Neuromuscular Disorders 55 (2025) 106236

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

279th ENMC international workshop: Classification, clinical care, outcome measures and biomarkers in childhood onset facioscapulohumeral dystrophy: towards standardizing clinical care and ensuring clinical trial readiness. Hoofddorp, The Netherlands, 1-3 November 2024

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ARTICLE INFO

Keywords:
Facioscapulohumeral dystrophy
Children
Clinical management
Trial readiness
ENMC workshop

ABSTRACT

The 279th ENMC workshop on childhood-onset facioscapulohumeral dystrophy (FSHD) was held on November 1–3, 2024. The workshop aimed to standardize classification based on disease severity, address implications for clinical trials and patient access, and improve clinical management of children and adolescents with FSHD. Key priorities included establishing a working party to address knowledge gaps in clinical management and outcome measures, defining a standardized minimal dataset in both research and clinical environments, and enhancing pharmaceutical engagement. Childhood-onset FSHD presents a spectrum, from early-onset progressive cases to later adolescent onset with a classical phenotype. Standardized care, including psychological support and transition planning, is needed. Challenges in trial design, such as disease heterogeneity and ethical considerations, were highlighted. Consensus that childhood-onset FSHD forms part of a disease continuum was reached. Two task forces were established to define minimal outcome measure datasets and paediatric-specific care guidelines, marking a crucial step toward improved clinical care and trial readiness.

1. Introduction and background

Facioscapulohumeral muscular dystrophy (FSHD) is a genetic muscular dystrophy initially affecting the facial, scapular, and upper limb muscles in a progressive manner, with subsequent involvement of the lower limbs, trunk, and other muscles. While FSHD is often regarded as an adult-onset disorder, a substantial subset of patients present with symptoms during childhood.

Despite growing recognition of the unique clinical course of childhood-onset FSHD, standardized care protocols and consistent methodologies for assessing disease progression in this population are lacking. Variability in data collection and outcome measure use across published studies complicates direct comparison and limits the development of robust clinical guidelines. Ongoing clinical trials of potential treatments targeting adult and adolescent populations underscore the urgent need for a comprehensive characterization of disease phenotypes in children, the establishment of standardized care recommendations, and the development of reliable biomarkers and outcome measures for childhood-onset FSHD.

To address these gaps, the 279th ENMC international workshop was held from November 1–3, 2024 in Hoofddorp, the Netherlands. The participants included clinicians and researchers from Australia,

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https://doi.org/10.1016/j.nmd.2025.106236
Received 26 September 2025; Received in revised form 30 September 2025; Accepted 30 September 2025
Available online 1 October 2025
0960-8966/© 2025 Published by Elsevier B.V.

Belgium, Brazil, Canada, France, Germany, Italy, Israel, Spain, Sweden, Switzerland, The Netherlands, UK and USA, as well as patient representatives (The Netherlands and USA) and two invited participants from industry (Avidity Biosciences and Dyne Therapeutics).

The workshop was introduced by Wilma van Hinloopen, Program Manager European Neuromuscular Centre (ENMC), who introduced the ENMC commitments and objectives.

The workshop's main aims were refining phenotypic classification and disease severity markers, harmonizing terminology, reviewing and updating clinical care guidelines, and identifying key challenges and facilitators for paediatric clinical trial design. Additionally, the workshop aimed to strengthen global collaborations among clinicians, researchers, and industry partners to optimize trial methodologies and ensure that emerging therapeutic interventions are applicable to the full spectrum of FSHD severity in children. A pre-meeting survey on classification of childhood-onset FSHD completed by participants helped to shape the discussion during the meeting. Fig. 1 presents the topics covered in each of the five workshop sessions.

2. Natural history and classification of clinical phenotypes

Tracey Willis introduced the session with an overview of childhood-onset FSHD. She highlighted that classical FSHD1 presentation and diagnosis usually occurs between 15–30 years of age with a prevalence of 1:15.000–20.000. The clinical course is generally that of slow progression, with 10 % experiencing loss of ambulation (10–20 % >50 years) [1,2] and minimal extra-muscular manifestations [1].

Historically early-onset FSHD has been defined by facial weakness <5 years and scapular weakness <10 years [3]. Compared to adult-onset FSHD, symptom onset in childhood has a prevalence of 5:100.000, with early symptom onset occurring in 1:100.000. A bimodal presentation is observed: infants (0–2 years) presenting with a more progressive disease course, more extra-muscular features and 40 % lose ambulation by the age of 18, whereas children diagnosed later in childhood show a more heterogeneous disease course with fewer extra-muscular features [4]. The disease presents along a spectrum, ranging from early-onset cases with a more progressive course to later-onset cases in adolescence, with a more classical presentation or relatively asymptomatic.

In the majority of FSHD1, the EcoR1 fragment is 4–10 repeat units (EcoR1 size 15–38 kb). Patients with large contractions of D4Z4 (1–3 repeat units and EcoR1 size 10–14 kb) can be associated with a more severe phenotype. Hypomethylation, related to contraction of D4Z4 repeats, leads to chromatin relaxation of the 4q35 region, which initiates DUX4 production. De novo mutations occur in 4 % of the classical phenotype compared to 46 % in the early-onset form [3]. There is some genotype/phenotype correlation, but this is imprecise. Duration of disease and age of onset are known to correlate with severity and loss of ambulation [5], although this relationship is uncertain due to potential delays in diagnosis.

There is some correlation with D4Z4 contraction size and frequency of hearing loss, cognitive impairment, and epilepsy [6]. In early-onset, there are reports of epilepsy in 8 % and developmental delay in up to 15 % of patients. Early-onset is associated with 40 % hearing loss detected in children of 0–7 years compared to no hearing loss in classical FSHD phenotype [3]. Retinal vasculopathy, which may progress to Coats disease, is seen in 37 % of children with early-onset (50–75 % classical FSHD) with 6 % vision loss in children with early-onset compared to 0.8–1.7 % in classical FSHD [7]. In children with early-onset, up to 11 % require respiratory intervention (1 % adult FSHD study) [8] and poor nutritional status is associated with the very early-onset subgroup [4].

In all FSHD patients fatigue (83 %), pain (63 %) and decreased quality of life (70 %) have been reported [4]. Childhood-onset FSHD therefore represents a heterogeneous group of patients, with a spectrum of disease presentation and progression.

Corrie Erasmus continued the session with a summary of six published studies from several European countries, the international CINRG (Cooperative International Neuromuscular Research Group) [9] and unpublished data from a recent Australian childhood-onset FSHD

Fig. 1. Overview of main topics addressed at the 279th ENMC workshop on classification, clinical care, outcome measures and biomarkers in childhood onset FSHD.

natural history study [4,10–13]. All cases published were genetically classified and involved affected family members, with a consistent age of disease onset across studies. However, all studies had small sample sizes, and various study designs using multiple clinical classification methods, including D4Z4 repeat size and Brouwer's classification which is based on facial weakness before age 5 and scapular weakness before age 10 [3]. These studies demonstrated that earlier onset does not correlate with a severe clinical outcome in every case, and significant clinical variability exists among children with early FSHD presentation. Longitudinal follow-up is essential to better understand disease progression in this population. The section emphasised the necessity to combine cohorts to achieve an adequate sample size in future.

To facilitate discussions a pre-workshop survey was designed to gather input from workshop participants on their clinical practices and opinions regarding the classification and severity assessment of childhood-onset FSHD. The survey was drafted by **Renatta Knox** and **Katherine Mathews** and reviewed and edited by the organizing committee (K. de Valle, C. Erasmus, and T. Willis) prior to distribution. There were 20 respondents, (13 neurologists (paediatric and adult), 3 patient advocates, 3 allied health therapists (physiotherapy and psychology) and 1 ethicist. Key results from this survey are shown in Box 1.

These results helped shape the end of session discussion and provide valuable information regarding focus areas for care consideration and outcome measure development in the future.

When considering childhood-onset FSHD classification, **Katherine Mathews** presented several options for disease classification including; 1) acknowledge a continuum and define specific subgroups, 2) describe rates of progression based on objective measures (D4Z4 repeat, MRI characteristics, motor function at a specific age), 3) define a specific biologically different group at one end of the disease spectrum or 4) some combination of these. In other paediatric diseases, classification is often based on motor outcome, but best motor outcome is not entirely applicable in FSHD where most milestones are typically achieved but slowly lost. Division into clinical subgroups must account for the context and purpose of the subgroup development. In the context of clinical trials, patient groups (such as the most severely affected) should not be excluded from access to future therapies or sponsors discouraged from including them in clinical trials. Therefore, terminology should be inclusive and disease classification per se should not be a reason to exclude individuals from access to future therapies or to exclude individuals from clinical trials. On the other hand, understanding factors that predict different rates of disease progression allows for clinical trial stratification or definition of a primary analysis subgroup (perhaps while including a broader range of participants as a safety cohort). The magnitude of the impact of genotypic variation should be considered in the context of a trial. In Duchenne muscular dystrophy (DMD), small differences in disease trajectories based on genotype were less important than clinical function at baseline when studied over one year [14]. In the context of clinical care, understanding different disease trajectories allows anticipatory guidance. In the context of research to understand FSHD, outside of clinical trials, it is often necessary to focus on specific well-defined subgroups (for example to understand the biological basis of hearing loss). Researchers should always be careful to describe the population they are studying, and one classification system might not work in all contexts. Further research is required to identify the best predictors of progression and disease trajectories.

Following session 2 presentations a whole group discussion reached consensus on the following. The term 'infantile-onset FSHD' will no longer be used as a descriptor. Childhood-onset FSHD equates to onset before 18 years of age and the group agreed that childhood-onset is a spectrum of disease; from more progressive early-onset (<10 years) with extra muscular features to later childhood/adolescent onset with a more classical adult phenotype. When studying childhood-onset FSHD, researchers should always define the population (or subpopulation) included. The population of interest can vary based on research context and might be defined by characteristics such as age at symptom onset or genetic test results.

3. Guidelines on clinical management

Bettina Henzi presented an overview on clinical management. Currently no standardized and unified guidelines for clinical management of childhood-onset FSHD exist. While research addressing single aspects of the clinical management exists, evidence on the management of childhood-onset FSHD in general is largely lacking.

For the follow-up of children with FSHD specialized multidisciplinary monitoring, coordinated by a paediatric neurologist, is recommended [15] with follow-up visits every 6 to 12 months. Consensus has been reached on the need for regular ophthalmological and auditory evaluations. However, clear criteria for referral – such as motor function, clinical symptoms, or genetic findings [16] – and the optimal frequency of these assessments remain undefined in the literature. Newly updated FSHD care considerations due for publication later this year will help guide care in this area.

Clinical visits should include standard paediatric measurements as weight and height [4] and the following subjects should ideally be addressed and the need for more in-depth evaluation determined [4,15,17,18]: Motor function, rehabilitation/sporting activities, respiratory problems, cardiac function, ophthalmological aspects, auditory evaluation, language/speech, psychomotor development/cognition, swallowing, nutrition, orthopaedic problems, quality of life, psychological aspects, and age related transition planning.

In conclusion, evidence based clinical management guidelines for children with FSHD are lacking. The aim of this workshop was to address

Box 1
- Key results of the pre-workshop survey on childhood-onset FSHD

94 % of clinician respondents see <20 children with FSHD, every 6–12 months

78 % of neurologists agreed to baseline hearing and retinal evaluation for all children

54 % of neurologists agreed to baseline respiratory screening

14/20 (70 %) respondents had seen at least one childhood-onset FSHD patient with CNS involvement such as learning problems or intellectual disability.

12/19 (63 %) respondents view childhood-onset FSHD as part of a continuum

10/18 (56 %) respondents felt that clinical motor outcome measure development should be focused on arm function

20 % clinician respondents use severity scales to monitor disease progression outside research

No consensus on disease severity classification (ie. repeat size, age at onset)

the need for care recommendations to standardise care for children with FSHD.

Focusing on the effect on quality of life, mental health, and social functioning, psychologist **Sam Geuens** discussed the psychological impact of FSHD on children. Children with FSHD often face challenges such as lower self-worth, social role dissatisfaction, and anxiety about the future, while illness identity—the degree to which they integrate their illness into their self-concept—plays a significant role in their psychosocial adjustment [19]. Adolescents with neuromuscular disorders frequently experience higher "engulfment," where the illness dominates their identity, compared to peers with other chronic conditions. Strategies harnessing a stronger sense of control can be adopted to reduce this effect [20]. Psychosocial support, active social participation and psychoeducation should form part of standard care, and research into mental health prevalence, risk factors, and effective coping strategies should be undertaken to help children manage the ongoing demands of FSHD.

These aspects were also taken up by **Pierre Laurian**, representing the DUX Foundation. He shared experiences and activities organised for children supported by the foundation. By organizing extra-ordinary group activities, the foundation aims to increase the self-confidence of children with FSHD and offer them a network of peers.

Talya Dor presented important considerations on different aspects of rehabilitation in childhood-onset FSHD. In children, the key to adoption and maintenance of physical activity is engagement and participation. Activities should be enjoyable, age appropriate, and part of everyday life. In children with neuromuscular diseases, the intensity of exercise should be reduced compared with healthy children to avoid overuse, muscle exhaustion, pain and fatigue. However, the same principles of exercise must be followed, since it is clear that physical activity benefits all individuals not just those with FSHD [21]. The key goals in rehabilitation of childhood-onset FSHD patients are to preserve and improve muscle function, to minimize disuse of specific muscles, and to improve flexibility and balance. To this end, the program of rehabilitation should be tailored to the individual's distribution of weakness. Exercise should include aerobic training, muscle strengthening and resistance training, flexibility and balance. We must recognize the barriers for effective physical activity in children with FSHD: fatigue, musculoskeletal pain, and lack of motivation. The latter can be enhanced by encouraging participation in competitive or sports of interest (specialized for patients), social engagement and joyful activities. Early-onset patients show a more severe phenotype, and their rehabilitation should involve experts from multiple disciplines including ophthalmology, otology and pulmonary medicine.

Thomas Sejersen presented important aspects of transition care planning. Transitioning is defined as a "purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems" [22]. It is crucial to separate this process, starting in the teens and continuing well into the twenties, from the one time act of transfer of care from paediatric to adult health care. Despite the importance of transitioning for patients with FSHD, there is currently no literature to guide best practices on transitioning for young people with FSHD. Lessons can be learned from other neuromuscular disorders (DMD and spinal muscular atrophy), on how to accomplish this. It will be important to include FSHD specific recommendations to assist in preparing and guiding young people and their families through the transition process in the development of care guidelines for childhood-onset FSHD.

In preparation for the workshop **Anke Lanser**, a patient representative, interviewed children, adolescents, adults, and parents with lived experience and contributed their expectations to the workshop. Patients and families emphasized the need for a doctor who makes them feel comfortable and safe, someone knowledgeable about FSHD but not necessarily with all the answers. At diagnosis, families need detailed information about FSHD, symptom progression, and the opportunity to make connections with other affected children and families if desired. A key consideration for parents is how and by whom the diagnosis is communicated to their child.

In the years following the diagnosis, patients and families need practical support for school, transport, lifestyle and nutrition. Guidance on balancing regular and adapted sports, as well as mental health support for both children and parents is essential. Patient organizations play a crucial role in addressing these needs.

Children with FSHD strive for a normal life, but can experience a reduced quality of life, with facial weakness and communication difficulties often impacting them even before diagnosis. Family dynamics are also affected, with challenges such as insecurity, invisibility, and comparisons of disease severity among relatives. Most respondents confirmed their participation in patient registries and willingness to join clinical trials if they are safe. Finally, Anke Lanser encourages clinicians to speak with the affected children without their parents being present at least for part of the consultation.

4. Clinical outcome measures

Acknowledging that growth, motor development and maturation need to be accounted for when measuring motor function in children, **Katy de Valle** presented on what is known about clinical outcome measures (COMs) used in childhood-onset FSHD. Fig. 2 provides an overview of the potential suitability of various COMs in children with varying levels of ambulation. It was acknowledged that normative reference data and robust COMs with evidence to support responsiveness are urgently required for clinical care, natural history studies and to ensure clinical trial readiness in childhood-onset disease. The inconsistency in COM use across studies complicates comparisons of function and associated disease progression [4,9,11]. Previous natural history data highlight disease heterogeneity and variable functional decline, providing further challenges to outcome measure selection [4,11].(de Valle (unpublished))

Emerging evidence supports the paediatric version of the FSHD-Composite Outcome Measure (FSHD-COM Peds) for assessing whole-body function, with preliminary data (n = 13) from the Australian childhood-onset FSHD natural history study (iFSHD-LOS) showing a similar rate of change over 24 months to adult FSHD cohorts. Larger changes in early-onset or participants with 1–3 D4Z4 repeats were evident when the cohort was stratified. Poor responsiveness and the presence of significant ceiling effects were found as limitations of using the Motor Function Measure to measure whole-body function in children with slowly progressive FSHD [11,23]. Other potential COMs include the North Star Assessment for Limb-Girdle type muscular dystrophies (NSAD) for lower limb/trunk function [24], the 6-minute walk test (6MWT) (though potentially insensitive to change), and the 100 m Timed Test (100mTT) which may be more sensitive [25]. The 10 m walk/run test (10mWRT) also shows promise, with longer times linked to early-onset disease. While the Performance of the Upper Limb (PUL2.0) is effective in DMD and LGMD [24,26], it needs further investigation in FSHD due to presence of different compensatory mechanisms.

It was concluded that measuring function in FSHD is complex and that normative data is important to help account for expected childhood growth and development. Ongoing COM refinement and development is necessary to establish a toolbox of suitable measures with the ability to detect change in stable and rapidly progressing, ambulant and non-ambulant individuals. Further work is needed to establish an agreed brief minimal functional dataset for use in clinical and research situations.

Meredith James discussed the role of patient-reported outcomes (PROs) in childhood-onset FSHD, emphasizing the need for standardized assessments to track disease progression, compare treatment effects, and guide clinical care. PROs should consider the needs of the child with FSHD within the World Health Organization biopsychosocial approach [27,28]. PROs reveal that children with FSHD experience significantly

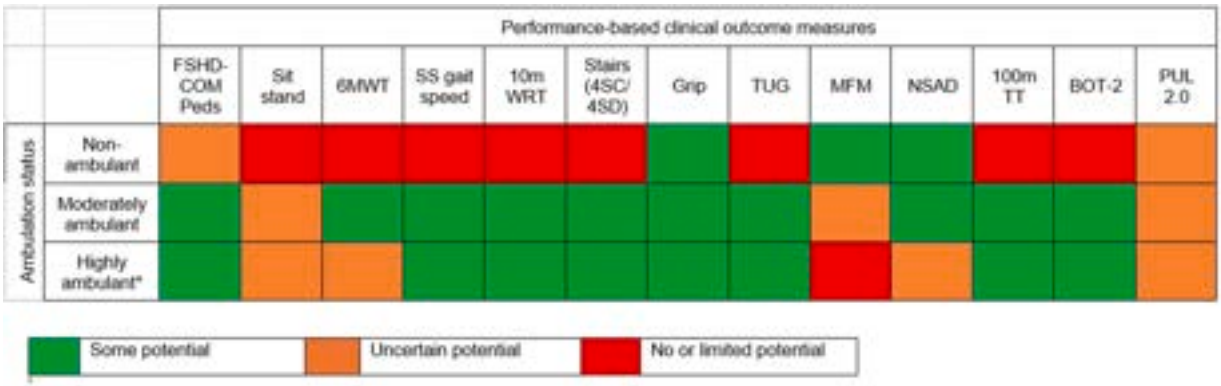

Fig. 2. Overview of the potential applicability of various COMs across different ambulation levels in children. FSHD-COM Peds – paediatric FSHD composite outcome measure, Sit-stand – timed sit to stand, 6MWT – 6-minute walk test, SS gait speed – self-selected gait, 10mWRT – 10 m walk/run test, 4SC – timed 4 stair climb, 4SD – timed 4 stair descent, Grip – hand held grip strength, TUG – timed up and go test, MFM – motor function measure, NSAD – NorthStar assessment for limb girdle muscular dystrophy, 100mTT – 100 m timed test, BOT-2 – Bruininks-Oserestky balance test, PUL 2.0 – performance of the upper limb.
*Highly ambulant – minimal symptoms affecting the lower extremities.

more pain and fatigue and report a lower quality of life than their age-matched healthy peers [5,20]. A qualitative study highlighted key psychosocial themes: a desire for normalcy, insecurity, uncertainty about the future, and reliance on family and friends for support, with a clear need for peer and psychological support [20]. Both generic and disease-specific PROs exist, with their use depending on disease stage, patient age, and context (e.g., clinical trials, registries, or clinical care). PROs reported have included pain score, Pediatric Quality of Life (QoL) Inventory Neuromuscular Module, Kidscreen [29] health related QoL screen, FSHD-Health Index paediatric version (FSHD-HI Peds) and NeuroQol fatigue domain. Standardization and harmonization are crucial to ensure consistency and meaningful application.

Linda Lowes reviewed literature on technology-assisted outcomes in FSHD, including activity monitoring, remote assessments, and gait analysis. Due to limited research in FSHD, findings from other neuromuscular disorders (NMDs) were considered.

Home-based activity monitoring may be useful and better reflect patients' overall function rather than single-day clinic visits. Activity levels may be particularly relevant in FSHD as fatigue is a common symptom. The 95th stride velocity has been used in other NMDs, but its validity in FSHD remains uncertain. A small study found changes in gait speed but not activity levels over four months [30]. Various activity monitors exist, but data variability across days and seasons provides challenges for data interpretation. Live-stream video assessments could reduce travel burden and improve patient access, though reliable internet is a limitation. Although data are not available for FSHD, reliable and valid results have been published in DMD [31]. The Duchenne Video Assessment, where caregivers record standardized functional tasks, may serve as a model for FSHD. Trained therapists analyse compensatory movements to track disease progression. A change in the number of compensations required to complete a pre-determined task indicates a change in the difficulty of completing that task [32]. Gait analysis could detect efficiency changes of a patient's walking before speed declines. Video-based, pressure-mapping, and 3-dimensional multi-camera systems are being explored, but cost and portability may limit their use in multisite trials. Research shows children with FSHD walk more slowly than matched peers [33] with disease progression leading to compensatory changes like foot drop and pelvic weakness. More studies are needed to determine gait analysis responsiveness and necessary system specifications.

In conclusion, there is sufficient evidence from other NMDs to suggest that high-tech endpoints could be useful in FSHD, however, validation is required prior to use.

Valeria Sansone outlined key factors in designing childhood-onset FSHD clinical trials: (i) the lower prevalence of childhood-onset FSHD leads to small cohorts, which poses challenges for Phase II/III trials requiring larger populations; (ii) childhood-onset FSHD exists on a continuum with the adult-onset forms, sharing common pathomechanisms and treatment targets. Trial design should include younger patients to prevent delays in access to future therapies; (iii) as clinical trials require homogeneity, the heterogeneity of FSHD complicates trial design. A potential solution is to include a core cohort of mildly affected individuals while allowing a predefined percentage of more severely affected patients. Functional status, rather than age or repeat size, should guide inclusion criteria to account for disease variability.

The discussion emphasized existing gaps in childhood-onset FSHD research, including the need to define meaningful outcome measures, disease progression rates, and respiratory involvement. Limited longitudinal data may delay the initiation of randomized controlled trials (RCTs). Striking a balance between the urgency to start trials and ensuring a robust study design is crucial, especially since physiological growth in children can confound treatment effects.

Additional considerations included test feasibility in younger patients. While muscle MRI, DUX4 regulators, and biopsy-derived biomarkers are key in adult trials, their applicability in children requires careful evaluation.

Despite ongoing challenges in data collection and trial design, the consensus was that trials for childhood-onset FSHD are approaching faster than expected. While we may not yet have a complete understanding of the disease trajectory, trials are likely to begin soon, making collaboration, consistent classification, and careful population description across studies all the more crucial.

Derek Willis discussed the ethical foundations of research, emphasizing its role in improving or introducing treatments. According to Hart's concept of fair play, patients who have benefited from past research have a responsibility to consider participation in future trials [34]. However, research must be clear and transparent about the differences between trials and established treatments, as the latter have known benefits, whereas trial outcomes remain uncertain [35].

A key ethical challenge in paediatric research is obtaining informed consent [36]. While infants rely on parental consent, older minors may have the capacity to consent despite legal restrictions. The group of young people in between may not be able to give consent – but have the ability to express their feelings about being involved and express their opinion about study design. This has been termed assent. Although assent lacks a universally clear definition [37], the principle of children and young people's involvement in study design and discussion of being in trials feels ethically justified.

Perspectives from regulatory agencies (**Violeta Stoyanova-Beninska**) and the pharmaceutical industry (**Amy Halseth** and **Ash Dugar)**

provided insights into the processes of biomarker validation, regulatory approval pathways, and strategies to optimize trial design for paediatric populations while balancing ethical and scientific challenges. For serious diseases the early initiation of pediatric studies may be well justified, following assessment of initial safety data and reasonable evidence of potential benefit. This is further discussed in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E11 (R1) guideline.. Robust natural history data are crucial for determining appropriate endpoints, sample sizes, and study duration, while factors like growth, puberty, and disease progression add complexity. While RCTs remain the gold standard, alternative trial design approaches – such as extrapolating adult data, biomarker-driven studies, or single-arm open-label designs – may be considered. Stakeholder input is essential; patients, caregivers, physicians, payers, and regulators must collaborate early and continuously to ensure trials are both meaningful and feasible. Key considerations include functional and digital biomarkers, extra-muscular features, patient-reported outcomes, and study execution. Ultimately, balancing scientific rigor with trial feasibility and patient burden is crucial to accelerating childhood-onset FSHD treatment development.

Ria de Haas concluded the session with the need for trial infrastructure and patient involvement to ensure fair access to future treatments [38–40]. Over twenty companies are currently developing therapies for FSHD, with clinical trials already underway and more expected. While this is promising, challenges remain, including insufficient clinical trial readiness, limited trial sites, and the need for a well-characterized patient cohort.

Once therapies are approved by the European Medicines Agency, national reimbursement processes can delay access, and restrictions based on age, disease subtype, or progression vary between countries, leading to inequities. Trial design can significantly affect future reimbursement and availability. Post-marketing surveillance, supported by structured patient registries and robust outcome measures, remains crucial for long-term safety and efficacy monitoring. To address these challenges, Project Mercury [41] was launched as a global initiative uniting patient advocacy groups, researchers, and industry leaders to accelerate therapy development and access. Within Europe, FSHD Europe [42] represents patient organizations across eleven countries, working to strengthen diagnostics, care, and research. The FSHD European Trial Network (ETN), founded by Prof. Nicol Voermans in 2021, facilitates collaboration on trial readiness through five working groups focused on genetic diagnosis, clinical outcome measures, biomarkers, imaging, and childhood-onset FSHD. ETN works closely with international networks such as the Clinical Trial Research Network [43], FSHD Society, TREAT-NMD [44], and European Reference Networks for Rare Diseases [45] to achieve these collaborative goals.

5. Biomarkers, clinical trial readiness and patient participation

The workshop's final session explored clinical trial readiness, patient participation, and the role of biomarkers in advancing FSHD research and treatment development. Key discussion focused on optimizing trial designs, ensuring robust patient involvement, and the need for reliable biomarkers to track disease progression and treatment efficacy.

Jeff Statland discussed the challenges of identifying biomarkers for FSHD clinical trials, highlighting issues such as sporadic DUX4 expression, variable age of onset and disease progression, asymmetry in muscle involvement, and on average a slow rate of change in strength and function. In chronic, progressive diseases like FSHD, biomarkers are crucial for monitoring disease progression, assessing treatment effects, and selecting individuals likely to experience faster progression. Muscle-based biomarkers, particularly those related to DUX4, are being explored, with a panel of DUX4-related genes proposed for molecularly targeted therapies and a strategy that involves enriching the sensitivity of biopsy for DUX4 targets, which utilizes MRI features (STIR positive, or fat fractions between 10–55 %) [46]. However, these biomarkers face challenges due to moderate test-retest variability, and only weak to moderate associations between DUX4 gene targets and muscle pathology, clinical severity, or strength. Use in clinical trials to date has been hampered by the high variability between individuals and from one time point to the next [47].

The inconsistency of muscle related biomarkers means that blood-based biomarkers, with the potential to characterize disease activity throughout the body, are of high interest. The most evidence obtained to date is related to inflammatory biomarkers (IL-6, complement, S100A8) [48,49]. Despite demonstrating promise, and potential associations with muscle MRI findings, these biomarkers have demonstrated only weak associations with disease severity. Avidity identified and only recently made public a DUX4-related circulating biomarker (KHDC1L announced in June 2025) responsive to their therapy in the setting of their research (phase I and II trials). Additional DUX4 related biomarkers in development include SLC34A2, and an array of micro RNAs [50]. MRI and other muscle quality measures, like ultrasound and electrical impedance myography, are also being explored as tools to track disease progression in clinical trials.

Jildou Dijkstra and **Ian Woodcock** discussed muscle imaging techniques in FSHD. Muscle MRI and ultrasound are both valuable techniques for visualizing and quantifying muscle pathology, with strong correlations to clinical outcome measures in adult FSHD. Additionally, these imaging modalities tend to correlate well with each other and appear to be more sensitive to change than most clinical outcome measures within the typical clinical trial period of 1–2 years [29,51]. As such, they can serve as visual biomarkers of disease severity, tracking changes in muscle pathology over time.

Ultrasound is particularly useful in detecting early structural changes in muscle, such as fibrosis, and may identify these changes before they are visible on MRI. However, quantitative ultrasound struggles to differentiate end-stage fatty-infiltrated muscle from healthy muscle [52]. In a childhood-onset FSHD Dutch cohort, follow-up data over 2–5 years showed significant increases in ultrasound z-scores, particularly in the rectus abdominis, rectus femoris, and trapezius muscles [11,53]. Interestingly, some apparent improvements were seen in 20 out of 88 muscles, largely due to the effects of normal growth: the increase in muscle volume altered the ratio between fascia (white) and muscle tissue (black), as illustrated in Fig. 3.

MRI has shown that DUX4 expression is highest in muscles with high T2w-STIR signal [49], which are more prone to fat replacement in follow-up scans compared to T2w-STIR negative ones. The number of T2w-STIR-positive muscles at baseline can predict radiological worsening at follow-up [54,55]. MRI is effective in tracking muscle fat infiltration and atrophy over time, which can serve as a visual biomarker of disease severity and potentially predict functional decline. However, MRI cannot distinguish between fibrosis and fat [56]. Muscle fat fraction percentage, as measured by whole body MRI, has demonstrated good correlation with functional outcomes and may be a useful severity biomarker in childhood-onset FSHD [57]. Unpublished data from an Australian cohort suggest that changes in fat fraction over time could serve as a surrogate biomarker for disease progression [57]. Similar to muscle ultrasound, further research is needed to account for the confounding effects of growth on muscle volume and fat fraction, and to establish the predictive value of MRI changes in children with FSHD.

Ally Roets is a parent and patient advocate, whose presentation highlighted the urgent need for interventional treatments for those living with early-onset FSHD, emphasizing that this group has been consistently overlooked in clinical trials. Along with other parents, she leads the Early-Onset Parent Chapter for the FSHD Society. These parent advocates highlight the slow progress in drug development and the challenges faced in convincing sponsors to include children and non-ambulatory adults (diagnosed in childhood) in clinical trials. The presentation called for changes in trial design, including more sensitive outcome measures, innovative trial structures like run-in, crossover, or platform trials, and a focus on including non-ambulatory patients and

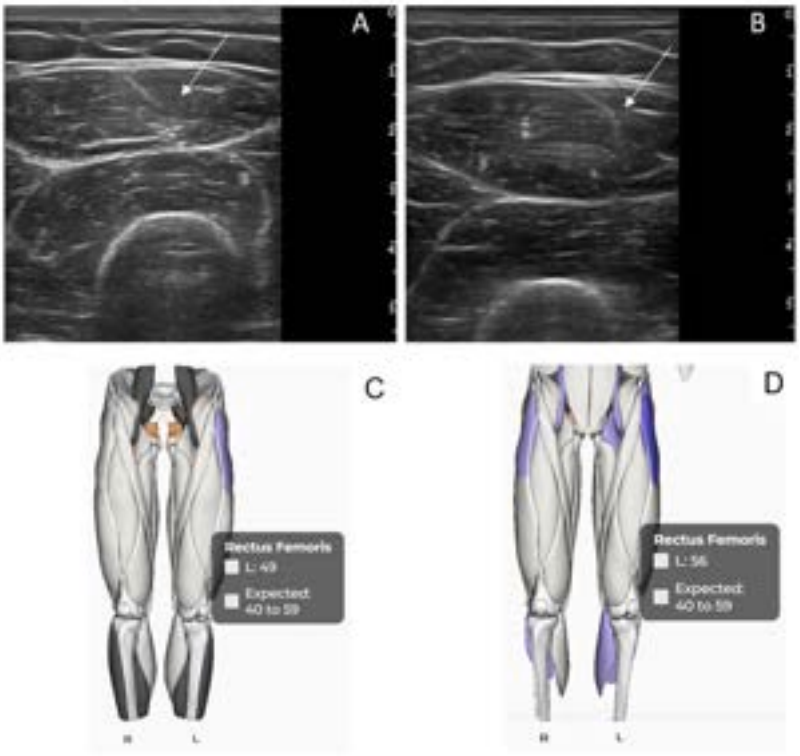

Fig. 3. Apparent improvement in echogenicity due to growth. (A) Transverse ultrasound image of the right rectus femoris on baseline in a 17-year-old female patient with FSHD. (B) Same muscle in the same patient at 5-year follow-up (age 22). (C) An apparent improvement in echogenicity measured with ultrasound (panels A and B) is observed, which is likely related to normal growth. The increase in muscle volume changed the relative proportion of fascia (hyperechoic; white) and muscle tissue (hypoechoic; black). (D) Springbok Muscle MRI image showing left rectus femoris muscle volume at baseline in a 19-year-old male with mild FSHD. (E) Same muscle showing increased muscle volume at 12-months follow-up (age 20).
An apparent increase in measured muscle volume in the rectus femoris muscle measured with whole body MRI (panels C and D) which is also likely related to growth.

children to broaden the safety and efficacy database. The importance of expanded access programs was underscored, urging sponsors to consider these patients to prevent life-threatening delays in treatment access. The presentation concluded with a powerful scenario, urging clinicians to imagine the difficult conversations they would have with families if treatments were only approved for specific subgroups, leaving vulnerable patients without access. The call to action was clear: include all affected populations in trials now to change the course of FSHD drug development and ensure equitable access to future therapies.

Michelle Mellion concluded this session by highlighting the role of the FSHD Society in advancing research and treatments for FSHD. The FSHD Society supports the operationalization of the ENMC outcomes and recommendations by leveraging its global platforms, including the FSHD Navigator (a concierge service providing guidance for all stakeholders), BetterLife FSHD (a digital health and research platform), FSHD Global Innovation Hub (focused on optimizing solutions for FSHD) and Project Mercury (a global infrastructure aimed at delivering treatments to families). These platforms engage stakeholders to address identified gaps and challenges by supporting research, building partnerships, and continued advocacy on behalf of individuals and families living with early-onset FSHD. The FSHD Society Early-Onset FSHD Chapter will play a key role in ensuring the success of these efforts.

6. Conclusions and workshop deliverables

This workshop marked a step toward improving the classification, clinical care, and trial readiness for childhood-onset FSHD. Consensus that childhood-onset FSHD forms part of the FSHD disease continuum was reached, highlighting the broad spectrum of age at onset, disease severity and disease progression. The need for standardized clinical management, including psychological care and transition support, was emphasized. Additionally, key knowledge gaps in outcome measures and disease biomarkers affecting trial readiness were identified. To address these challenges, two task forces were established: one to define a minimal core dataset for clinical and research use and another to develop paediatric-specific care guidelines. Participants from patient organisations agreed to support the revision of the FSHD Society 'Guide for Schools' brochure and to the inclusion of a paediatric-specific perspective in a 'FAQ about FSHD' (frequently asked questions) document prepared by the FSHD diagnosis working group, Spierziekten Nederland. Strengthening collaboration with industry partners and establishing early dialogue, guidance and engagement in due process with regulators (including FDA (USA), EMA (Europe), other country specific organizations) was also recognized as essential to facilitate the inclusion of children in clinical trials. These deliverables lay the foundation for improved patient care, harmonized research efforts, and future therapeutic advancements in childhood-onset FSHD.

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Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Funding

This workshop was supported by FSHD Society, FSHD Global, Avidity Biosciences, Epicrispr biotechnologies, Fulcrum Therapeutics and Kate Therapeutics.

CRediT authorship contribution statement

Jildou N. Dijkstra: Writing – original draft, Conceptualization. **Bettina C. Henzi:** Writing – original draft, Conceptualization. **Katherine D. Mathews:** Writing – review & editing, Conceptualization. **Corrie E. Erasmus:** Writing – review & editing. **Renatta Knox:** Writing – review & editing. **Tracey Willis:** Writing – review & editing, Conceptualization. **Katy de Valle:** Writing – review & editing, Conceptualization.

Declaration of competing interest

Jildou N. Dijkstra has nothing to report. **Bettina C. Henzi** has the following declarations of interest: Advisory board: Italfarmaco and Biogen. **Corrie E. Erasmus** has the following declarations of interest: co-chair Working group Pediatrics of the European Trial Network FSHD, board member Duchenne Center Netherlands, advisory board Pfizer, Roche. Research grants received from the Dutch Prinses Beatrix Spierfonds, Spieren voor Spieren, FSHD Stichting. **Tracey Willis:** has the following declarations of interest: co-chair Working group Pediatrics of the European Trial Network FSHD, member of FSHD UK steering group. Not connected to FSHD: Honoraria for symposia and advisory board participation from; Biogen, Novartis, Lupin Neurosciencs, PTC, Roche, Sanofi Genzyme, Sarepta and Santhera. **Renatta Knox** has the following declarations of interest: she has been a paid consultant for CapVision, ClearView and Guidepoint. She has served on a Scientific Advisory Board or Data Safety Monitory Bord for Avidity Biosciences and Epicrispr Biotechnology. She has received funding from the NINDS, American Academy of Neurology and the Muscle Study Group for FSHD related research. **Katherine D Mathews** has the following Declarations of Interest: Advisory board: Muscular Dystrophy Association, FSHD Society. Board member: Friedreich ataxia research alliance (FARA). Research funding: NIH, CDC, FARA. Consulting or Safety board review: Sarepta, Edgewise, MLBio, Trinds, Dyne, Solid. Site PI for clinical trials: PTC Therapeutics, Sarepta Therapeutics, Capricor, Edgewise, Larimar, ML Bio, AskBio, Biogen, Biohaven, Scholar Rock, AMO, Avidity, Reata. **Katy de Valle** has the following declarations of interest: FSHD Global Scientific Advisory Board, no other

Acknowledgements

The workshops and next generation programme are made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and its Full Partners: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Spierfonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Spierziekten Nederland (The Netherlands), Telethon Foundation (Italy). In addition, we would like to thank the Associated Partners: Österreichische Muskelforschung (Austria), SMA Europe, TREAT-NMD, World Duchenne Organisation, World Muscle Society (WMS), and the members of the ENMC Company Forum: Amicus Therapeutics, Dyne Therapeutics, Lupin Neuroscience, Novartis, Roche, Sanofi, Santhera and Sarepta.

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