Getting relevant health economics data from the clinical development pre-marketing phase of MS products

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TIME MATTERS IN MS

Getting relevant health economics data from the pre-marketing clinical development of MS products

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EU Medicines Authorisation

The EU has developed a single market through a standardised system of laws that apply to all its Member States. The same rules and harmonised procedures apply to all the 28 Member States regarding the authorisation of medicines and the supervision of the safety medicines.

EU Member States: 28

The European Economic Area (EEA) is formed of the 28 EU Member States plus:

Accession to the EU means a commitment to apply the “acquis communautaire” (the body of EU legislation and guidance) to ensure that all EU Member States operate to the same standards.

GDP
€ 12.9tn

Populations
>500m

24 official languages

Medicines regulatory authorities 50+
Marketing Authorisation and Market access (EU)

Clinical development

Health technology appraisal + Priority-setting Decision-making

Reimbursement

Market Authorisation

> ONE YEAR LAG

Full Market Access
Marketing Authorization

3 hurdles to market ...

Safety
Efficacy
Quality
Benefit
Risk
Marketing Authorization

4th hurdle...

Cost-effectiveness
Therapeutic added value +
Value for money

And 5th...

Affordability
Classical triangle

Third payer:
Investment in future health gain
WITH
Cost control (containment)

Drug financing
Decision making

Pharmaceuticals:
Just Reward for the investment risk in I&D

Patients / society:
Prompt and unrestricted access to innovative medicines
Early (phase 2/3) HTA quality data

**Phase 2 trials**
- Population
  - Homogeneous, RMS / PMS
  - EDSS 3-4.5 / 5-6 / >6
  - Small sample
- Short, proof of concept trial
- Biomarker based endpoint
  - MRI
- **Secondary / Exploratory endpoints in extension studies**
  - Disability endpoints
  - Up to 5 year data

**Phase 3 trials**
- Population
  - More heterogeneous, RMS + PMS
  - EDSS 3-6
- Medium duration trial
- Time to event endpoint
  - Lack of sustained double-blind follow-up
  - Event: relapse / sustained disability
- Disability endpoints
HTA in Multiple Sclerosis

• Delay / freezing of disability
  – Motor skills
  – Pain / sensation
  – Cognition / behaviour
  – ...

• Improvement of patient capacity

• Cure
  – With sequelae
  – Without sequelae
# Disability in Multiple Sclerosis

## Functioning and Disability

<table>
<thead>
<tr>
<th>Domain</th>
<th>Body Functions</th>
<th>Activities and Participation</th>
<th>Environmental</th>
<th>Personal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Functions</strong></td>
<td>Body functions</td>
<td>Life areas (tasks, actions)</td>
<td>External influence On disability</td>
<td>Internal influence On disability</td>
</tr>
<tr>
<td><strong>Construct</strong></td>
<td>Change in body function (physiological)</td>
<td>Capacity: Executing tasks in a standard environment</td>
<td>Facilitating or Hindering impact of features of the physical, social and attitudinal world</td>
<td>Impact of attributes of the person</td>
</tr>
<tr>
<td><strong>Positive aspect</strong></td>
<td>Functional and structural integrity</td>
<td>Activities Participation</td>
<td>Facilitators</td>
<td>Facilitators</td>
</tr>
<tr>
<td><strong>Negative aspect</strong></td>
<td>Impairment</td>
<td>Activity limitation Participation restriction</td>
<td>Barriers / hindrances</td>
<td>Person role</td>
</tr>
</tbody>
</table>

**Change in body function (physiological)**

- **Capacity:** Executing tasks in a standard environment
- **Performance:** Executing tasks in the current environment

**Facilitating or Hindering impact of features of the physical, social and attitudinal world**

**Impact of attributes of the person**
Disability in Multiple Sclerosis

<table>
<thead>
<tr>
<th>Examples of activities limited by disability in MS</th>
<th>Walking fast</th>
<th>Keeping up appointments / double tasking</th>
<th>Reading magazines / leaflets</th>
<th>Using cutlery, writing, keyboard</th>
<th>Family decisions, having fun</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body functions impaired</td>
<td>Walking</td>
<td>Higher cognitive functions</td>
<td>Sight</td>
<td>Muscle power/movement control</td>
<td>Higher executive functions/Mood</td>
</tr>
<tr>
<td>Components of body function</td>
<td>Speed</td>
<td>Speed of thought/ Memory/ Attention</td>
<td>Visual acuity/ visual fields</td>
<td>Fine hand use/ Eye-hand coordination</td>
<td>Planning/ Depression</td>
</tr>
<tr>
<td>Assessment tools</td>
<td>T25FW</td>
<td>SDMT/ CVLT/ BVRT/ 7-24 SRT/ Stroop</td>
<td>LCVA</td>
<td>9-HPT</td>
<td>MADRS</td>
</tr>
</tbody>
</table>

T25FW: Timed 25-Foot Walk test; SDMT: Symbol Digit Modalities Test; CVLT: California Verbal Learning Test; BVRT: Benton Visual Retention Test; 7-24 SRT: 7/24 Spatial Recall Test; Stroop: Stroop Test; LCVA: Low-contrast visual acuity; 9-HPT: 9-Hole Peg Test; MADRS: Montgomery–Åsberg Depression Rating Scale
HTA assessment tools in MS

**Multiple specific tools**
- Detailed information (each test informs about specific MS items)
- Too cumbersome to apply all tests to all trial participants
- Most are not Patient oriented (not PROs), and provide information on clinical signs rather than daily life functioning
- Less variability
- Good to confirm that stabilisation / improvement is related to a change in MS

**Global functional tools**
- Clinical Global Impression (CGI)
- Patient Global Impression
  - Change
  - Improvement
  - Severity
- High variability
- Depression bias
- Training issues
- Must be complemented with other scales to confirm that improvement is related to MS symptom improvement
Good News!

- Academia, Pharmaceutical Industries, Patient representatives and Regulators on the same path: