

Challenges in Validating Digital Biomarkers from an Academic Perspective

ACT EU multi-stakeholder methodology workshop

23rd November, Amsterdam

Martin Daumer

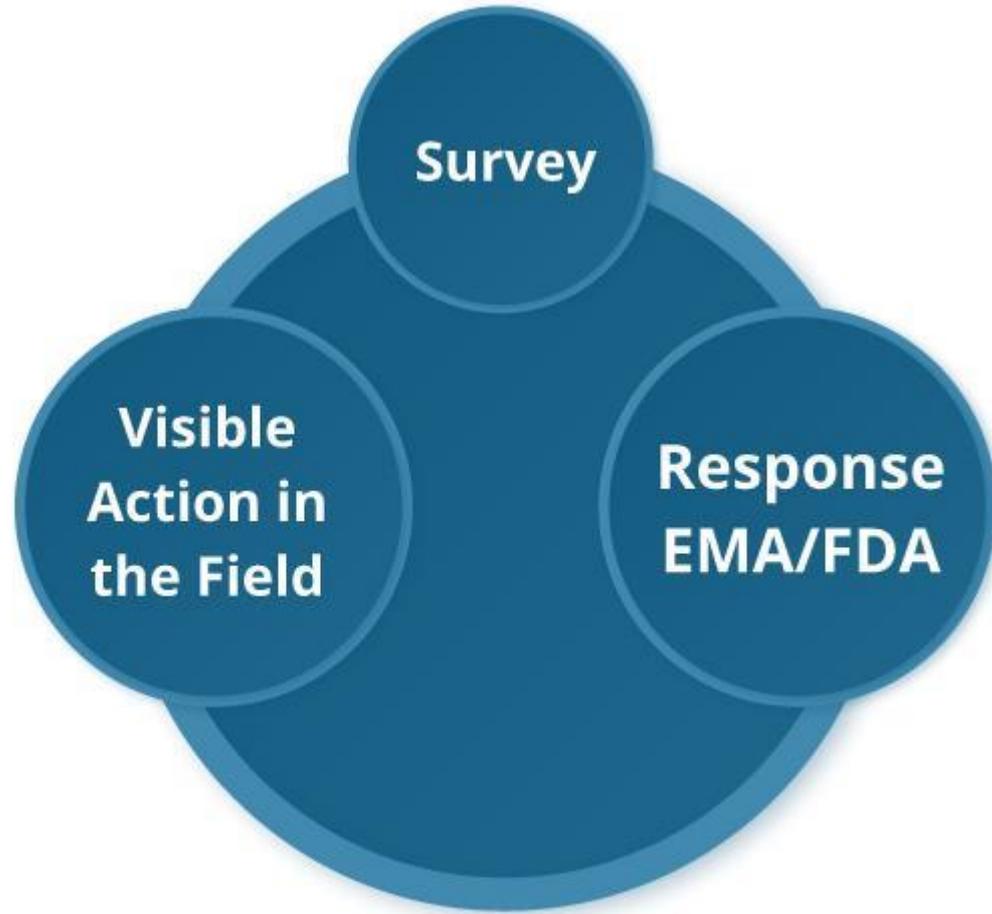
Director, Sylvia Lawry Centre for Multiple Sclerosis Research e.V. -

The Human Motion Institute

TUM Professor for Computational Medicine,

TUM School of Computation, Information and Technology





How do you rate the importance of the following typical barriers for using digital biomarkers as outcome in clinical trials?

Top 2:

Regulatory approval and validation (lack of established standards)
> 79% very high or high

Endpoint Validation (establishing clinical relevance, endpoint variability)
>76% very high or high

EMA logo and text: EUROPEAN MEDICINES AGENCY

26 July 2022
EMEA/CHMP/121713
Information for Medicinal Products for Human Use (MPL)

Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies

Draft agreed by Scientific Working Party (SWP)	01 September 2022
Adopted by CHMP for issuance for consultation	02 September 2022 ¹
Start of public consultation	29 February 2023 ²
End of consultation (deadline for comments)	09 April 2023
Issued by CHMP	20 July 2023

Keywords Qualification of Novel Technologies, Customer Muscular Dystrophy studies, Digital Health Technology, efficacy endpoints, wearable sensor

¹ Last day of written consultation meeting.
² Date of publication in the EMA website.

EMA website: www.ema.europa.eu/en | EMA contact information & procedures

EMA logo and address: European Medicines Agency, L-1511 Luxembourg

EMA website: www.ema.europa.eu/en | EMA contact information & procedures

EMA website: www.ema.europa.eu/en | EMA contact information & procedures

Survey

Regulatory Acceptance of Digital Biomarker Survey: perception of the field

This survey - based on Google Forms - is a cooperative effort of the University of Oxford - MDUK Oxford, Neuromuscular Center, Department of Pediatrics, the TUM - School of Computation, Information and Technology, the Friedrich-Baur-Institute, Neurologische Klinik und Poliklinik, LMU Munich, Else Kröner Fresenius Center for Digital Health, Technische Universität Dresden, The Critical Path Institute and the SLC e.V. - The Human Motion Institute, Munich. The aim is to get a snapshot of the perception in the field of the status and the expectations about the development of the field of digital biomarkers, with a particular focus on the path toward regulatory acceptance of novel endpoints based on data from wearables in clinical trials. A milestone in the field is the positive qualification opinion of the CHMP, July 20 2023 "[Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies](#)". It is planned to make the results publicly available at conferences and peer-reviewed journals. We hope to contribute to be able to inform the field about perceived importance and barriers. Overcoming these barriers requires collaboration among researchers, clinicians, regulatory agencies, technology companies, and patients. As the field of digital biomarkers continues to evolve, addressing these challenges will be essential to harness the full potential of remote monitoring and real-world data in clinical research.

We assume that by filling in the survey, you give your consent. The survey is anonymous. Thank you for your support, the organizers. Martin Daumer and Benedikt Schoser

34 respondents (9.10-30.10.2023)
58% Uni, 21% pharma, 21% other

85% Prof or PhD/MD

Overall, how important is the usage of digital biomarkers as outcome measure in phase 3 clinical trials - trials aiming at the approval of medicines in the future?
> 91% very important or important

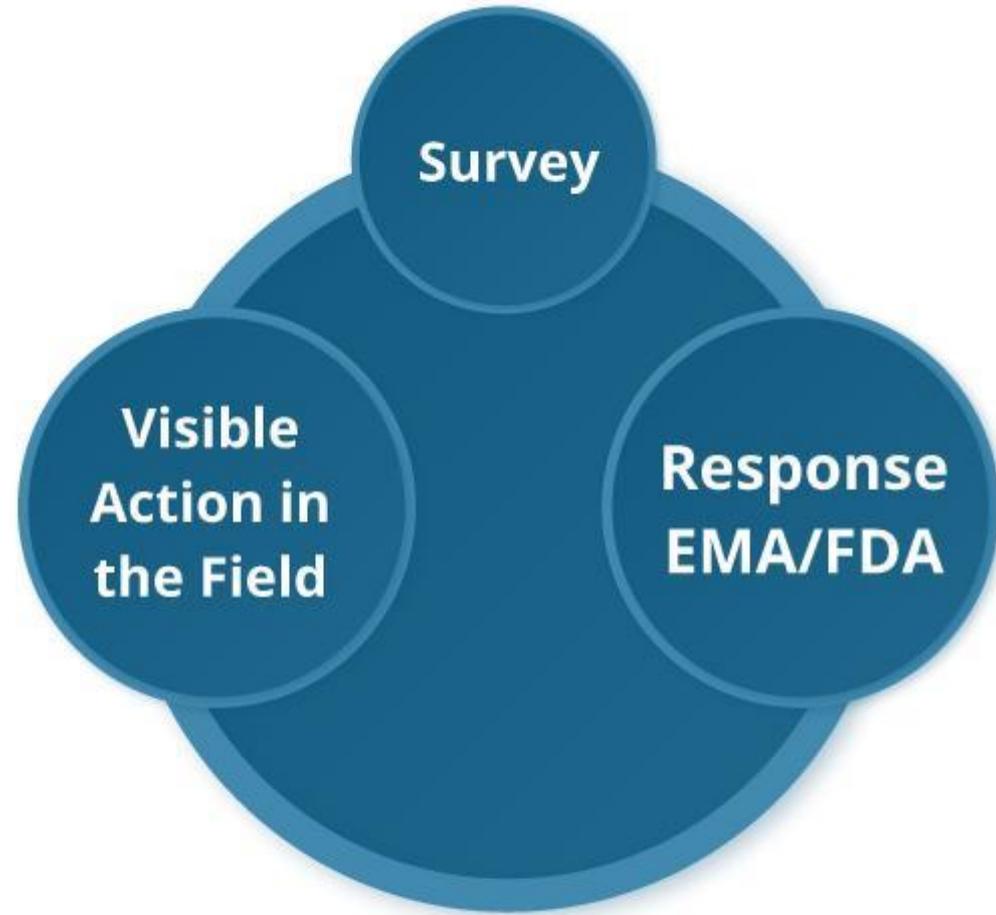
How promising is the concept of the digital biomarker "real world walking speed" as outcome measure in phase 3 clinical trials for diseases other than Duchenne muscular dystrophy?
>79% very important or important

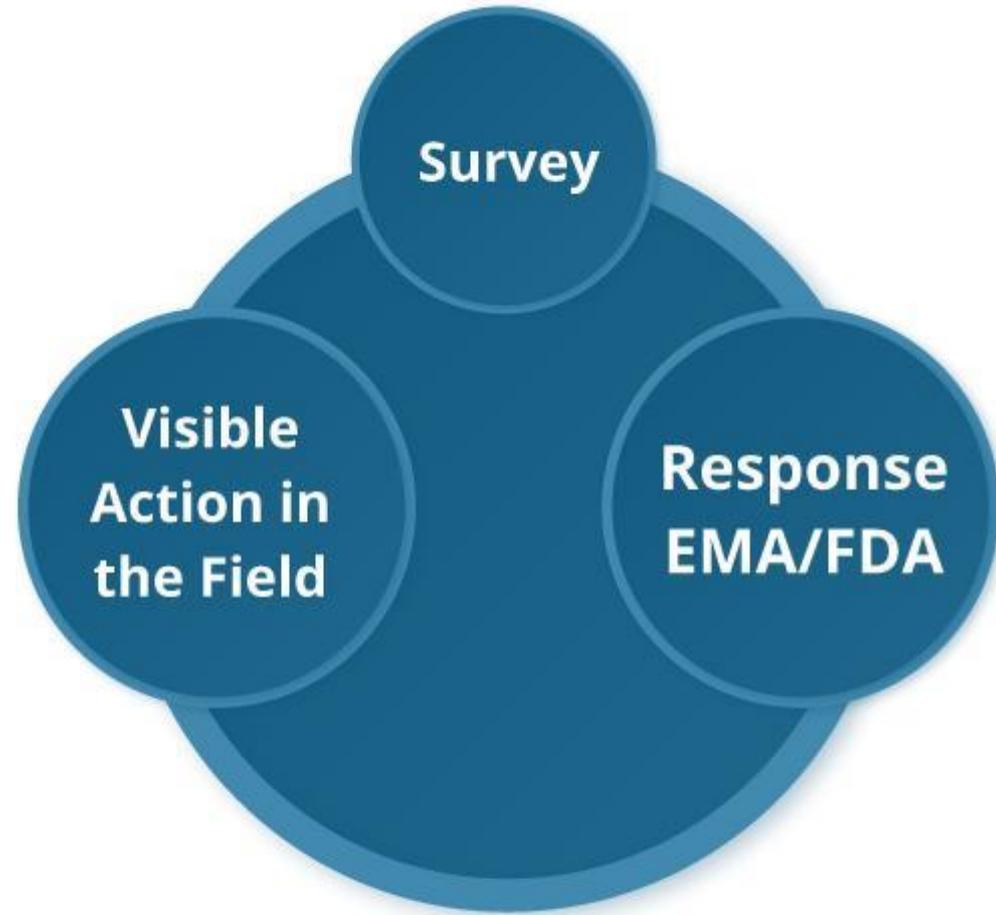
scale from 1 negligible to 5 very important

It has been discussed for MS studies. However, I'm not aware that it has been implemented.

As per relevant EMA and FDA guidance, collaborative groups such as consortia and industry trade associations are encouraged to initiate qualification of new measures as endpoints. This is mainly due to the efforts and amount of data needed for a successful qualification. Accordingly, activities as led by the IMI consortia are ongoing to qualify mobility outcome in different indications, e.g. COPD, HF, and MS (e.g. IMI consortium Mobilise-D).

Yes, this is the work done by the Mobilise-D consortium





Letter of support for Mobiize-D digital mobility outcomes as monitoring biomarkers

On 26 October 2019 the Applicant, Mobilize, S.L., on behalf of the EMA consortium Member 1, requested qualification advice for Digital Mobility Outcomes (DMOs). This letter constitutes part of the Mobilize-D user access to a patient-centric DMOs (User Access to Mobile Health, wearable devices and associated algorithms) as biomarkers for clinical benefit (U.S. as a surrogate, primary or key secondary endpoint) to predict clinical trials for treatment of disease or health conditions that impact motor mobility. An incremental approach is being taken, with qualification of monitoring biomarkers in Parkinson's Disease (PD), as the first stage.

During its meeting held on 09 - 12 March 2020, the SAMP agreed on the advice to be given to the Applicant. During its meeting held on 21 - 26 March 2020, the CHMP adopted the advice to be given to the Applicant.

Mobiize-D is a consortium led and run under the Innovative Medicines Initiative (IMI) (https://www.imi.europa.org/). The consortium consists of a multidisciplinary combination of international research partners of leading universities and pharmaceutical / medical companies.

The overall purpose of this application is to obtain qualification advice on the steps required for the biomarker derived from suitable mobile wearable devices and their associated algorithms to be accepted as biomarkers of clinical benefit. It is, as a surrogate, primary or key secondary endpoint in clinical clinical trials for treatment of disease or health conditions, motor mobility is a core clinical outcome in the context of this request for qualification advice. The Mobiize-D consortium is pursuing an incremental approach to this end. The consortium seeks qualification advice on the use of DMOs as monitoring biomarkers of disease status (other observations with changes in the degree or extent of the disease) in patients affected by PD. In a subsequent submission the consortium plans to seek qualification advice on the use of DMOs as monitoring biomarkers of disease status in multiple diseases, including Parkinson's Disease (PD), Chronic Obstructive Pulmonary Disease (COPD), Heart Failure (HF), and outcomes of a Neuronal Network Failure (NNF).

The applicant intends to pursue regulatory qualification for a new methodology to quantify motor performance continuously over a week in real world settings, using a multi-sensor smartphone and associated algorithms that connect to various DMOs by wearing the new sensors connected to the device. The Consortium intends to use this measurement as an additional monitoring biomarker to quantify motor performance in assessing the efficacy of new treatments for Parkinson's Disease (PD) patients. This approach is complementary to their already in use, that assesses only the patient's perception of mobility (patient reported outcomes, PROs) and motor capacity (performance based outcomes, PBOs), such as gait and walk distance.

The applicant proposes that Digital Mobility Outcomes can be used as biomarkers in PD in addition to the outcome domains: Usual Gait Speed (m/s), Usual Gait Length (m), PDQ-39, Consortium 1 & 2 (U.S. as a surrogate), primary or key secondary endpoints of the patient's perception of mobility, and the PRO-PBOs. It provides a clinical report measure of motor capacity, change from baseline performance during the visit. The Mobiize-D DMOs can quantify in addition to PROs, performance measured continuously in the real-world, to demonstrate the validity of the DMOs, the applicant will evaluate their clinical

Public advice: Innovative Medicines Initiative 4 - Horizon Researcher & Patient Centred
Administrative and contact information: EMA/CHMP/018019
Public advice number: EMA/CHMP/018019/2020

validity, predictive capacity, and ability to detect change. The applicant intention is to qualify DMOs as secondary endpoints, complementary to the PRO-PBOs (1) and (2) in order to demonstrate the validity of the biomarker. The consortium plans to perform an objective technical validation, and a large scale observational clinical trial. The technical validation will verify the accuracy of the device and algorithm to measure a range of different DMOs. The change of the study is based on a mid-range approach, where state of the art human measurement analyses will be used to quantify the accuracy and precision of a multi-sensor wearable in a population, assumed to be of an order of magnitude more accurate than the wearable sensors. This validation is then used to quantify the accuracy and precision of the wearable sensors in real world conditions, on a small cohort of healthy volunteers with outcomes affected by PD. In a second stage, clinical validation will be obtained in an observational multicentre clinical trial involving a longitudinal 24 months cohort study with 6 monthly follow-up in patients chosen for each disease of interest, where disease progression is monitored from a clinician's and patient's perspective using the accepted gold standard in each disease. The Mobilize-D consortium also plans to use the Labelled Features & Quality Endpoints (LQFE) as a disease independent outcome of mobility disability, to validate the use of DMO's across all the target diseases. At least six month assessment each patient will be asked to wear the device continuously for seven days. The use of DMOs in the device will be validated through a sensor digital information, and analysed with the Mobiize-D analytical algorithms, that calculate a number of metrics for each patient. The clinical and patient reported outcomes will be used to assess construct validity, predictive capacity, and ability to detect change for each DMO.

Summary of the Qualification Advice
The EMA supports the general objective of the Mobilize-D consortium to pursue the qualification of DMOs as biomarkers of motor performance in real world settings.

U.S. as a surrogate primary endpoint
It is agreed that digital measurement of motor capacity can be an end-to-end, treatment response, to complement other measures that quantify efficacy.
Digital quantification of mobility control, at this stage, to be considered a primary endpoint, as a full validation of a single biomarker is required.

Key functions of the system or apparatus evaluated here is to measure, with standardized quantification of real world mobility and respective digital mobility outcomes as a useful to complement existing functional tests and PROs to inform regulatory decisions in drug development.
The proposal to standardize real world data using continuous measurements of digital mobility is welcomed as a complement of other tests and PROs.

Technical Validation Approach
Mobiize-D approach to validation of DMOs will cover relative validity, construct validity, predictive capacity (the ability to predict clinically relevant outcomes) and ability to predict change (the ability to change in relative with clinically relevant changes in related concepts) or to change after clinically relevant events), in the initial validation study. The approach to the technical validation of the DMOs is acceptable.

Clinical validation in Parkinson's Disease
The Mobilize-D consortium hypothesizes that mobility biomarkers, measured over a week in real world conditions, is a further important dimension to evaluate mobility, in addition to patient's mobility perception and motor capacity.
To confirm this, the consortium plans to demonstrate construct validity of a Digital Mobility Outcome (DMO) obtained with the Mobiize-D measurement protocol by showing that they are a valid measure of the construct "mobility". They compare with related constructs, they identify differently sensitive disease groups of PD patients expected to have different motor performance, and do not correlate with PDQ-39 (that is a not correlated with mobility). Predictive capacity will also be tested against the PRO-PBOs. The ability to detect change will be evaluated by analyzing the longitudinal validity against change changes, calculating the minimal important difference (MID) using PRO-PBOs. U.S. as a surrogate and other outcomes relevant to patients or clinicians as primary, surrogate or secondary of the DMO will be tested in relation to interventions that are known to be effective.
EMA considers U.S. as a surrogate acceptable.



Qualification advice Actibet (Real World Making Behaviour)

On 22 December 2019 the Applicant Therun Analytics Online GmbH requested qualification advice for Change of G-protein mediated walking speed measured by a mobile accelerometer for seven consecutive days for use as primary endpoint to determine efficacy of a drug of cardiovascular in treated clinical trials primarily in the following indications: MI, high features, patients in Japan (EU/18/18 of Regulation (EU, EUC/18/18 of the European Parliament and of the Council).

Dr Susan Sheehan and Dr Jerin John were appointed as reviewers. The Qualification Team consisted of Dr Maria Hahmbach, Dr Andre Eder and Dr Maria Magalhães. The EMA Scientific Officer for the procedure was Dr Francisco Cordeiro. The procedure started during the SAMP meeting held on 09 - 12 March 2020. Qualification Team meetings took place during the SAMP meeting held on 09 - 20 March 2020.

At its meeting during SAMP meeting held on 09 - 12 March 2020, the SAMP agreed on the advice to be given to be addressed by the Applicant during its clinical meeting. The applicant's meeting with the Applicant took place on 08 April 2020.

During its meeting held on 23 - 26 July 2021, the SAMP agreed on the advice to be given to the Applicant.

During its meeting held on 21 - 23 July 2021, the CHMP adopted the advice to be given to the Applicant. This is presented in this letter.

The regulator given by the CHMP is based on the questions and supporting documentation submitted by the applicant, considered in the light of the current state of the art in the relevant scientific fields.

London, 26 July 2021



DDT COA #000106: Actibet® in Multiple Sclerosis

Request for Qualification Plan

Dr. Maria Damer
TEAM Professor for Computational Medicine
Director Verily-Lever-Ludwig Multiple Sclerosis Research e.V.
The Helmholtz Institute
Managing Director Therun Analytics Online GmbH
Helmholtzstr. 1,
8077 Munich
+49-89-28620320
info@tumorlab.de
damer@tumorlab.de

Dear Dr. Damer:
We have completed our review of the letter of intent (LOI) submission for DDT COA #000106 received on August 26, 2020.

DDT COA #000105: Actibet® in Sarcopenia

Request for Qualification Plan

Dr. Maria Damer
TEAM Professor for Computational Medicine
Director Verily-Ludwig Center for Multiple Sclerosis Research e.V.
The Helmholtz Institute
Managing Director Therun Analytics Online GmbH
Helmholtzstr. 1,
80777 Munich
+49-89-28620320
+49-1777692094
damer@tumorlab.de

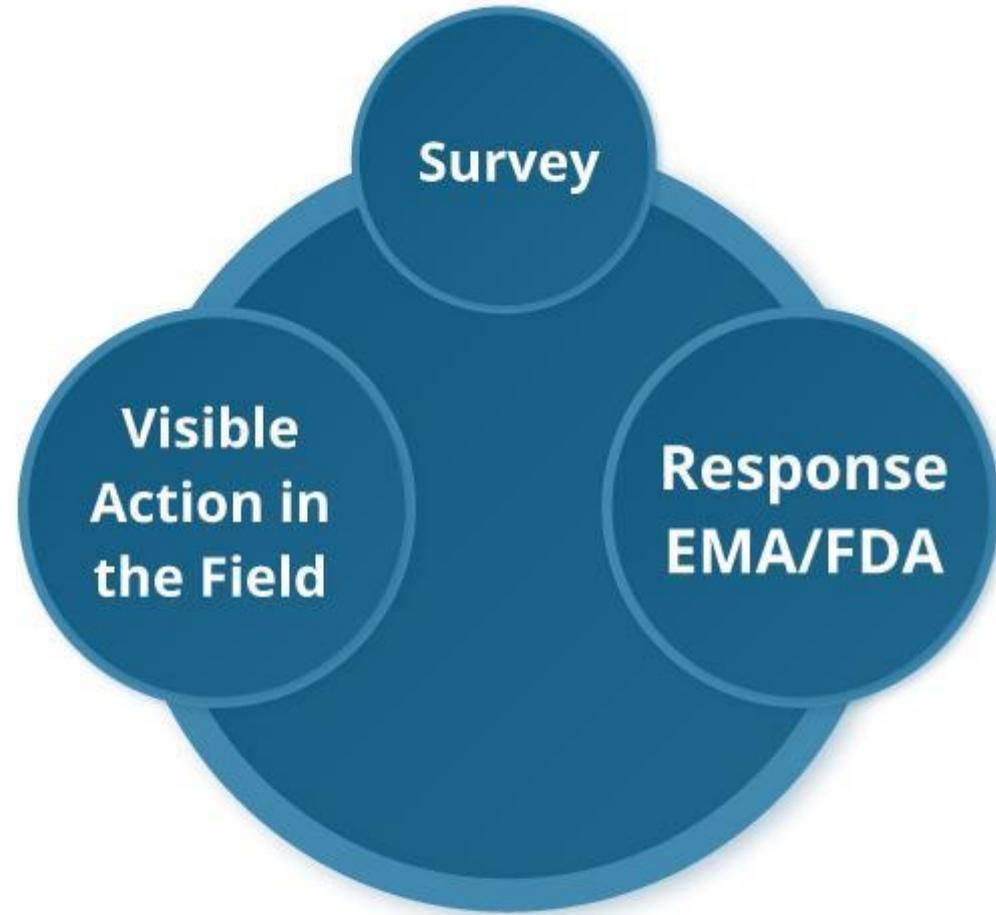
Dear Dr. Damer:
We have completed our review of the letter of intent (LOI) submission for DDT COA #000105 received on August 26, 2020.

DDT COA #000103: ActiMyo®

Clinical Outcome Assessments (COA) Qualification Submissions
Office of Neuroscience (ON)
Division of Hematology (DH)

Dr. Maria Damer
TEAM Professor for Computational Medicine
Director Verily-Ludwig Center for Multiple Sclerosis Research e.V.
The Helmholtz Institute
Managing Director Therun Analytics Online GmbH
Helmholtzstr. 1,
80777 Munich
+49-89-28620320
+49-1777692094
damer@tumorlab.de

Dear Dr. Damer:
We have completed our review of the letter of intent (LOI) submission for DDT COA #000103 received on August 26, 2020.



Challenges in Validating Digital Biomarkers from an Academic Perspective

ACT EU multi-stakeholder methodology workshop

23rd November, Amsterdam

Martin Daumer

Director, Sylvia Lawry Centre for Multiple Sclerosis Research e.V. -

The Human Motion Institute

TUM Professor for Computational Medicine,

TUM School of Computation, Information and Technology



Open Collaborative Platform for Digital Biomarkers

algorithms and raw data
disease agnostic
device agnostic

The International Federation of Multiple Sclerosis Societies is pleased to announce funding for an exciting new research initiative.

International Multiple Sclerosis Trials, Research and Resource Center (IMSTRARC)

All the leaders of our global research vision in the vital task of continually building momentum to develop new and more effective ways of monitoring MS and finding a cure.

The Federation is launching the International Multiple Sclerosis Trials, Research and Resource Center (IMSTRARC) which sophisticated statistical methods will be used to identify clinical and MRI predictors of the course of MS. The Center is being set up in an appropriate operational research and/or statistical institution. The aim is to develop alternative approaches to clinical trials which will reduce the necessity for placebo controls. The key resource will be a large database containing clinical and MRI data.

Expressions of interest should be submitted on no more than five A4 pages to include a brief outline of needs. The proposal document is available on request.

Please send submissions, quoting reference F20K, to: Prof. Ian McQuinn, International Federation of MS Societies, 16 Haddon Street, London W18 7LL, UK. Email: ifmss@ifmss.org.uk. Tel: +44 (0)20 7558 9120.

Closing date: 21 May 2020

Journal Article

The Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMRC) - Clinical research Society for the 20th anniversary

Abstract: 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100%

Highlights

- 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%)
- 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%)
- 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%) | 100% (100%)

Abstract



Initial focus on human motion - walking speed? MS? Hip/ankle? 6MWT?

"acceleromics"



Save the date - 11th **Winter Symposium** of the Human Motion Project - Munich - March 26, 2024
"A philosophical garden for digital biomarkers"

Challenges in Validating Digital Biomarkers from an Academic Perspective

ACT EU multi-stakeholder methodology workshop

23rd November, Amsterdam

Martin Daumer

Director, Sylvia Lawry Centre for Multiple Sclerosis Research e.V. -

The Human Motion Institute

TUM Professor for Computational Medicine,

TUM School of Computation, Information and Technology

