Regulatory approval of digital outcome: Experience in Duchenne, and first step in MS

Margaux Poleur, Alexis Tricot, Damien Eggenspieler, Dimitri Lozeve, Alexandra Goodyear, Paul Strijbos, Laurent Servais

************
Laurent Servais, MD, PhD
laurent.servais@paediatrics.ox.ac.uk
Background

Clinical Gold Standard → New Biomarker Qualification

Major challenges of current state (1)

All measures performed in the hospital, it remains a single point assessment, and highly dependant on patient’s form and motivation

\[ \int_{B}^{A} E(\text{placebo}) \, dt \]

\[ \int_{B}^{A} E(\text{treat}) \, dt \]

\[ E(\text{placebo}) > E(\text{treat}) \]

\[ p(E(\text{placebo}) - E(\text{treat})) > 0.05 \]
Background

Clinical Gold Standard → New Biomarker Qualification

Major challenges of current state (3)

Patients with rare disease may travel a lot to access the research center
To evaluate patients with wearable devices is just the sense of History. The only question that remains is how long we need to understand that it is a much more robust solution than hospital-based assessments.

The Rapid Evolution of Digital Endpoints: Are We Headed in the Right Direction?

The number of unique digital endpoints being used in industry-sponsored trials of new medical products is skyrocketing, but is more always better?

Just over a year ago, we launched our crowdsourced library of digital endpoints, aiming to shine a light on digital measures being used in industry-sponsored trials and galvanize the field around specific measures to speed adoption. During our most recent update of the library, we were struck by the astronomical growth of digital endpoints over such a short time span.

Let the numbers speak for themselves:

- The number of unique digital endpoints increased from 34 to 166 in the last 14 months, and the number of sponsors actively collecting digital endpoints in clinical trials of their medical products has increased from 12 to 52.
So why are wearable devices not more used as primary outcome??

What can I do with that??

Clinical trial
I will offer you the moon.

Thank you. But I prefer a Holter of Movement.

What do you mean exactly?

Being able to identify all the movements of the patient.

And then to quantify them precisely.

In uncontrolled environment.

During 2 years, without shift over this time period.

Internet transmission and data security... Be compliant!!

Are you sure the moon is not enough?
The long and winding road of SV95C

Technical development timeline

2010
Prototype

2011
V2.0

2012
V3.0

2017
Clinical trial

2019
Medical device

2021

2022

Controlled environment —> unsupervised usage

Identification of the variables

Validation during NHS

What do we need??

Medical device

2017

Identification of
the variables

Validation
during NHS

What do we need??
DMD add on value

\[ n = \frac{2\sigma^2}{\Delta_L^2} (z_{1-\alpha} + z_{1-\beta})^2 \]

Risk \( \alpha \) = probability to wrongly conclude to treatment efficacy
\[ => \alpha : 5\% \quad Z= 1.96 \]
Risk \( \beta \) = probability to wrongly conclude to treatment inefficacy
\[ => \beta : 20\% \quad Z= 0.842 \]

\( \sigma \) = 80m (~20%)
\( \Delta_L \) = 30m (~7%)
\( \Delta_L = -8.5\% \)

6MWT \( n = 112 \)

ActiMyo \( n = 14 \)
Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

<table>
<thead>
<tr>
<th>Draft agreed by Scientific Advice Working Party</th>
<th>12 April 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adopted by CHMP for release for consultation</td>
<td>26 April 2018</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>21 September 2018</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 November 2018</td>
</tr>
<tr>
<td>Adopted by CHMP</td>
<td>26 April 2019</td>
</tr>
</tbody>
</table>

Keywords: Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

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

<table>
<thead>
<tr>
<th>Draft agreed by Scientific Advice Working Party (SAWP)</th>
<th>01 September 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adopted by CHMP for release for consultation</td>
<td>15 September 2022</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>28 February 2023</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>10 April 2023</td>
</tr>
</tbody>
</table>

Comments should be provided using this template. The completed comments form should be sent to ScientificAdvice@ema.europa.eu

Keywords: Qualification of Novel Methodology, Duchenne Muscular Dystrophy studies, Digital Health Technology, efficacy endpoint, wearable sensor
Extension to other diseases... ALS

The SV95C is a very robust outcome, because it relies less on motivation & patient environment.
Extension to other diseases... ALS

With the SV95C, we need 20 times less ALS patients to power a clinical trial compared to traditional gold standard.
ActiMS: one project, two study protocols

Controlled environment

Aim: *Analytical* validity

- Validate stride algorithms in this context of use & patient population:
  - **Stride detection** is specific & selective
  - **Stride reconstruction** is precise & accurate
- Elaborate additional capabilities:
  - suitable algorithms for specific MS clinical manifestations (ataxia, spasiticity, asymmetry).

Non-controlled environment

Aim: Feasibility to assess MS real life function & early sign of endpoint *clinical validity*

- Evaluation of non specific measures (95SVC, walking perimeter):
  - Concurrent validity
  - Robustness
  - Measure sensitivity to change
- Establishing disease agnostics measure (eg spasiticity, ataxia, etc. in real-life)
  - 1st results
Gait lab (Motion capture set up: 12 cameras, various heights and orientations, total recording space = 7 × 3 m)
exercises:
- Comfortable 120m walk
- 120m walk with double task (listing unique animals names)
- Fastest 25ft walk (performed twice)
- 3 * 180° turns while walking at a normal pace
- 7m fast walk, 3m normal walk, 7m run
Results

Over 99% of strides identified using the Motion Capture were accurately detected by the IMU device (99% recall), and measured with a centimetric precision (< 3% error on the stride length). There was no significant impact of the level of disability on the error.
EDSS 5.5

EDSS 2

Stride lateral deviation

Stride length

Final swing relative speed = \frac{|V_{\text{final}}|}{|V_{\text{exp}}|}

Stance duration percentage = \frac{\text{Stance duration}}{\text{Stride duration}}
ACTIMS: non-controlled environment
Compliance

On 49 recording period, 45 include enough data for analysis: **91% compliance**

19 patients have completed so far the 1 year data
Analytical plan

1. Reliability
2. Validity
3. Longitudinal evolution
### 1. Reliability

<table>
<thead>
<tr>
<th>Metric</th>
<th>ICC</th>
<th>SEM</th>
<th>Avg</th>
</tr>
</thead>
<tbody>
<tr>
<td>nb_strides_per_hour</td>
<td>0.93</td>
<td>24</td>
<td>181</td>
</tr>
<tr>
<td>distance_per_hour</td>
<td>0.93</td>
<td>23</td>
<td>169</td>
</tr>
<tr>
<td>stride_velocity_95</td>
<td>0.99</td>
<td>0.03</td>
<td>1.44</td>
</tr>
<tr>
<td>stride_length_95</td>
<td>0.99</td>
<td>0.02</td>
<td>1.46</td>
</tr>
<tr>
<td>stance_percentage_median</td>
<td>0.97</td>
<td>0.66</td>
<td>64.4</td>
</tr>
<tr>
<td>stance_duration_median</td>
<td>0.97</td>
<td>0.03</td>
<td>0.76</td>
</tr>
<tr>
<td>walked_distance_90</td>
<td>0.78</td>
<td>13</td>
<td>50.9</td>
</tr>
<tr>
<td>swing_duration_median</td>
<td>0.93</td>
<td>0.01</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Internal reliability evaluation**

ICC : Intra-Class Correlation, computed on two periods formed by the two halves of the first recording period for each patient. Ability to auto-correlate.

SEM : standard error measurement, computed using standard deviation & ICC

→ All variables demonstrate a good stability, at the exception of walked distance (90th percentile). Results will be refined with other percentiles in clinical validation phase (e.g., ICC of median is higher)

→ Results include 2 outliers (patients 01-002 and 01-031) with relatively high variability. An analysis with clinicians is ongoing to understand how to interpret this data in the results
2. Discriminant Validity

Mann Whitney test

<table>
<thead>
<tr>
<th>Feature</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nb_strides_per_hour</td>
<td>0.016</td>
</tr>
<tr>
<td>distance_per_hour</td>
<td>1.6e-07</td>
</tr>
<tr>
<td>stride_velocity_95</td>
<td>2e-05</td>
</tr>
<tr>
<td>stride_velocity_coef</td>
<td>0.47</td>
</tr>
<tr>
<td>stride_length_95</td>
<td>0.00079</td>
</tr>
<tr>
<td>walked_distance_90</td>
<td>1.1e-07</td>
</tr>
<tr>
<td>stance_percentage_median</td>
<td>-</td>
</tr>
<tr>
<td>stance_duration_median</td>
<td>-</td>
</tr>
<tr>
<td>swing_duration_median</td>
<td>-</td>
</tr>
</tbody>
</table>

→ Differences between MS patients & controls are statistically significant
2. Convergent Validity

<table>
<thead>
<tr>
<th></th>
<th>Correlation coeff. (Spearman)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDSS</td>
</tr>
<tr>
<td>nb_strides_per_hour</td>
<td>-0.348</td>
</tr>
<tr>
<td>distance_per_hour</td>
<td>-0.493</td>
</tr>
<tr>
<td>stride_velocity_95</td>
<td>-0.474</td>
</tr>
<tr>
<td>stride_length_95</td>
<td>-0.510</td>
</tr>
<tr>
<td>stance_percentage_median</td>
<td>0.402</td>
</tr>
<tr>
<td>stance_duration_median</td>
<td>0.278</td>
</tr>
<tr>
<td>walked_distance_90</td>
<td>-0.536</td>
</tr>
<tr>
<td>swing_duration_median</td>
<td>-0.176</td>
</tr>
<tr>
<td>Benchmark – sv95c on DMD patients</td>
<td></td>
</tr>
</tbody>
</table>

p-value <0.01

Moderate but significant correlation observed between EDSS/T25FW and SV95C, SL95C & median stance duration
2. Convergent Validity

> Correlation of stride length with EDSS consistent with current literature

\[ R^2 = 0.41 \]

\[ R_s = 0.51 \]

Vienne-Jumeau and al., 2019

Meta analysis of 36 studies, 524 patients

Linear regression line
Correlation between digital and gold standard variable (*p<0.05, **p <0.01)
3. Sensitivity to change?

Yearly change of SV95C (%)

EDSS better by 0.5
EDSS Stable
EDSS worst by 1 point

SRM: 0.72

Progressing
Relapsing Remitting

SRM: 1.85
SRM: 0.23
1. Status update on ActiMS study

2. Preliminary results based on existing variables

3. Conclusion & Next steps
Next step

• Patients’ follow-up and longitudinal data collection
  • Study extension

• Analysis of the completed baseline and longitudinal data:
  • Algorithms development and validation
  • Identification of « best outcome ... or portfolio of outcome
The Liege CRMN Team

Olivier Schneider
Fabian dal Farra
Manon Huystincks
Margaux Poleur
Laura Buscemi
Manon Duclos
Laurane Mackels
Laurie Medard
Charline Dubois
Stephanie Delstanche
Aurore Daron