Stride Velocity 95th centile as a Secondary Endpoint in Duchenne Muscular Dystrophy Measured by a Valid and Suitable Wearable Device

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Laurent Servais Elektra Papadopoulos
Francesca Cerreta

Remote Digital Monitoring Workshop
February 18 – 19, 2020
SV95C Case Study session outline

- **Disease Background and Statement of Need (5 mins)**
  - Pat Furlong, Parent Project Muscular Dystrophy
    - Duchenne Muscular Dystrophy
    - Statement of need

- **SV95C measure development & submission (25 mins)**
  - Dr. Laurent Servais, Oxford University
    - Development: device selection, partnerships
    - Usage: Intended use/context of use
    - Validation: accuracy & validity, sensitivity to change

- **EMA perspective (10 mins)**
  - Francesca Cerreta, EMA
    - What happened in specific case that made it easy or hard to review
    - EMA pathway
    - Translation to general guidance/takeaways for submissions

- **Discussion (30 mins)**
  - Ieuan Clay (Evidation), Pat Furlong (PPMD), Laurent Servais (Univ. of Oxford), Francesca Cerreta (EMA), Michelle Campbell (FDA)
Flow of data from biology to decision

Each step needs evidence!

- Raw data
- Raw processing
- Processed data
- Final device processing
- Transmit Data
- Data security
- Data Analysis
- Data Interpretation
- Data Aggregation
- Evidentiary Criteria Evaluation
- FDA Qualification
- Tool use
- Data Storage
- Receive Data
- Biology (Biomarker or COA)

Data transfer can occur at any step

* Stakeholder input should be addressed as appropriate
The Importance of Digital Measures for Duchenne Muscular Dystrophy

Pat Furlong, CEO
Parent Project Muscular Dystrophy
...The disease is one of the most interesting, and at the same time most sad, of all those with which we have to deal:
Interesting on account of its peculiar features and mysterious nature;
Sad on account of our powerlessness to influence its course, except in a very slight degree, and on account of the conditions in which it occurs. It is a disease of early life and of early growth. Manifesting itself commonly at the transition from infancy to childhood, it develops with the child’s development, grows with his growth so that every increase in stature means an increase in weakness, and each year takes him a step further on the road to a helpless infirmity, and in most cases to an early and inevitable death.

Gowers gave his name to “Gowers' sign” (a sign of muscular weakness)
Duchenne Muscular Dystrophy Third Edition: A. Emery and F. Muntoni
Duchenne Muscular Dystrophy

79 EXONS
2.4 Million base pairs

Multi-system Disease:
• Skeletal Muscle
• Heart
• Bone
• Smooth Muscle
• Cognitive Function
• 100% Fatal

• 60-70% Deletions
• 10% Duplications
• 10-15% point mutations and other small changes
Schematic Natural History of Duchenne Muscular Dystrophy
(Adapted from Bushby and Connor Clin Investig (Lond). 2011; McDonald et al. Muscle & Nerve 2013)

Prior to treatment 1960’s

5 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

9 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

14 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

20 Years
- Death


5 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

9 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

14 Years
- Ventilation

20 Years
- Death

Contemporary: with Steroids and Improved Cardiac Management

5 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

9 Years
- Loss of Standing
- Loss of Ambulation
- Loss of Self Feeding

14 Years
- Ventilation

20 Years
- Death

3) Steroids affect disease progression in DMD over the entire course of the disease prolonging clinically meaningful functions (time to loss of milestones)
Duchenne is complex and expensive

Annual Care Visits/Labs/Evaluations

Duchenne Progression

Early Ambulatory
- AFO’s
- PT/OT
- Supplements
- Scooters
- C-PAP (OSA)
- (Casting)

Late Ambulatory
- AFOs
- Electric wheelchair
- Stander/standing features on wheelchair
- PT/OT
- Assisted cough
- (Scoliosis surgery)
- Cardiac medications
- Supplements
- Bed features
- Nighttime NIV
- Home modification

Early Non-Ambulatory
- AFOs
- Hand splints
- PT/OT
- Wheelchair w/features
- Daytime/nighttime NIV
- Cardiac medications
- Bed features
- Assisted cough
- (G-tube)
- PCA Paid Caregiver
- Modified vehicle/accessible transportation
- Home modifications
- Pain Management

Late Non-Ambulatory

Lifelong FDA Approved Therapies

- AFOs
- Manual chair
- Assisted cough
- PT/OT
- Assisted cough
- (Heel Cord surgery)
- Sleep Study
- Electric wheelchair
- PT/OT
- Assisted cough
- (Scoliosis surgery)
- Cardiac medications
- Supplements
- Bed features
- Nighttime NIV
Clinical trials in Duchenne
Heterogeneity in disease progression is a challenge for drug development in DMD
SV95C Measure Development and Submission

Prof. Laurent Servais
Oxford University
Major challenges of current state

All measures performed in the hospital, it remains a single point assessment, and highly dependent on patient’s form and motivation.
Patient training every Monday to enter the trial...
Short duration tests are deeply influenced by patients' reflexes, longer tests by motivation.

Patient performs the 6MWT...

... then flies away after
Patients with rare disease may travel a lot to access the research center
The long and winding road of SV95C

Technical development timeline

**Identification of the variables**

**Prototype**

2010

**2011**

**V2.0**

**2012**

**V3.0**

**Validation during NHS**

**Controlled environment to unsupervised usage**

**Medical device**

2017

**Clinical trial**

2019

**What do we need??**
Validating accuracy versus 6MWT

Distance measured with ActiMyo systematically longer than the reference by about 5%
Validating accuracy versus 6MWT
Variability in real-world monitoring
Variability measurements

Variability
Variability decreases with increasing length of monitoring

- Averaged variation stabilises at 3.3% after 180 hours (15 days) monitoring
- 15% variability currently “acceptable” for 6MWT
Why 95th Percentile Stride Velocity?

95th percentile (SV95C) is the top performance of patients at home. It is also the most sensitive value, with the lowest delta/SD.
SV95C distinguishes DMD patients from healthy age-matched controls

DMD and healthy controls correlated with 6MWT
... and correlates with established measures

<table>
<thead>
<tr>
<th>ActiMyo® Variables</th>
<th>6MWT</th>
<th>NSAA</th>
<th>4SC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ρ</td>
<td>r</td>
</tr>
<tr>
<td>50th Percentile (median) stride length (m)</td>
<td>45</td>
<td>0.552**</td>
<td>0.649**</td>
</tr>
<tr>
<td>95th Percentile stride length (m)</td>
<td>45</td>
<td>0.679**</td>
<td>0.772**</td>
</tr>
<tr>
<td>50th Percentile (median) stride velocity (m/s)</td>
<td>45</td>
<td>0.652**</td>
<td>0.758**</td>
</tr>
<tr>
<td>95th Percentile stride velocity (m/s)</td>
<td>45</td>
<td>0.542**</td>
<td>0.616**</td>
</tr>
<tr>
<td>Distance walked/hour</td>
<td>45</td>
<td>0.371*</td>
<td>0.436**</td>
</tr>
</tbody>
</table>
...and distinguishes DMD from healthy controls

Clear separation between healthy controls and DMD groups
Longitudinal trends in SV95C

>6yr and <450m in 6MWT
Mean decrease : -8.5%
SD : 7.9%
P-value : 0.00
N : 20
SV95C is sensitive to positive change

Patient starting steroid treatment
Minimally clinically important difference

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean</th>
<th>SD</th>
<th>Intra-correlation</th>
<th>MCID</th>
<th>Relative MCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>50th Percentile (median) stride length</td>
<td>0.825 m</td>
<td>0.087 m</td>
<td>0.957</td>
<td>0.0179 m</td>
<td>2.17%</td>
</tr>
<tr>
<td>95th Percentile stride length</td>
<td>1.101 m</td>
<td>0.129 m</td>
<td>0.951</td>
<td>0.0284 m</td>
<td>2.58%</td>
</tr>
<tr>
<td>50th Percentile (median) stride velocity</td>
<td>0.836 m/s</td>
<td>0.116 m/s</td>
<td>0.942</td>
<td>0.0278 m/s</td>
<td>3.33%</td>
</tr>
<tr>
<td>95th Percentile stride velocity</td>
<td>1.578 m/s</td>
<td>0.391 m/s</td>
<td>0.937</td>
<td>0.0985 m/s</td>
<td>6.24%</td>
</tr>
<tr>
<td>Distance walked/hour</td>
<td>162.6 m/h</td>
<td>87.9 m/h</td>
<td>0.839</td>
<td>35.3 m/h</td>
<td>21.7%</td>
</tr>
</tbody>
</table>
SV95C is not influenced by varying compliance

Absence of correlation between compliance and performance
The long and winding road of SV95C

Regulatory development timeline

2016
- June: Start work on application
- December: « we need your dossier to accompany the letter of intent… »

2017
- July: « I am pleased to inform you that the SAWP appointed the coordinators »...

2018
- November: First teleconference: ‘List of questions (2 months deadline)’
- February 21st: Invitation for March 1st
- April 12th: Draft agreed by SAWP

2019
- April 26th: Adopted by CHMP

2020
- May: Dossier application
- September 21st: Start of public consultation
- September 30th: End of consultation on the different points sent to EMA
- March 7th: Scientific Advice Working Party: 2.5 hours meeting

November 21st: Start of consultation
Regulatory feedback and considerations

- **An automatic measurement is very attractive but we need to know what it measures**
  - What are we qualifying, is it the device, a variable, which variable?
  - How does it work for the measurements at study time points, should it be worn for one month before the study start?
  - We need some data from interventional study to validate the study

- **The patient needs to be willing to walk in order for the ActiMyo to measure**
  - How do you ensure patients willingness? In clinical center, the motivation can be given by the clinician.
  - How can you say that the patient is not cheating at home
    - Can the device be used in the enrolment phase to detect this kind of effect?

- **We are in an age where technology can help and the more real-life the measurements, the better. The device can measure stride length and speed and other variables.**
  - How can the 6MWT be assessed with ActiMyo?
    - You need normative values and I am glad that you use drugs and steroids to create an effect but there can be many consequences of steroids.
    - How long steroids take to show an effect with 6MWT?
  - Can you investigate the gait, the balance, the strength, the fear of the patients? What else can you explain, what else can you measure with the device?
    - Have you considered using 3 sensors?

- **You have done a lot of work with normative data, sensitivity to change which we appreciate. But for qualification as a primary endpoint, we need interventional data**
  - You may not necessarily need a positive treatment if you have enough patients in a natural history for example.
  - You may not need to see positive effect, it could also be acceptable if you can measure a negative effect.
  - Is it intended as primary or secondary endpoint?

- **The ActiMyo device is interesting, are there competitor devices?**
CHMP qualification has been achieved thanks to the support of a broad community
EMA considerations on digital mobility monitoring

Acknowledgements and thanks: Jane Moseley, Spiros Vamvakas

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The presenter does not have any conflict of interests.

Presented by Francesca Cerreta
Scientific Advice, EMA European Medicines Agency
EMA qualification procedure

Voluntary, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

**Qualification advice**

On future protocols and methods for further development towards qualification
Evaluation of scientific rationale and on preliminary data
Confidential

100 days

**Qualification opinion**

On the acceptability of a specific use of the proposed method in an R&D context
Assessment of submitted data
Publicly available

130 days + 60 days public consultation
General considerations for digital mobility measures (1)

- **Continuous** measure: Minimises variability/event singularity (outliers?)
- Advantage over supervised test: can help distinguish between **performance** (what you can normally do) and **capacity** (what you can maximally do- but this may be more important in some contexts!)
- If properly validated might become a primary (**at present: secondary**)
- Data privacy and protection to be respected
- **Impact of device/internet access** in excluding part of the population
- **To be accompanied by a best practice**: guidance for implementation in clinical trials for optimum use (measuring time, whether in all environments, what training or support, whether feedback or monitoring, how will compliance be assessed.)
General considerations for digital mobility measures (2)

- Discuss **advantage over conventional** ambulation endpoints
- **Anchor** the digital measure to a clinically recognised instrument, discuss critically existing measure limitations, DT advantage
- Context of use and anchoring instrument will define **generalisability** to other conditions
- **COU fundamental**, may evolve during procedure
- Mobility or falls not **linked to progression** in all diseases.
- **Evolution of the device** throughout the validation studies.
- If device **agnostic**, justify
- **Patient** compliance and burden
- **Missing data** handling
Learnings from S95C procedure (from CHMP questions)

- Make detailed proposal for context of use
- How to adjust confounding covariates and the impact of extending duration of recording on 6MWT vs 180hrs SV95C
- Distribution of data recording, possible patterns (AM/PM/every day)
- Analysis of discrimination between more or less severe baseline groups, and discussion of clinical relevance of findings
- The longitudinal correlation of change between 6MWT and SV95C
- Best practice annexed
Learnings from S95C procedure (from procedure)

- Dedicated and responsive point of contact
- Well supported by scientific team: smoothing presubmission, scope finding, several rounds of questions
- Access to non-public data from other trials (were kept confidential)
- Supported a completely transparent opinion
- Patient involvement
- ...including in Best practice development
Flow of data from biology to decision

Each step needs evidence!

Data transfer can occur at any step

**Raw data**
- Biology (Biomarker or COA)

**In Device**
- Raw processing
  - Convert to readout
  - e.g. Heart rate or Blood O₂
- Processed data
- Final device processing
  - Packaging; or alerting
- Transmit Data
  - Data security
  - Data transfer can occur at any step

**From Device**
- Raw sensor data
- Convert to readout
- Data security

**Data Storage**
- Receive Data
  - Data transfer can occur at any step

**Data Analysis**
- Data Interpretation
- Data Aggregation

**To Analysis**
- Evidentiary Criteria Evaluation
- Data security
- Stakeholder input should be addressed as appropriate

* Stakeholder input should be addressed as appropriate
Back-up Slides
Discussion Panel Questions

• Involvement of stakeholders in the process: bringing patient needs into the drug development process

• Application beyond DMD: is SV relevant in other indications? What is the regulatory pathway for expanding usage of a novel accepted outcome?

• Importance of collecting longitudinal evidence early (e.g. as an ”at risk” exploratory outcome)

• Data flow from devices into outcomes. is it possible to separate an outcome from the device that captures it? Fit for purpose and required level of precision
Further Reading and References

https://www.fda.gov/media/119253/download
https://doi.org/10.1016/j.nmd.2019.06.003

eSource Qualification opinion:

Stride velocity 95 centile Qualification Opinion:

Guidance on qualification of novel methodologies:

Data privacy workshop:

"Big data "workshop:

Are novel, non-randomised analytic methods fit for decision-making?
How to prepare a successful DT qualification submission?

1) Have a **clear research question**. **Step-wise** qualification is possible (starting from proof of concept).

2) Identify **remit(s)**

3) Use EMA support: **pre-submission discussion** and guidance (SA, ITF, regulatory)

4) Understand that legal and regulatory frameworks will **apply also to DT**. Clarify how you will meet these: GCP, ISO, GDPR, ethics, clinical and statistical guidelines, documentation trail, sponsor compliance responsibilities.

5) Focus your questions on the uncertainty areas, **framing** the questions from the **perspective** of your interlocutor (EMA, HTA, NB) as there are grey areas.

EMA is willing to support multi stakeholder dialogue, but several pieces of the puzzle may have to be put together for a complete qualification picture.

**Contacting EMA in advance helps preparation**