Virtual Journal club

Digital Biomarkers

Quantifying the Benefits of Digital Biomarkers and Technology-Based Study Endpoints in Clinical Trials: Project Moneyball

Aug 3, 2022 11am ET
But first, housekeeping

- Please note today’s session is being recorded
- To ask a question for discussion during Q&A, please:
  - Either ‘raise your hand’ in the participant window and moderator will unmute you to ask your question live, or
  - Type your question into the chat box
- Slides and recording will be available after today’s session
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Aug 3, 2022 11am ET
Moneyball - our inspiration

Your goal shouldn’t be to buy technologies.

Your goal should be to buy clinical study successes.

In order to buy clinical study successes in terms of p-value,

you need to buy true responders.

There is an optimized study design we can afford.

Win with digital biomarkers

How digital technologies drive study success

- Increase proportion of true target patients in recruited cohort
- Detect therapeutic response more effectively

Improved study design with more true responders, leading to:
- Smaller sample size,
- Shorter monitoring period, or
- Smaller p-value

Clinical study results = f (Study sample size, Patient selection accuracy, Drug effect rate, Outcome measurement accuracy, Therapeutic response threshold, Outcome detection duration)
Roche – SYSNAV – University of Oxford Partnership
Cocreating novel wearable technology and functional dEPs

Prof Laurent Servais
Neuromuscular Centre, University of Oxford UK

Paul Strijbos
Collaboration & Strategy lead

Damien Eggenspieler
Healthcare lead

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ActiMyo® and Syde® wearable technology enables measurement of disease progression in the real world.

Commercialized by SYSNAV Navigation Technologies

- Magneto-inertial technology
- Validated and sophisticated fusion algorithms
- Class I MD, GDPR Compliant, QMS
- Measures movement continuously during daily living with high accuracy and precision
- Pediatric and adult use
- Optimized for clinical trial use

ActiMyo®/Syde® can be worn in different configurations (usually worn on the ankles).

The participant wears the sensors during waking hours. Sensor data are uploaded to a secure cloud environment every night.
Development of a new real-world endpoint: SV95C

SV95C is a digital measure of peak ambulation performance during normal daily living. It represents the minimum velocity of the 5% of the fastest strides taken by a wearer\(^1\)

- Differentiates healthy boys from boys with DMD
- Is sensitive to therapeutic intervention (steroids)
- SV95C MCID compares to that seen with NSAA, 6MWT
- Correlates with 6MWT, NSAA and 4SC
- In DMD, detects early decline in natural history or improvement due to the initiation of corticoid treatment
- SV95C precedes loss of performance in DMD with 6MWT

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Regulatory qualification of SV95C: An industry first

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>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft agreed by Scientific Advice Working Party</td>
<td>12 April 2018</td>
</tr>
<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>

2017 2018 2019 2020

COA, clinical outcome assessment; SV95C, stride velocity 95th centile.


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Regulatory qualification of SV95C
Final EMA opinion

“Stride velocity 95th centile (SV95C) measured at the ankle...”

...is an acceptable secondary endpoint in pivotal or exploratory drug therapeutic studies for regulatory purposes...

...when measured by a valid and suitable wearable device...

...to quantify a patient’s ambulation ability directly and reliably in a continuous manner in a home environment and as an indicator of maximal performance

- Quantifies baseline performance
- Monitors disease progression and treatment benefits
- Complementary to traditional endpoints in collecting efficacy evidence and potential to replace traditional endpoints

EMA, European Medicines Agency; SV95C, stride velocity 95th centile.
Dramatic impact of SV95C on study design and patient burden

Robust assessment of MCID ensures clinical studies are adequately powered to demonstrate meaningful change

<table>
<thead>
<tr>
<th>MCID</th>
<th>6MWT</th>
<th>SV95C</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-meter difference</td>
<td>0.1 m/s (~6.24% decline, 36-meter difference on 6MWT) (Studies ongoing to confirm validity)</td>
<td></td>
</tr>
<tr>
<td>Sample size required</td>
<td>&gt;100 patients per treatment arm</td>
<td>14 patients per treatment arm (DMD &gt; 7 years of age; 6MWT baseline &lt; 450m)</td>
</tr>
</tbody>
</table>

- **Improved sensitivity** and reliability of SV95C versus 6MWT
- The ability to conduct smaller, shorter clinical studies using SV95C confers a significant advantage in rare diseases (where there are fewer patients) over traditional endpoints

6MWT, 6-minute Walk Test; DMD, Duchenne muscular dystrophy; MCID, minimally clinically important difference; SV95C, stride velocity 95th centile.

What does SV95C mean for DMD?¹

Multi-stakeholder impact, benefiting the entire health ecosystem

Benefits of using highly sensitive digital endpoints in drug development

Sample size → Trial duration → Burden → Inclusion

DMD, Duchenne muscular dystrophy

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Core components of quantitative model

Use digital technologies?

Study endpoint?

“Digital”

“Traditional”

Study population?

“Enriched”

“Not enriched”

Treatment effect

Active trt

Control (placebo)

Statistical significance

Successful trial

Modelling and Monte Carlo simulation performed using
Components of quantitative model
- some details and extension
Components of quantitative model - some details and extension
Components of quantitative model - some details and extension
Components of quantitative model - some details and extension

- Study endpoint?
- Use digital technologies?
- Study population?
- Biomarker
  - Prevalence
  - Sensitivity
  - Specificity
- True treatment effect
  - Positive subgroup
  - Active trt
  - Control (placebo)
  - Random variation
- Standard deviation
- Sample size
- Standard error
- Statistical significance
- P-value
- Observed trt effect
- Successful trial
- Decision criterion
- Successful project
- Design, rest of project
- Market
  - NPV
  - Time to launch
  - ROI
  - Study duration
  - Smaller N req
  - PoSS
Components of quantitative model - some details and extension
Components of quantitative model - some details and extension
Biomarkers can reduce sample size

Simulation for sample size impact

To achieve 80% PoSS at p<0.05

<table>
<thead>
<tr>
<th>Enrichment with DaTscan</th>
<th>Study endpoint with SV95C-like</th>
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<tbody>
<tr>
<td>1 Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 No</td>
<td>Yes</td>
</tr>
<tr>
<td>3 Yes</td>
<td>No</td>
</tr>
<tr>
<td>4 No</td>
<td>No</td>
</tr>
</tbody>
</table>

With DaTscan enrichment and SV95C-like endpoint
N = 325

Without technologies
N = 620

CAUTION: This figure represents a hypothetical model case for PoC. Each model user needs to make study-specific assumptions.
Or time to market

Simulation for time to signal

For $N = 700$ to meet $p < 0.05$

With DaTscan enrichment and SV95C-like endpoint 5 months

Without technologies 15 months

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Aug 3, 2022 11 am ET
Nocturnal Scratch as a Digital Endpoint for Atopic Dermatitis

Public launch event
Sept. 8, 2022 | 10 a.m. ET
Virtual Journal club

Digital Biomarkers

Considerations for Conducting Bring Your Own “Device” (BYOD) Clinical Studies

September 15, 2022 11am ET

Pirinka Georgiev
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Pfizer
Minnesota, USA

Krishna Jhaveri
Clinical Lead
Motion BioSensors Group
New York, USA

Jen Goldack, MBA
CEO
DiMe Society
Moderator
THANK YOU

Hiro Mori, MBA, CNS Solution Owner - Koneksa Health
Brussels, Belgium

Stig Johan Wiklund, PhD, Chief Scientific Officer - Captario
Gothenburg, Sweden

Dr Paul Strijbos PhD, Product Development Neuroscience - F.
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