Experimental Drug Development Centre

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Will Digital Endpoints Become a Cornerstone for Future Drug Development?

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Passion Made Possible

Setting the Frame

- **Pharmaceutical innovation needs to become more patient centric**, and digital applications are set to revolutionize clinical research, delivering a wealth of individual patient data

- The former FDA commissioner sees a **role of wearables** to better understand a patient's well-being and needs*

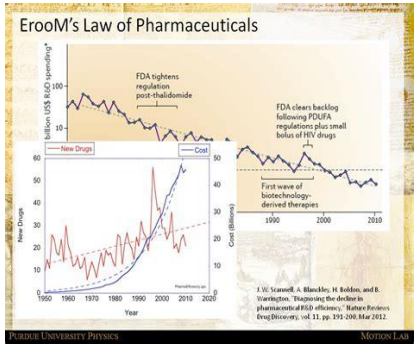
- Typically, endpoints accepted by the FDA include how a **patient feels or functions** and/ or if they live longer

- **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

* FDA (2018) Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's Efforts to Enhance the Patient Perspective and Experience in Drug Development and Review. FDA

Setting the Frame

- The approvals granted based on surrogate medical evidence are often subject to **post-approval Phase 4 studies** to confirm and/or strengthen the evidence
- **Health technology assessment (HTA) agencies increasingly** want to evaluate evidence regarding clinical and cost effectiveness, safety, and overall patient benefit of the pharmaceutical intervention
- 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*
- This phenomenon is known **'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**

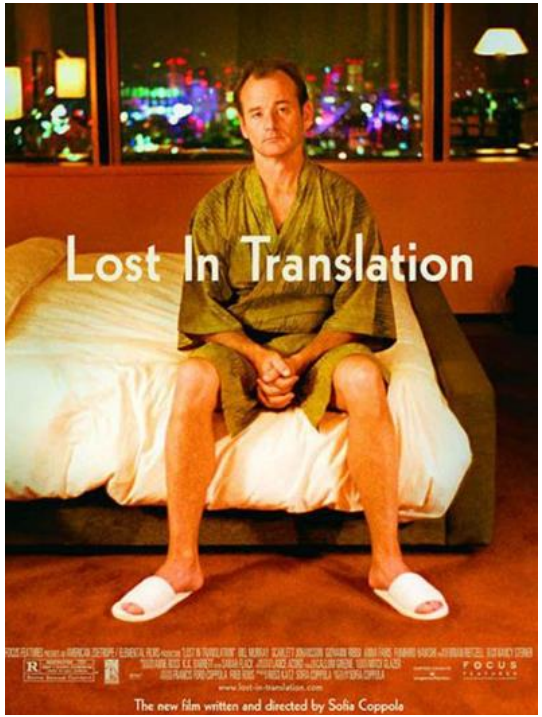


* Mullard, A. (2016) R&D returns continue to fall. Nat. Rev. Drug Discov. 16, 9 5

** Scannell, J.W. et al. (2012) Diagnosing the decline in pharmaceutical R&D efficiency. Nat. Rev. Drug Discov. 11, 191–200

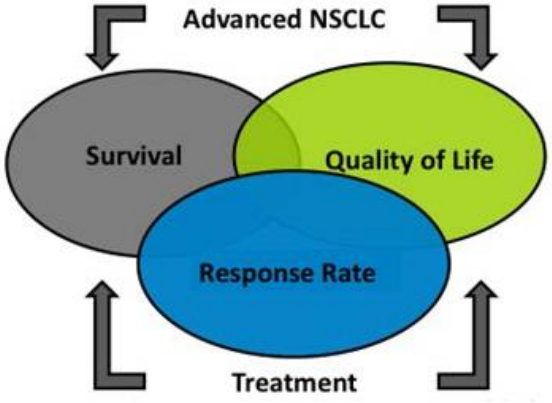
Setting the Frame

- A question that needs to be asked then is **whether preclinical scenarios are disconnected from real clinical outcomes**:
  - If yes, then **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 poorly reflecting patient burden

- In general, clinical endpoints, such as mortality, only reflect **one aspect of a patients disease burden**
- A disease may significantly limit the patient's **quality of life**
- Current clinical study designs, where only intermittent evaluations occur, only allow for **snapshot assessments of enrolled patients**, with long periods during which important data points are routinely not collected

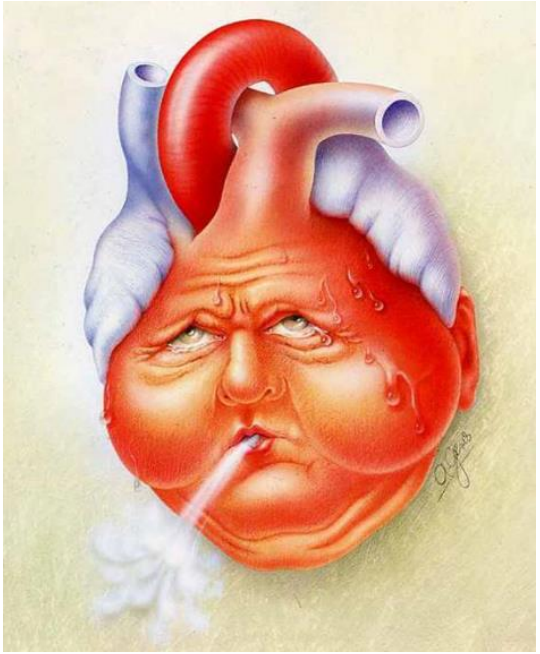


Clinical endpoints poorly reflecting patient burden

- A good example is heart failure with a preserved ejection fraction (HFpEF), which has a **significant disease burden with a reduced quality of life but a low rate of events** (e.g., mortality) that lend themselves for regulatory approval

- However, **drug development 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



Digital endpoints as new armamentarium for clinical development reflecting patient burden

- A view that is gaining 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

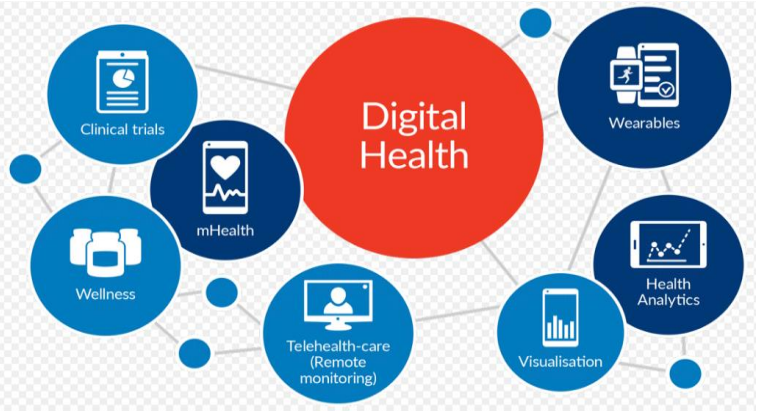
- Recently, the Prescription Drug User Fee Act (PDUFA VI) was implemented in the US. FDA is now required to consider the **‘patient’s experience’** to be an integral part of the **benefit versus risk of new drugs** to facilitate successful product development

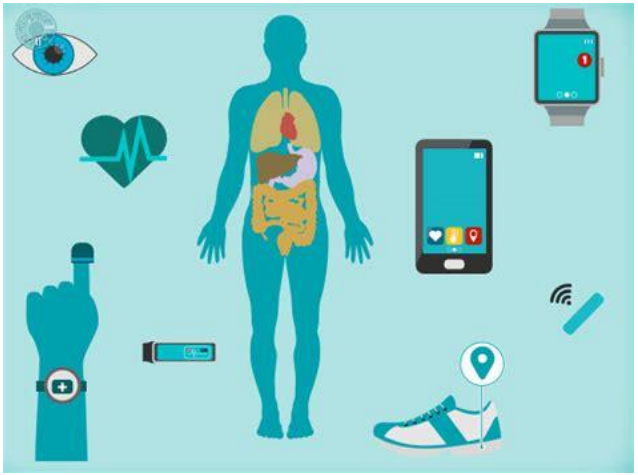
Digital endpoints as new armamentarium for clinical development reflecting patient burden

- To measure these patient benefits, new methods, including **wearable devices, medical applications (apps),** and even **machine-learning programmes**, will be needed

- Tools for capturing the **patient's experience**, be they quantitative or qualitative, **can transform many aspects of therapeutics development**

- Although a clinical assessment can currently be supplemented by several digital phenotypes, one **key integrating concept is physical activity**





Digital endpoints as new armamentarium for clinical development reflecting patient burden

- **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., COPD), heart (e. g., heart failure) or neurological and/or neurodegenerative [e.g., multiple sclerosis (MS)] diseases

- 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 recognised regulatory endpoint

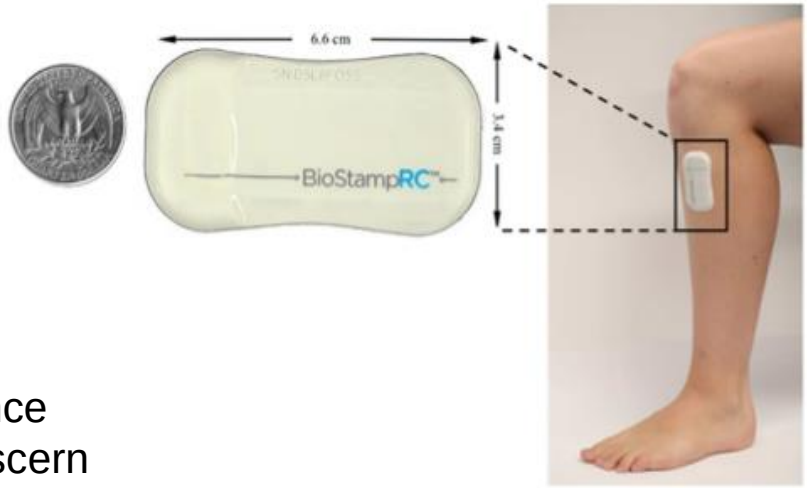
Digital endpoints as new armamentarium for clinical development reflecting patient burden

- Studies that currently assess activity and mobility as primary endpoints often use **patient's self-reported outcomes or performance testing** (e.g., 6-min walking distance), both of which have **significant short-comings** and vary among different classes of disease and clinical setting.
- **Emerging digital technologies can now measure many aspects of mobility in the 'real world**' on a continuous and long-term basis. Results suggest that those real-life approaches have the **potential to fundamentally change clinical trials** across different indications.

Digital endpoints as new armamentarium for clinical development reflecting patient burden

- **Digital trackers and wearables allow for continuous mobility end-point 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*

* Moon, Y. et al. (2017) Monitoring gait in multiple sclerosis with novel wearable motion sensors. PLoS One 12, e0171346

Digital endpoints as new armamentarium for clinical development reflecting patient burden

- Today there are **over 400 apps available** with various different functions, such as mobility tracking
- Collection of data, education, and remote monitoring of patients are also feasible with these apps*
- Merilathi et al. have demonstrated an **association of daily mobility with a patient's well-being and functional status** using a smartphone app**
- 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***

In Yae Cheong et al

* Bondaronek, P. et al. (2018) Quality of publicly available physical activity apps: review and content analysis. JMIR Mhealth Uhealth 6, e53

** Merilahti, J. and Korhonen, I. (2016) Association between continuous wearable activity monitoring and self-reported functioning in assisted living facility and nursing home residents. J. Frailty Aging 5, 225–232

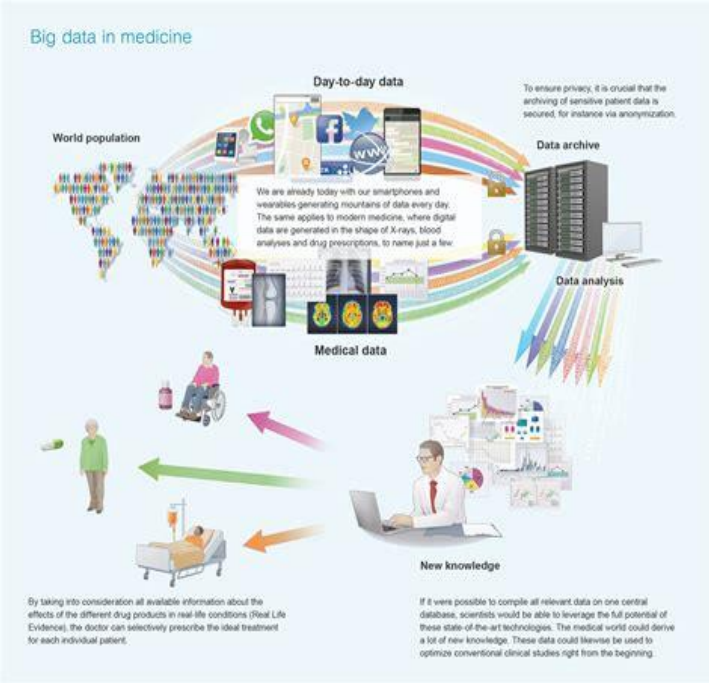
*** Cheong, I.Y. et al. (2018) Efficacy of mobile health care application and wearable device in improvement of physical performance in colorectal cancer patients undergoing chemotherapy. Clin. Colorectal Cancer 2, e353–e362

Potential of digital endpoints

- Studies with digital technology will likely **show higher recruitment rates** and **more data points** can be evaluated
- Currently, **most digital end points refer to activity and mobility**. Given that medical device and technology companies offer a range of digital devices, **the potential of digital endpoints is limitless** and could include implantable biosensors that can sense blood glucose or digital imaging biomarkers
- The success of **Apple's HealthKit** has 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 The IoMT is defined as wireless devices connected to each other via the internet to improve healthcare delivery
- 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 **2 to 3 connected medical devices per person worldwide**

Challenges to using digital endpoints

- 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
- **Data security and privacy** need to be addressed, with regulatory uncertainty remaining
- 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



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 i**n the EU
- MOBILISED-D is designed to **establish a robust, device-agnostic, publically available algorithm to detect RWS**
- 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

Digital endpoints are not limited to clinical development

- 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 in-stead done by retrospective analysis of large clinical studies, this setting is changing through the advent of the IoMT
- Outcomes can now be **measured on an individual level continuously in real-time** together with a new medical intervention before or after its market launch
- Thus, in the frame of **value-based care**, which defines value as outcome divided by costs of an healthcare intervention 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 will now be able to show **increased physical activity resulting from the intervention as proof its value**. It will become a competitive advantage to include digital parameters such as **activity end-points** in drug development projects

Conclusions

- 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

- Initiatives such as MOBILISED-D have a major role in the transformation of the pharmaceutical industry