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Conference Report

Illuminating the True Nature of Disease

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Digital Biomarkers: The Future's Key Data

Sensors are already heavily used in other industries. Where have they been used in clinical trials so far? The *Digital Biomarkers in Clinical Trials Summit* held on June 20, 2018, hosted at Roche's headquarter in Basel, Switzerland, did not only answer this question. In very enthusiastic talks and engaged panel discussions, the experts explored how digital biomarkers and wearable sensors will shape the clinical trials of the future and how this is done while serving the patient's needs first. In the following, you will find a few comments and observations on the core themes of the Summit.

The State of Digital Biomarkers Today

What are digital biomarkers? This is nicely illustrated by a far-advanced example of continuous patient monitoring which has been used by Roche in clinical trials since February 2015. The home-grown, mobile app-based, data capture workflow, incorporating active tests and passive monitoring, allows the remote monitoring of motor symptoms in patients with Parkinson's disease (PD) with greater sensitivity and frequency than ever before. The technology has the potential to detect signals that have not been visible previously to the clinician whilst also allowing to measure patient characteristics in-between visits at the doctor – characteristics that might have been lost previously.

So, what are the characteristics of digital biomarkers? As is the case with every emerging field, there are several working definitions. Some of them also came up at the Summit. Very short ones like: "Digital biomarkers are consumer-generated physiological and behavioral measures collected through connected tools." or: "The frequent and mobile measurement of clinically relevant signals using sensors to quantify and/or predict health-related outcomes and support diagnostic processes." Or a more poetic one by Mike Baker, Group Lead for Digital

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Health at Roche's Medical Affairs, who mentioned that digital biomarkers are "illuminating the true nature of disease." He based his opinion on the leveraging smartphone and sensor-based remote monitoring platform for patients with multiple sclerosis in the Floodlight program. In this case, digital biomarkers designed to detect the first signs of cognitive or motor impairment could even pave the way for more precise assessments of disease progression and inform treatment strategy. Another interesting opinion was "that data becomes a digital biomarker when a relationship is drawn to health-related outcome." The patients' phenotype is a product of both their environment and their genotype. And as it turned out, the prediction of an asthma attack is more likely done by measuring air pollution in the environment.

The most comprehensive definition is certainly this one: "Digital biomarkers are defined as objective, quantifiable, physiological, and behavioral data that are collected and measured by means of digital devices such as portables, wearables, implantations, or digestibles. The data collected is typically used to explain, influence, and/or predict health-related outcomes. Digital biomarkers also represent an opportunity to capture clinically meaningful objective data." [1]

Irrespective of their definition, "there are three pillars of digital biomarker analyses," said Christian Gossens, Global Area Head Digital Biomarkers at Roche's Pharmaceutical Research and Early Development, speaker, host, and one of the organizers of the event. These pillars are:

- Adherence – meaning that patients collect data regularly
- Agreement – meaning that sensor data correlate with today's clinical scales
- Augmentation – meaning that sensor data provide novel insights beyond clinical scales

Best Practices for Capturing Source Data for Digital Biomarkers

As Peter Groenen, Head of Translational Sciences, Idorsia, emphasized: "Disease is a process and not a state." So, the continuous monitoring with wearables really offers new opportunities to capture this process, especially in diseases characterized by fluctuations. However, as several examples at the Summit demonstrated, when it comes to data capturing, intensive preparation is necessary. Ideally, this preparation should involve the patient's voice and ensure that data capturing is extremely user-friendly and enabling medical insights. Furthermore, although it is always a challenge to find a balance between accuracy and convenience, the setup should be made in a way that:

- There is a remote monitoring system able to capture raw data accurately and conveniently.
- The sensors are in the right place on a patient.
- There is patient compliance, because they perceive the measurement as an asset rather than a burden.

Moving Data from the Capturing Source to Internal Data Analytics Systems via Pipelining

The validation of endpoints and more harmonized approaches are needed. This is both an opportunity and a necessity to collaborate amongst the industry. So, the experts raised and discussed questions like: What is the right experimental setup for a specific clinical measurement? Which sensor should be used to translate the human phenotype into a digital signal? How should we store and handle digital biomarker information? How do we ensure

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patients' data privacy? How do we ensure that digital biomarker data will be F.A.I.R. (i.e., findable, accessible, interoperable, and reusable)? As technology is advancing quickly, how do we ensure we are using the correct tools? For instance – coming back to the example of clinical trials with PD patients – the scientific community is still exploring multiple approaches for using a smartphone's accelerometer and gyroscope to measure the mobility of patients and their gait (to assess motor control). Regarding the documentation, as Philippe Marc, Global Head, Integrated Data Sciences, Novartis, mentioned, exploratory solutions should also be very well-documented as they can turn out to be the permanent solution. Keeping in mind that "correlation is not causation," was the advice from another expert.

Best Practices on Analyzing Source Data for Digital Biomarkers

How long will it be until novel digitally derived endpoints become more standard for clinical trials? And what is needed for that? In short, what is needed is a convergence of the digital biomarker measures and features, a validation of the resulting endpoints, and a focus on measures that are meaningful to patients. When it comes to the details, questions that all players in the field are facing are: Should we really store all raw sensor data, given the very high numbers of data points collected with continuous monitoring? Will it be necessary to go back to the raw data for re-evaluations, because – as it has been mentioned several times – "correlation is not causation"? How do we ensure that we look at what the data tell us and do not fit the data to the disease?

Current Landscape of Opportunities and Regulatory Hurdles to Overcome for Digital Biomarkers

When can we expect the broader use of digital biomarkers in clinical trials? Gergely Vértes, Solution Accelerator Lead – Wearables for Epilepsy, UCB, is convinced that "70% of clinical trials will use wearables by 2025." Even stronger is the opinion of Medidata experts: "Clinical trials that do not use digital biomarkers are not likely to exist in 2025."

Going back to the question above: How long will it be until novel digitally derived endpoints become more standard for clinical trials? When asking experts from pharma companies, their first estimation is that it could take additional 10 years until digital biomarkers are accepted endpoints because of the necessary validations and because it is always difficult to change endpoints. However, given that the development in this area is so fast, they take into consideration that the timeline could be much shorter.

"The success of digital biomarkers will depend on building a strong community," said Christian Gossens in summing up his talk. First steps towards these communities have been taken. There is the Transcelerate – Patient Technology workstream, which aims at enabling and accelerating the uptake of patient technologies in clinical trials. "One of the objectives of the Patient Technology workstream is looking specifically at novel digital endpoints and aims to build upon the work of the Clinical Trials Transformation Initiative (CTTI) to the benefit of regulatory engagement and to facilitate collaboration across the industry," John Batchelor reported, a Senior Outcomes Measurement Scientist at Roche.

Last year, the CTTI published recommendations for developing novel endpoints generated by mobile technology for use in clinical trials.

Emilio Merlo Pich, Head of Digital Medicine, CNS, Takeda, and Christian Gossens reported on the cross-industry efforts together with the Critical Path Institute. There is currently a digital biomarker focus being built up for PD, and they invited other Summit attendees to join.

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At the Summit, it became very clear, the sooner we have these digitally derived endpoints, the better for clinical trials, which will benefit from more reliable and faster outcomes. Especially, the delivery of time-stamped information based on more objective measurements reveal patient characteristics that have not been detected with the episodic, and sometimes highly variable, subjective evaluations of raters. As Eddy Foster, a participant working at Roche's Biometrics Department, put it into words after the Summit: "This new class of data will become a key part of not only evidence generation for our trials, but I could also imagine a future where it is a key part of therapeutics in the clinic."

In a nutshell, at this *Digital Biomarkers in Clinical Trials Summit* organized by Christian Gossens (Global Area Head Digital Biomarkers at Roche's Pharmaceutical Research and Early Development), Alain Bindels (Director of Roche's Digital Innovation Lab), Doug Lavender (CEO and CoFounder of PanAgora Pharma), and Laurenz Baltzer (Managing Director at the Karger Publishing Group), the most burning questions in this area were addressed and discussed. The case studies provided interesting new insights into a rapidly evolving area. The Summit paved the way for precompetitive collaborations and some immediate actions.

Disclosure Statement

The author is currently an employee of F. Hoffmann-La Roche Ltd. and declares no further potential conflicts of interest.

Reference

1 https://www.volarhealth.com/digital-biomarkers/