcome divided by costs of an healthcare intervention [30], future drug effects might be 'monitored' through IoMT applications that measure their activity, efficacy, and safety. The pharmaceutical industry may find itself among other non-pharma competitors that may now be able to show increased physical activity resulting from the intervention as proof its value. Therefore, it might become a competitive advantage to include digital parameters such as activity endpoints already now in development projects.

Concluding remarks

As the IoMT and, along with it, the possibilities to capture digital endpoints emerge, a new world of medical data interpretation, management, and collection will open to the pharmaceutical industry. Activity tracking and its application in clinical studies is only the beginning. In addition, the potential of these technologies is far from being fully exploited by the pharma industry and, therefore, initiatives such as MOBILISED-D have a major role in the transformation of the pharmaceutical industry. As soon as initiatives such as MOBILISED-D become successful in translating encouraging results from research to regulatory acceptance and technical feasibility for clinical studies, these endpoints will become cornerstones in drug development. Given the traction that MOBILISED-D is currently receiving, we consider that that this will happen sooner rather than later.

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