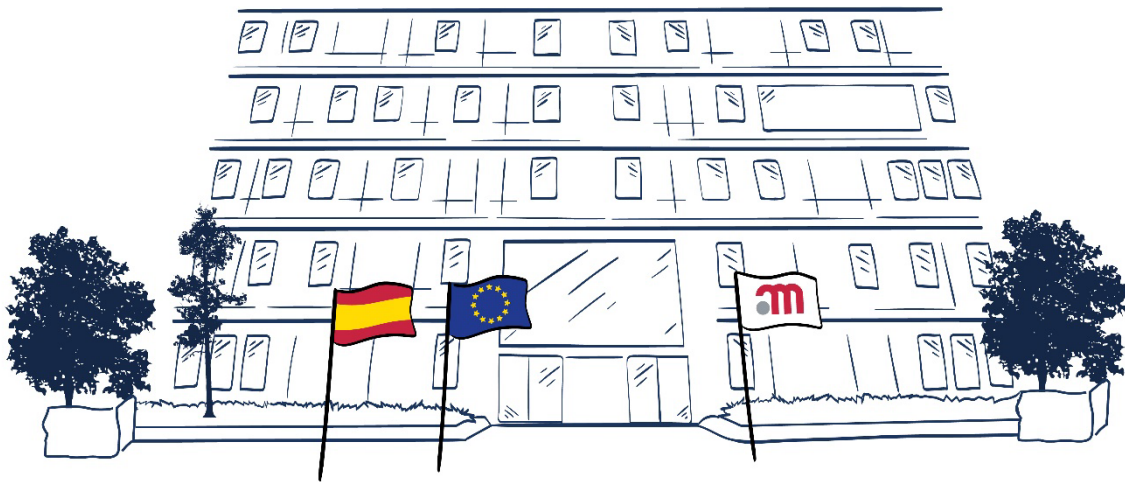


Multistakeholder workshop on Real-World data collection in Duchenne Muscular Dystrophy

Session 1: Current challenges in clinical development and regulatory decision-making



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Bridging the gap: aligning Therapeutic Potential with Evidence Requirements

Health technology assessment is a **scientific evidence-based process** that allows competent authorities to determine the **relative effectiveness of new or existing health technologies**. HTA focuses specifically on the **added value** of a health technology in comparison with **other new or existing health technologies**.

(Regulation 2021/2282 on Health Technology Assessment)



Quality, Efficacy, Safety
Benefit-risk assessment



The HTA Evidence Gap

Added Therapeutic Value,
Long-term Outcomes, Sustainability of the System

1. Evidence Evolution	2. Comparator alignment	3. Patient-centrity
• One pivotal CT • Surrogate outcomes • Short-term follow-up • Small and homogeneous populations • Multiple evidence, but gold standard RCT • Clinical and long-term Outcomes • Large cohorts and heterogeneous populations	• Placebo • Suboptimal comparators • Retrospective external comparators • Real World Practice • Relevant comparators	Systematic incorporation of clinical and patient perspectives: the real utility and place of the therapy in the market





Technical hurdles that make HTA evaluations difficult for DMD treatments

POPULATION (P)



• **Low prevalence, rare disease** → **Sample Size:** statistical significance in ultra-small cohorts.

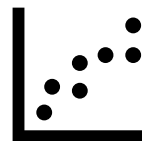
• **Extrapolation risk:**

- ❑ **Genetic heterogeneity:** deletions, duplications, point variants, etc.
- ❑ **Clinical variability** in the age of onset, progression, and clinical manifestations (ambulatory vs non-ambulatory patients).

Related phenotypes, such as Becker muscular dystrophy, ...

• **Late diagnosis. Incomplete or inconsistent understanding of the progression of the disease.**

COMPARATOR (C)



- The ethical and technical complexity of designing **appropriate external natural controls (instead used as complementary data)**.
- **Corticosteroids as SoC.**
- **Current therapeutic landscape.**
- **Alternative non-pharmacological treatments:** off label, physiotherapy, orthopedic support and technical aids, respiratory support (bronchial hygiene techniques, non-invasive ventilation), nutritional support, school adaptations.

OUTCOMES (O)



- **Pleiotropic disease with multiple manifestations:** muscle atrophy and weakness, development of dilated cardiomyopathy, respiratory failure and cognitive and language impairments.
- **Surrogate Endpoints:** tension between *biomarkers* (e.g., dystrophin or microdystrophin levels) versus *tangible clinical benefits* (functional improvement, motor function and muscle strength, time to loss ambulation, time to assisted ventilation, quality of life, general and specific validated questionnaires/scales and in advanced stages: impact on survival, respiratory function and cardiac function).
- **Limited availability of long-term data (trial duration and follow-up period):** uncertainty about long-term safety and durability of the treatment effect.



Evidence beyond Clinical Trials: use of RWD

- Early HTA JSC
(in parallel with EMA)
- Joint HTAb-EMA scientific
working group

Work on the early diagnosis and
clinical validation of surrogate endpoints
(retrospective registries)

Clear definition of the disease spectrum
being addressed and therapeutic objective.
Is it curative? Is it a DMT? Identify the needs

Robust RWD: Implementing prospective, high-quality
observational studies (centralized European registries)
to complement CT in parallel/ Other methodologies
(Target Trial Emulation, Platform Trials)

Non clinical HTA assessment: pharmacoeconomic, social, organizational,
logistical, environmental as well as legal and ethical aspects

Combine the prospective observational studies with interventional post-
marketing CT: protocolized visits





Take-home Messages



RWD as a Necessity:

Real-World Data is not an "optional extra" but a critical requirement to bridge the evidence gap but each **medicine follows a different evidence-generation pathway.**



Patient-Centre Value: Value must be measured not only by surrogate endpoints but by functionality and Patient-Reported Outcome Measures (PROMs).



Early Alignment:

Industry, Regulators, and HTA bodies must align on endpoints and evidence requirements before the trial design phase.



¡Thank you very much for your attention!
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