FSHD europe

THE John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE

NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

FSHD EUROPEAN PATIENT SURVEY REPORT

2022

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Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is a rare, genetic condition, which causes muscles to weaken and waste over time. The name FSHD reflects the muscles most often affected: the facial muscles (facio), shoulder girdles (scapulo) and upper arms (humeral). FSHD can present with considerable variation in the onset and severity of symptoms, even within the same family.

Treatments for FSHD

There are currently no treatments to cure FSHD. Current treatment options aim to slow the progression of the disease or enhance the patient's quality of life, such as physical therapy, pain management and surgery for scapular fixation.

Developing new treatments in rare diseases is challenging. There are small numbers of patients, with different genetic diagnoses and presenting with a variety of differing symptoms. Therefore, finding enough patients who would fit within the inclusion criteria of a clinical trial can be difficult. Trial centres can ask patients from outside of their region to take part, but this would mean the patient having to commit to travel and spending nights away from their home.

Why are we doing this study?

Stakeholders such as industry and regulators are increasingly seeking patients' thoughts and opinions to help them understand the disease and the patient community's needs.

Patient groups have a unique understanding of the preferences and limitations of their patient communities. It brings significant value if the voice of the patient is included in trial design and recruitment.

There is a growing interest from several pharma companies to run clinical trials in FSHD across Europe. This study aimed to understand the FSHD community's perspective, so that when clinical trials are developed, they are designed and organized in a way to maximize patient involvement and participation.

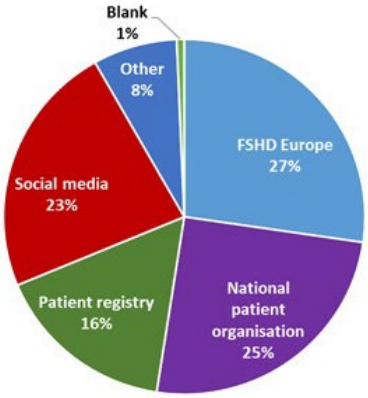
FSHD European Patient Survey

The purpose of this study is to find out what FSHD patients and their caregivers want from future clinical trials and what would encourage them to participate. This information will be used by FSHD Europe and pharmaceutical companies to ensure that when trials are developed, they are designed and organised in a way to maximise patient involvement and participation.

In order to achieve this, we conducted a large-scale survey of patients across Europe to find out what they want from a clinical trial and what might encourage them to participate. FSHD Europe provided funding to the John Walton Muscular Dystrophy Research Centre at Newcastle University to develop, manage and analyse this survey.

The survey was made available online for patients with FSHD and caregivers to complete in 2022.

The survey was shared widely by FSHD Europe and their member organisations. This included patient organisations, patient registries and social media. Participants noted where they had seen the survey, in the pie chart on the right.



Areas of the survey

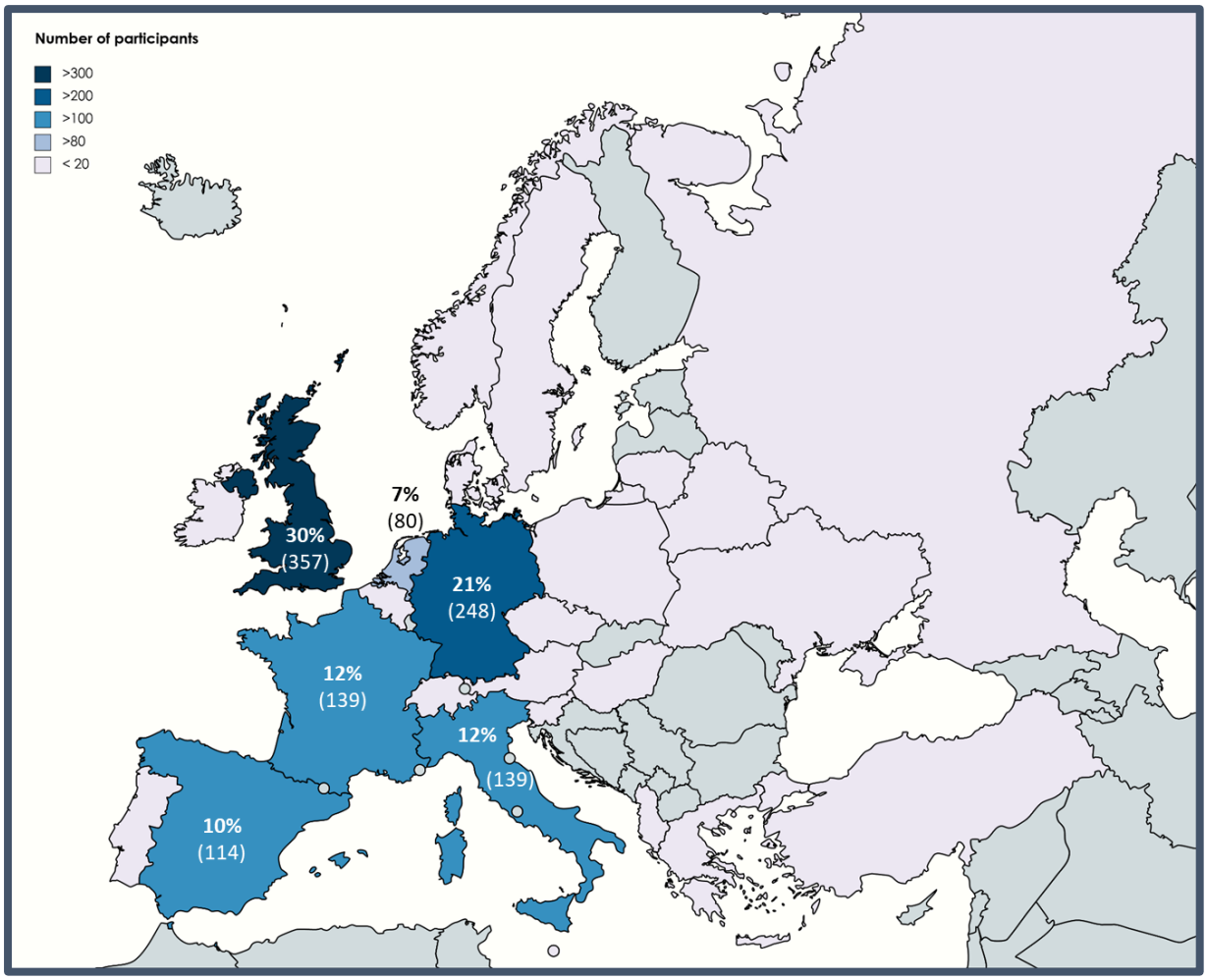
1. *Participant demographics:* Demographic information to understand the representation and diversity of participants across Europe.
2. *Progression of FSHD and impact on daily life:* This section was designed to understand the current level of mobility of people with FSHD. We also wanted to know how effective they felt their current medications and therapies were at treating their symptoms.
3. *Deciding to take part in a clinical trial:* What might encourage or discourage someone from taking part in a clinical trial?
4. *Expectations of a clinical trial:* What do people want from new therapies for FSHD? What would people see as a good outcome from a clinical trial?

Participant Demographics

In total, 1147 people took part in the survey. 92% of the participants were FSHD patients themselves, with 5% being caregivers, and 3% identifying as both a patient and a caregiver of someone with FSHD.

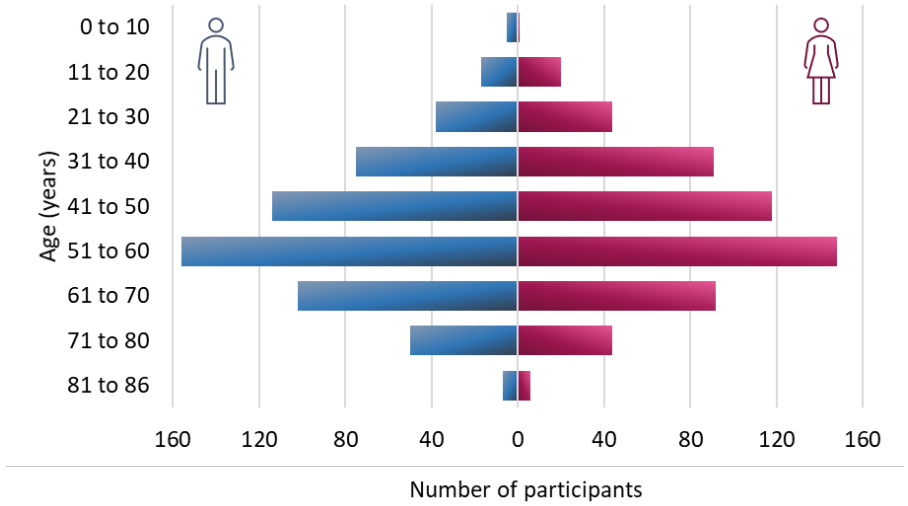
Participants represented 26 countries across Europe. The map below shows the representation of participants in each country.

The survey was available in Dutch, English, French, German, Italian and Spanish. The countries who had their first language available had the highest proportion of responses.



Age and gender of participants

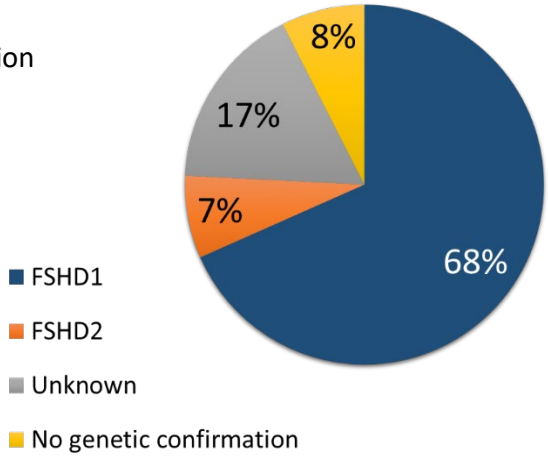
50% of respondants were female, 49% were male. The age of individuals with FSHD ranged from 2 to 86 years old, with an average age of 50.5 years.



FSHD diagnosis

FSHD may be diagnosed based upon a clinical examination, identifying key characteristics of the condition, family history and genetic testing. Participants were asked if they had received genetic confirmation of their FSHD diagnosis.

- 68% of participants reported to have a diagnosis of FSHD Type 1
- 7% of participants reported to have a diagnosis of FSHD Type 2
- 17% of participants reported that they had a diagnosis of FSHD, but did not know the genetic diagnosis
- 8% of participants had no genetic confirmation



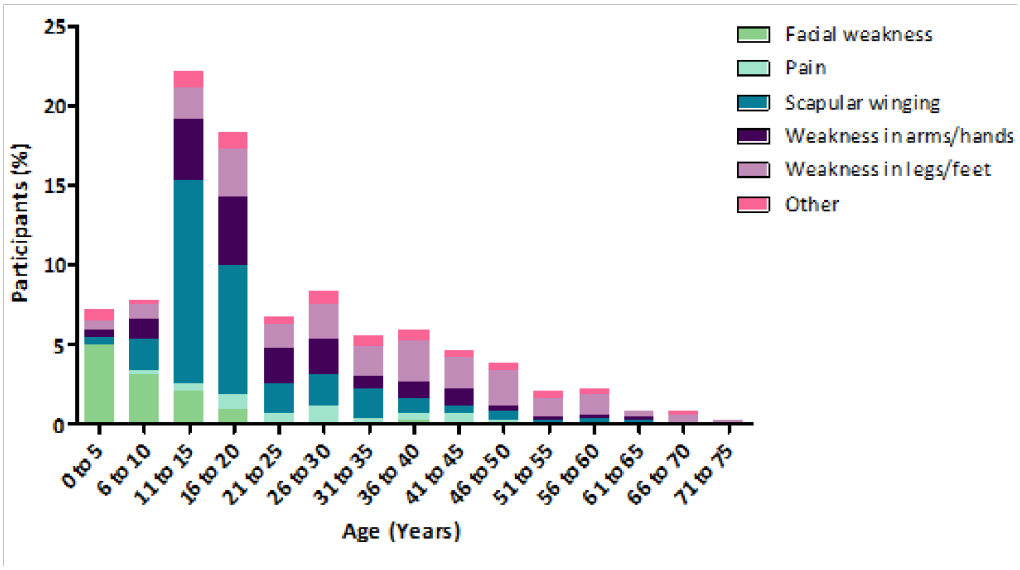
Progression of FSHD and impact on daily life

Participants were asked questions about their current condition, the progression of their FSHD, and how this impacts their daily lives. This section will help to understand where there are gaps in treatment and overall healthcare for people with FSHD.

Symptoms and diagnosis of FSHD

FSHD can present with a variety of different symptoms and severities. The graph below shows the age of the participants when they first experienced symptoms of FSHD. It also shows what the first symptom was, by colour.

Age when symptoms of FSHD began and first symptom experienced

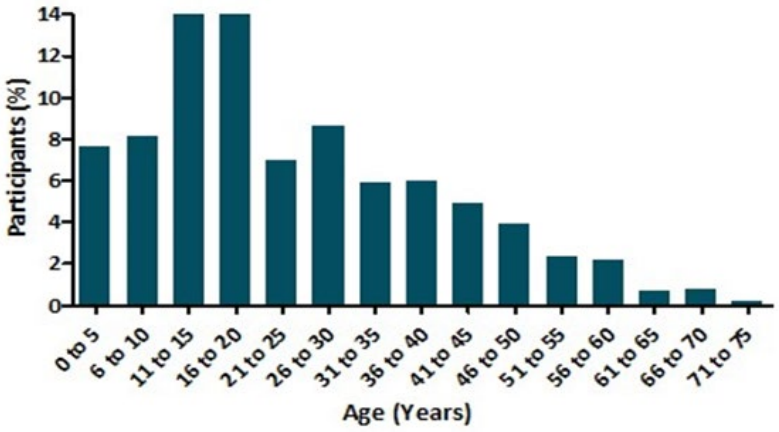


This graph demonstrates the variability that can be seen with presentation of FSHD.

40% of patients first experienced symptoms of FSHD between the ages of 11 – 20. Across all ages, scapular winging was the highest reported initial symptom (31%), followed by weakness in the legs/feet (22%) and weakness in the arms/hands (19%).

The variability of symptoms between individuals with FSHD can often delay their diagnosis. The age at which patients were diagnosed with FSHD can be seen in the bar graph below.

Age when diagnosed with FSHD



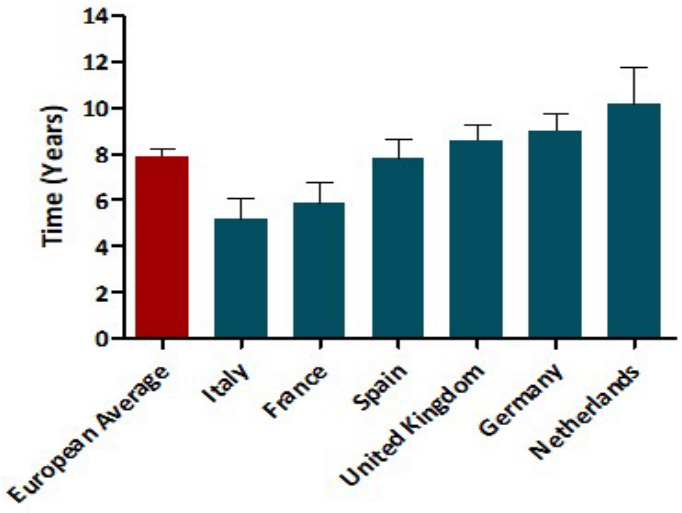
The next graph shows the average length of time it took from the first symptom of FSHD appearing to diagnosis of FSHD patients in different countries across Europe.

As seen on the previous page, FSHD can present with a variety of symptoms, distribution of muscle weakness and clinical severity. This variability can lead to further clinical investigations delaying diagnosis.

In general, the average time for accurate diagnosis of a rare disease is 4-5 years, but can be as long as a decade[1].

The average time from onset to diagnosis across participants from all countries (shown in red) was 7.9 years. The diagnostic gap varied between countries, with Italy having the smallest at 5.2 years and the Netherlands having the largest average at 10.1 years.

Time from first symptom to diagnosis

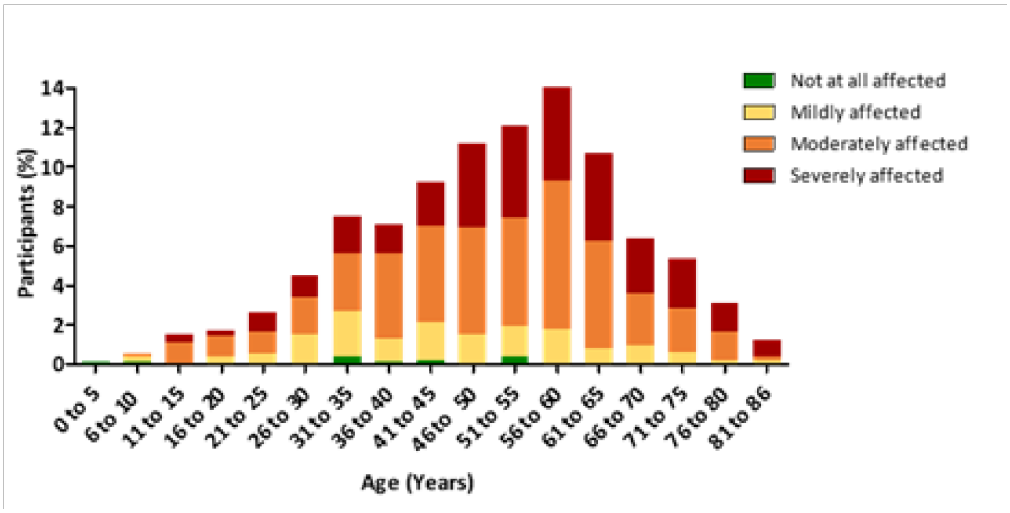


[1] Marwaha S, Knowles JW, Ashley EA. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. Genome Medicine 2022;14:1-22.

Reported severity of FSHD

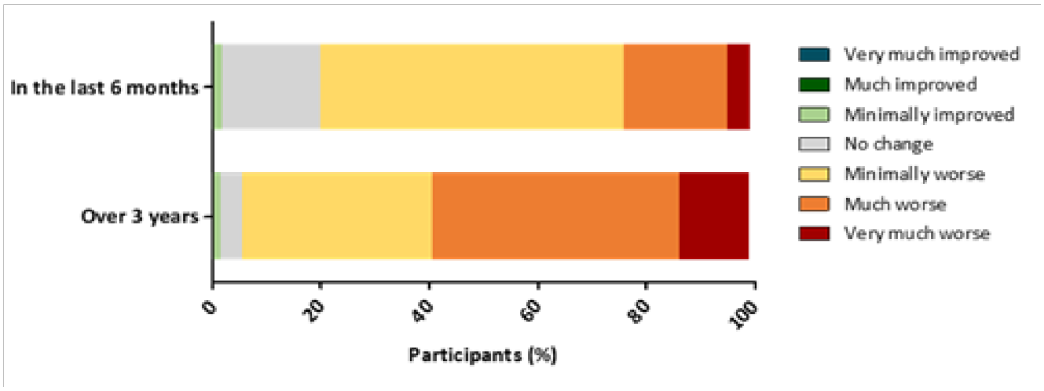
Participants were asked to report their severity from not at all affected, mildly affected, moderately affected, or severely affected. The results from this are shown in colours green, yellow, orange, and red respectively, and are plotted by the patient's age in the graph below.

How severe participants feel their FSHD is at their current age



The next graph shows how participants felt their condition had changed over time. The majority of respondents (55%) reported that their condition had got minimally worse in the past 6 months. 18% of respondents reported no change in their condition in the past 6 months. 46% of respondents reported that their condition had got much worse, and 13% reported their condition had got very much worse over the past three years.

Change in condition over time



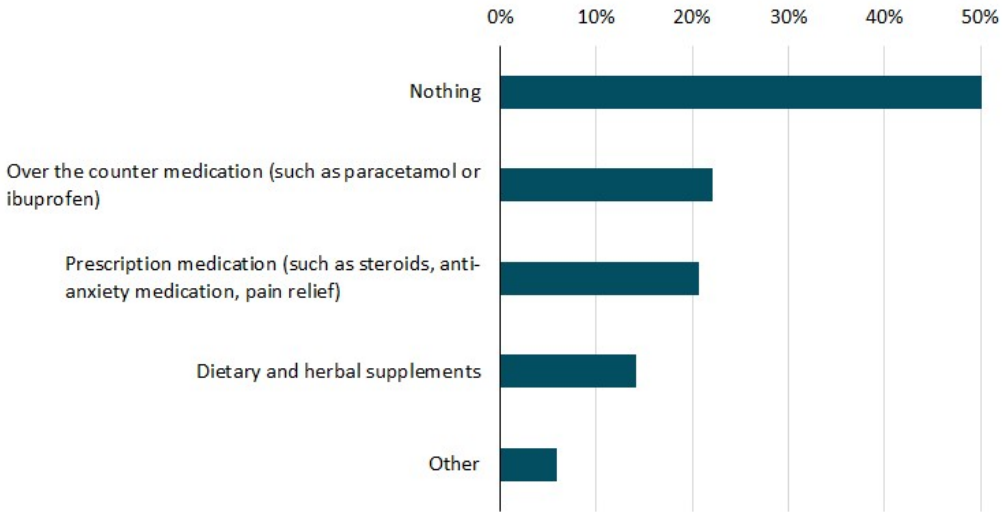
Current medications and therapies being used

There are no curative treatments for FSHD, with current treatment options aiming to slow disease progression or enhance the patient's quality of life.

Despite most participants in this study reporting to be moderately or severely affected by their FSHD, half reported they were not taking any medications to help their condition. Approximately 30% of participants felt that their treatment regimen did not control their overall condition and symptoms or controlled them 'very little'.

Many participants were taking several medications to manage a wide range of symptoms, such as pain relief, anti-inflammatories, anti-anxiety or anti-depression medications, medications for gastro-intestinal symptoms or hypertension.

Medications used to manage symptoms of FSHD



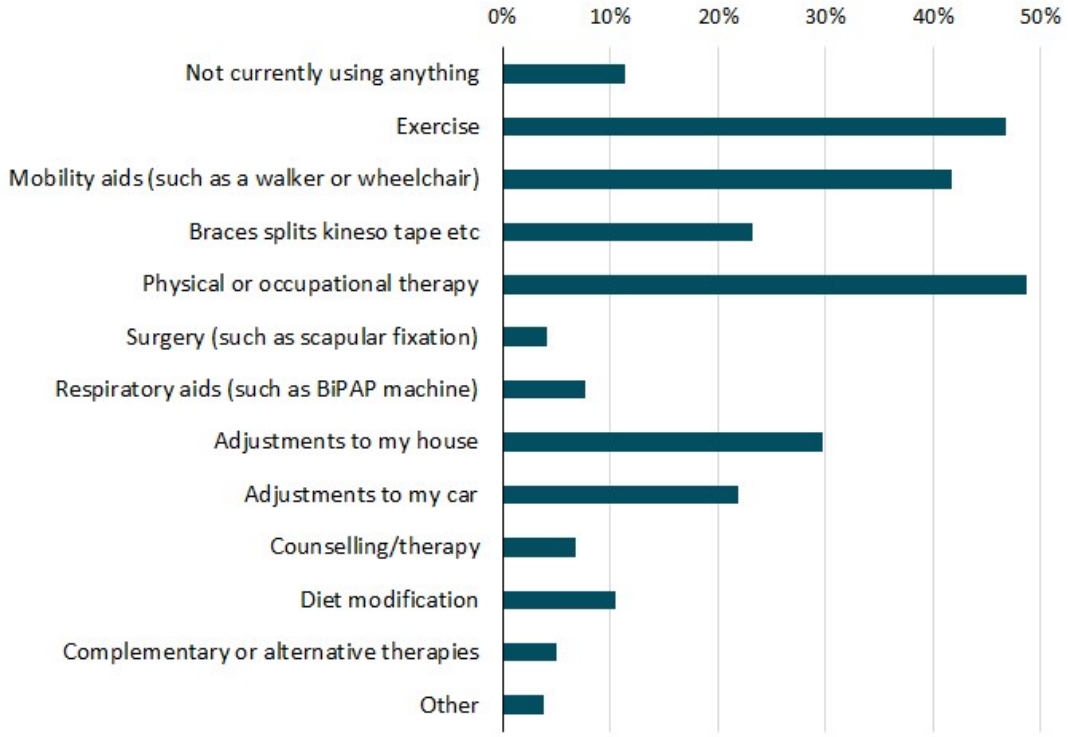
Painkillers were most frequently mentioned, with patients often taking several types of painkillers with varying strengths depending on their pain level. These included medications such as paracetamol, ibuprofen, amitriptyline, tramadol, codeine and morphine. Several respondents also reported that cannabis was part of their treatment regimen.

14% of respondents reported that they are taking dietary or herbal supplements to help their condition. Several participants mentioned the clinical trial which took place in the University

Hospital in Montpellier, France[2], and reported to be taking a combination of vitamin C, vitamin E, zinc gluconate and selenomethionine supplements.

Participants were also asked what therapies, other than medication, that they are currently using to help manage their symptoms of FSHD. Their responses can be seen in the bar graph below.

Therapies currently used to manage FSHD other than medication



The majority of participants were using some therapy to help with their condition, with 11% reporting that they were not currently using anything.

The largest proportion of respondents reported that they were using physical or occupational therapy, exercise and use of mobility aids to manage their condition.

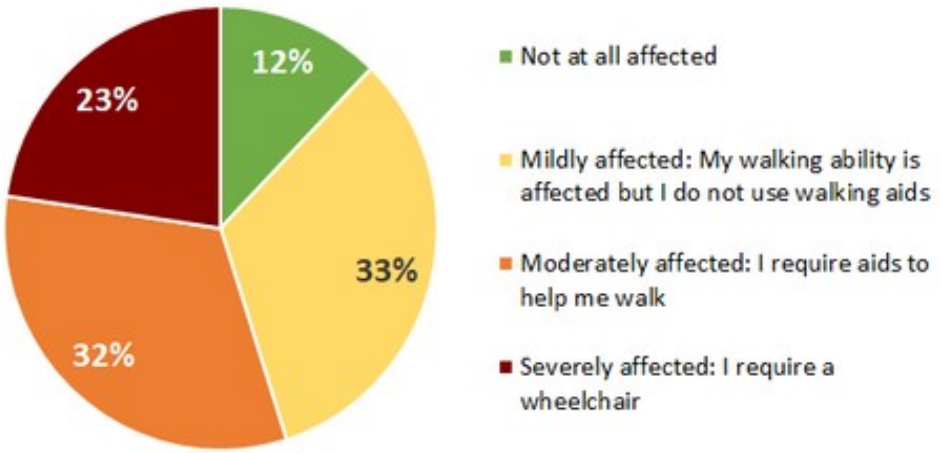
Free text "other" responses included massage, osteopathy, acupuncture, speech therapy, heat pads, hearing aids, carers or domestic help and adjustments to workstation.

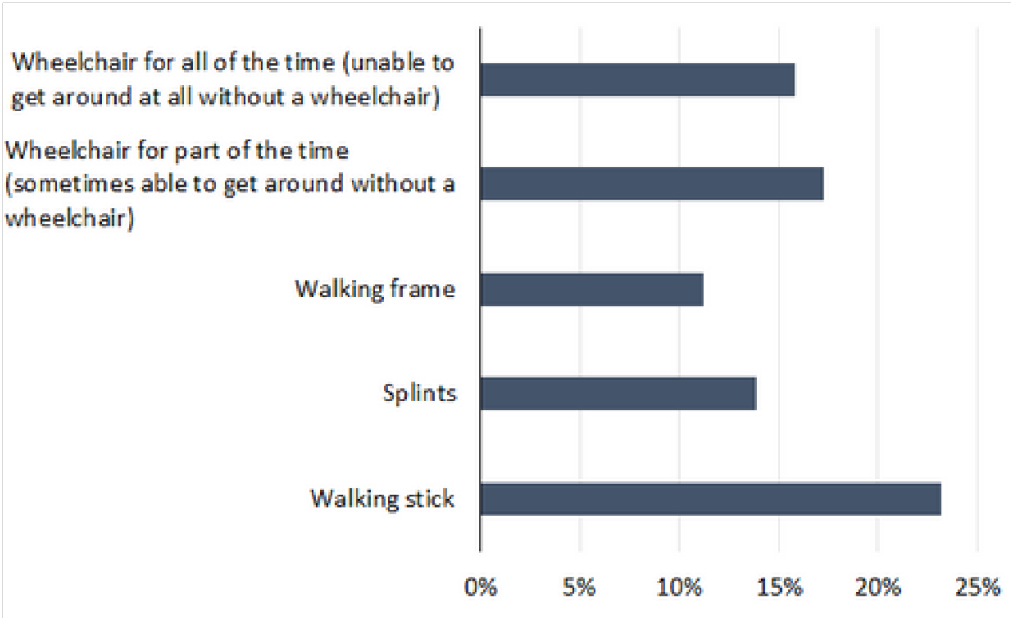
[2] Passerieux E, Hayot M, Jaussent A, et al. Effects of vitamin C, vitamin E, zinc gluconate, and selenomethionine supplementation on muscle function and oxidative stress biomarkers in patients with facioscapulohumeral dystrophy: a double-blind randomized controlled clinical trial. Free Radical Biology and Medicine 2015; 81:158-169.

Participants walking ability

Participants were asked how they felt their walking ability had been affected by FSHD, which can be seen in the pie chart below.

This shows that 55% of participants use walking aids or a wheelchair due to their FSHD. These people answered a further question about what aids they use to help them walk (shown in the bar graph)

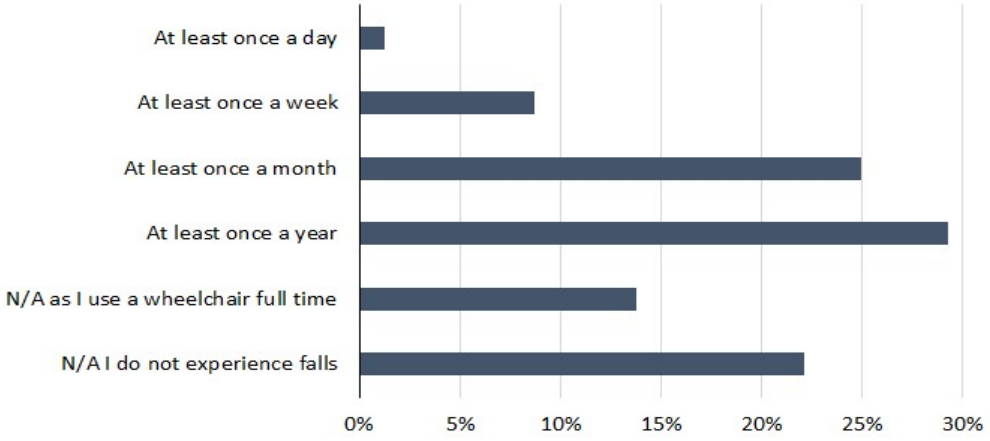




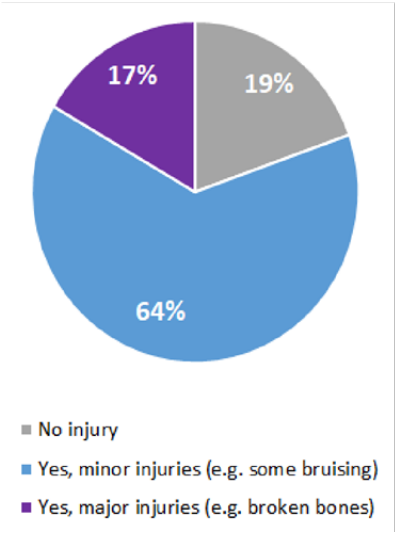
Weakness in muscles of the lower legs can lead to a condition called foot drop, which affects walking and increases the risk of falls[3]. Participants described how often they experienced falls due to their FSHD in the graph below.

The majority of people had experienced an injury due to a fall. 17% of people had experienced major injuries, such as a broken bone. Participants noted that the muscle weakness was the most common cause of their fall, followed by poor balance, and fatigue.

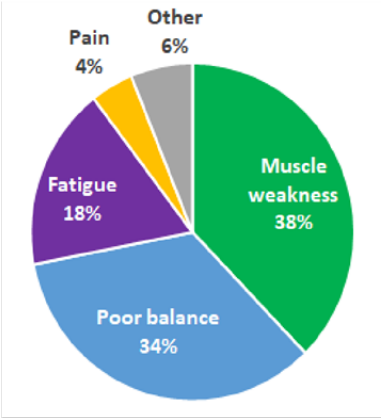
How often participants experience falls



Have participants experienced injuries due to a fall?



What causes participants to fall?



[3] Horlings, Corinne GC, et al. "Epidemiology and pathophysiology of falls in facioscapulohumeral disease." *Journal of Neurology, Neurosurgery & Psychiatry* 80.12 (2009): 1357-1363.

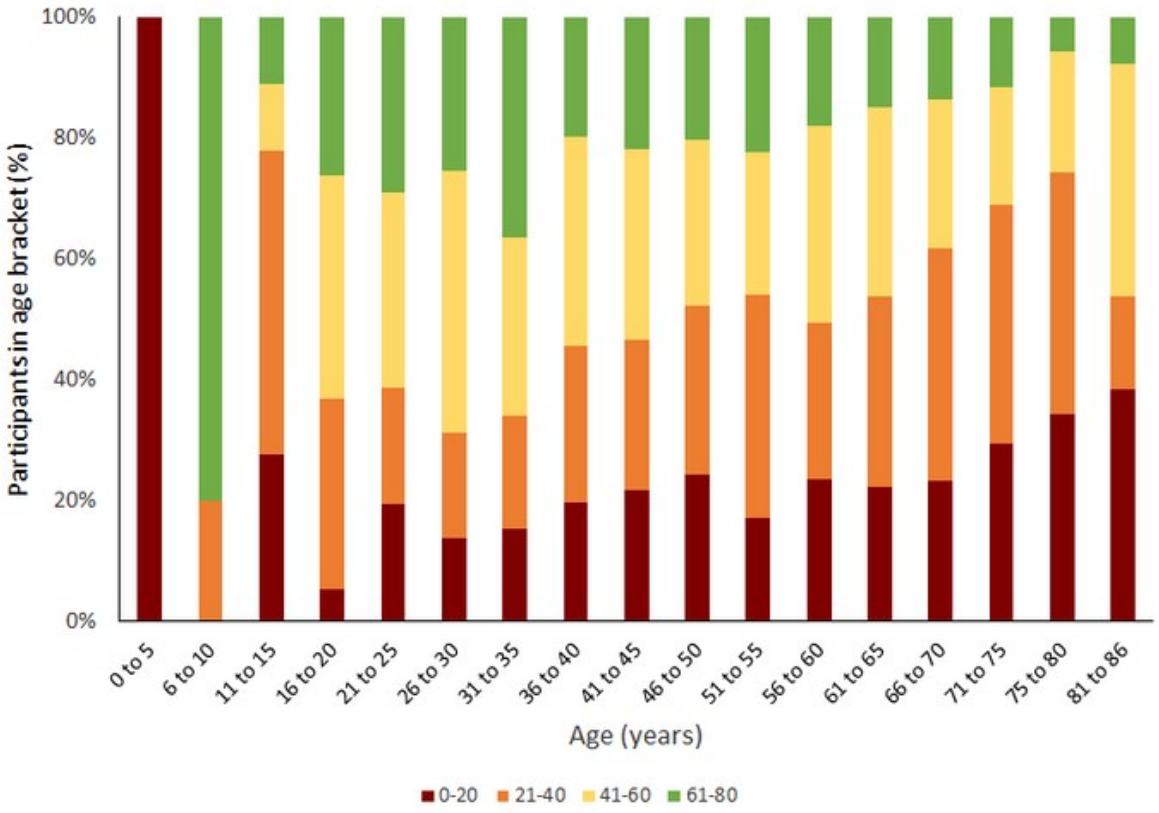
Participants upper limb mobility

Participants' upper limb function was measured using the "20-item Upper Extremity Functional Index" (UEFI-20). This index is used in individuals with upper extremity (including the shoulder, elbow, wrist and hand) mobility problems[4].

Each item on the index (e.g. brushing your hair, driving, and opening a jar), uses a scale for participants to rate difficulty in performing that activity using their shoulders, arms and hands. The scale goes from 0 (extreme difficulty or unable to perform activity) to 4 (no difficulty).

Adding the scores from all 20 items gives a total score from 0 (worst) to 80 (best) points.

Upper limb function by age of participants



The graph above shows the upper extremity function of participants by age group. The results show that the participants arm and shoulder function gradually gets worse with age.

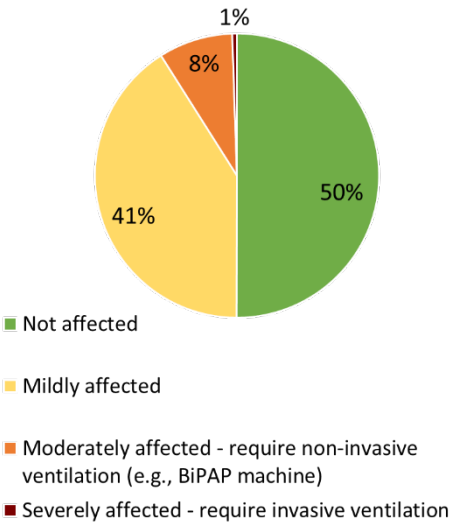
There was one participant under 5 years old, aged 2 years old.

[4] Stratford PW. Development and initial validation of the Upper Ectremity Functional Index. Physiother Can 2001; 52:259-267.

Other symptoms of FSHD

Respiratory health

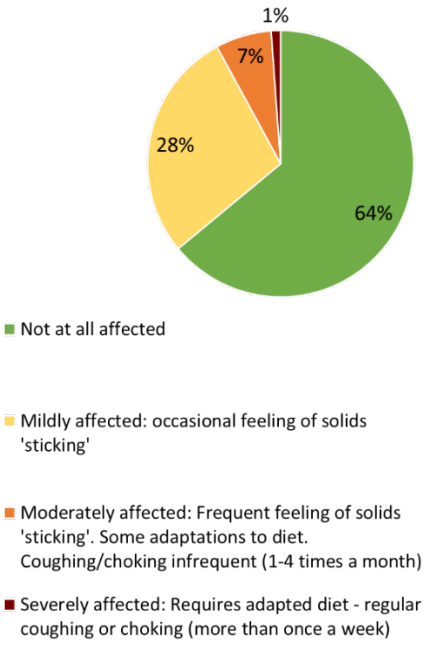
Previous studies have reported that approximately 10% of patients have some respiratory problems, most commonly in more severely affected patients[5]. This is similar to what was found in this survey, with 8% of participants requiring non-invasive ventilation (such as the use of a BiPAP machine) and 1% requiring invasive ventilation.



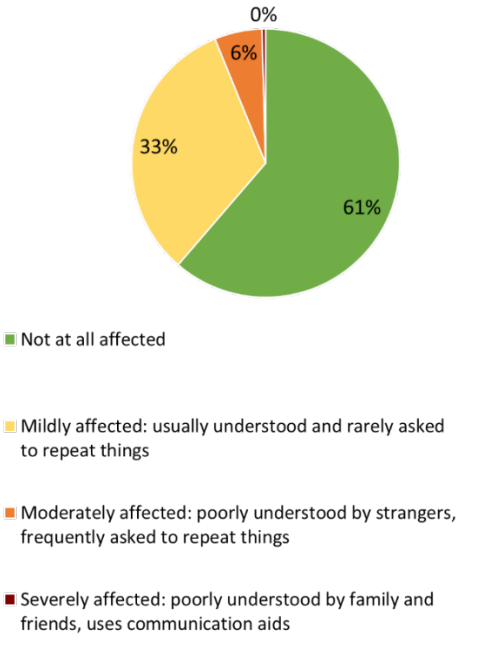
Weakness in facial muscles

Weakness in the muscles of the face and tongue can cause swallowing and communication difficulties in people with FSHD[6]. The graphs below show that these symptoms are experienced by the minority of people with FSHD.

Difficulties in swallowing



Difficulties in speech



[5] Jeffrey Statland RT. Facioscapulohumeral Muscular Dystrophy. Neurologic Clinics 2014;32

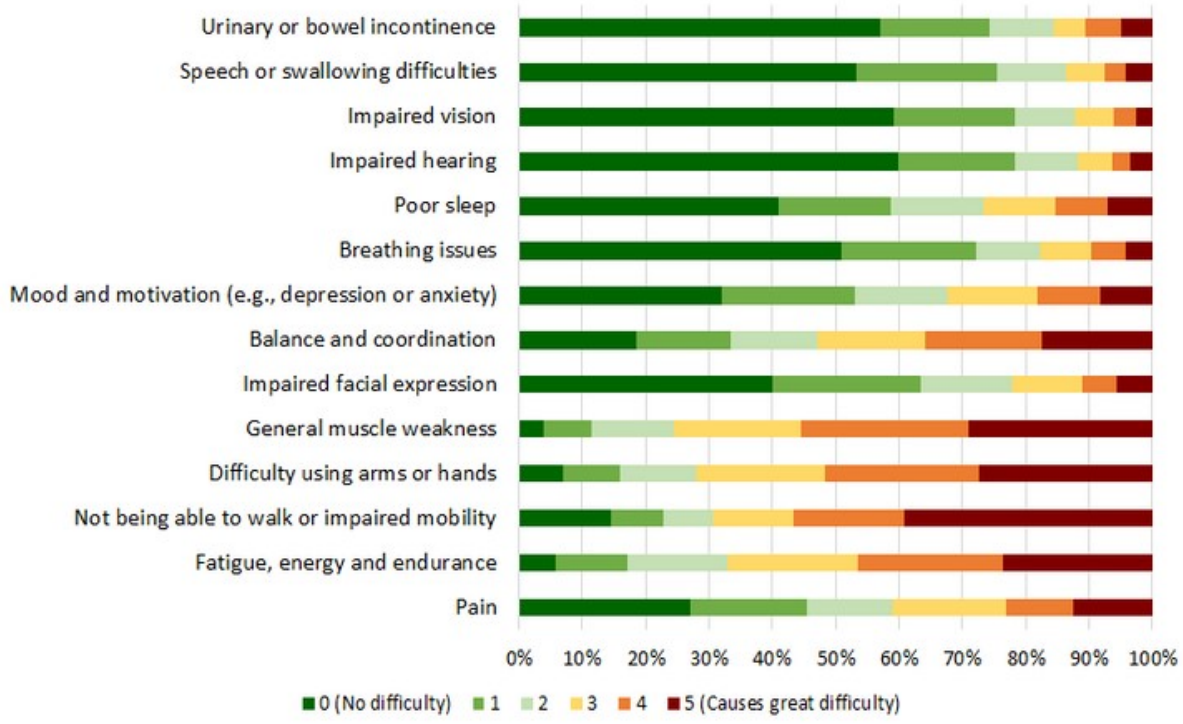
[6] Mul K, Berggren KN, Sills MY, et al. Effects of weakness of orofacial muscles on swallowing and communication in FSHD. Neurology 2019;92: e957-e963.

Which symptoms of FSHD cause the most difficulty in daily life

Participants were asked to rank how particular symptoms caused difficulty in daily life from 0 (no difficulty - shown in green) to 5 (causes great difficulty - shown in red).

Not being able to walk, or impaired mobility was the most commonly reported symptom to cause difficulty in daily life. This was followed by general muscle weakness, difficulty using arms and hands, and fatigue energy and endurance.

The symptoms causing the least difficulty in daily life for participants included impaired vision or hearing, and speech or swallowing difficulties.

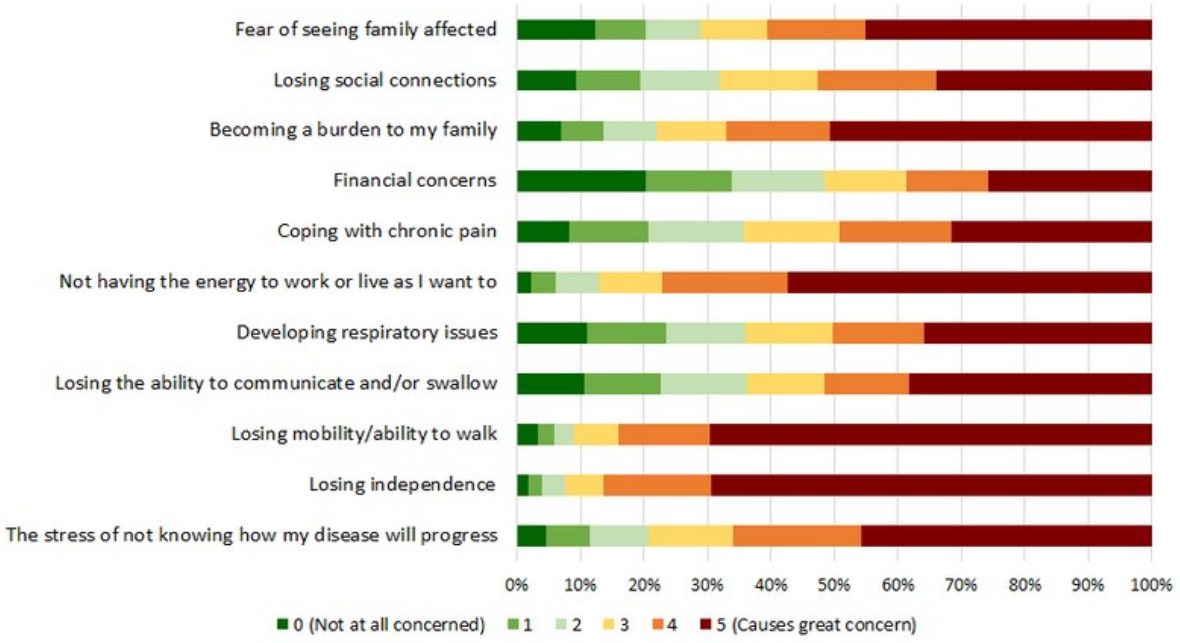


Concerns for the future

Participants were asked to rank what concerned them most about the future from 0 (not at all concerned – shown in green) to 5 (causes great concern – shown in red).

Participants reported that losing independence or the ability to walk concerned them the most, as well as not having the energy to live or work as they want to.

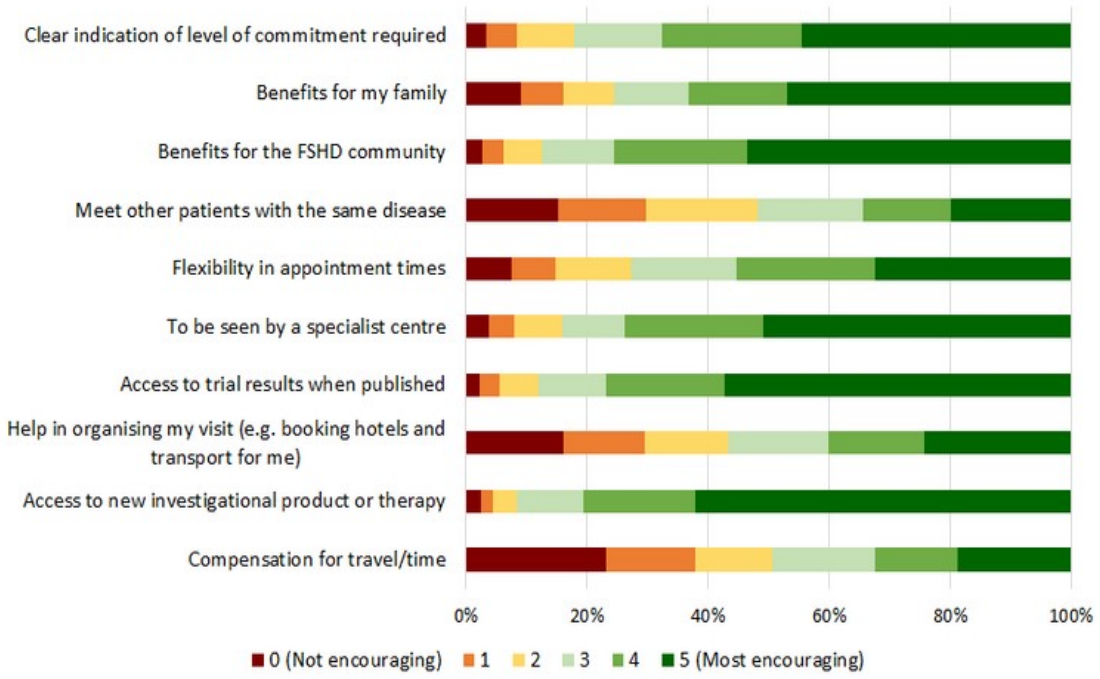
Finances were reported to be the least concerning for participants looking into the future, however over 50% of participants reported some level of concern.



Deciding to take part in a clinical trial

What would encourage participation in a clinical trial

Participants were asked to rank what factors would most encourage them to participate in a clinical trial from 0 (not encouraging – shown in red) to 5 (most encouraging – shown in green).



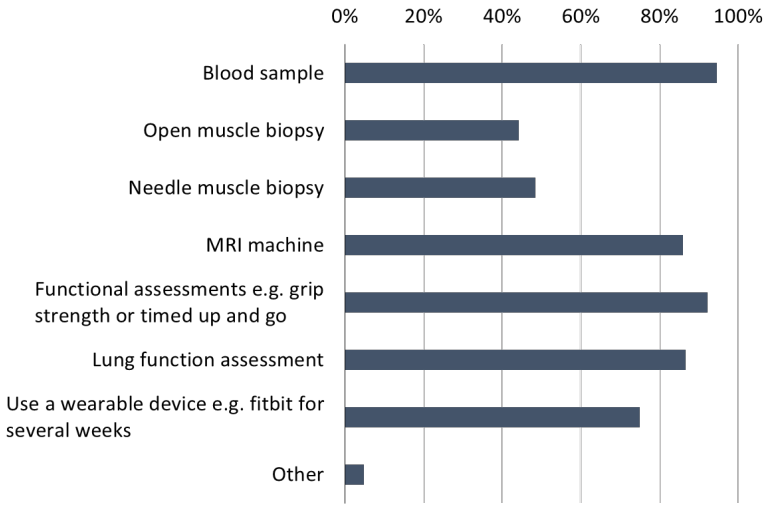
The most encouraging factor for patients to take part in a clinical trial was access to the investigational product or therapy. This was followed by access to trial results when published and benefits for the FSHD community. Participants could also note other factors not included in the list above, which are condensed into the bullet points below.

- Being seen locally or remotely (i.e. over video call) would be encouraging, which would remove the need for long travel.
- A thorough explanation of the trial and the risks involved, as well as a transparent selection process
- Many participants cited altruistic reasons, such as helping scientific research or helping family members and future generations with FSHD.
- Flexibility around work would be encouraging when participating in a clinical trial.
- Psychological support throughout the trial would be encouraging, as well as allowing for a companion to attend the trial (e.g. partner or friend).

Thoughts on clinical trial procedures

Participants were asked what procedures they might be willing to take part in during a clinical trial. The majority of participants were willing to take part in many of the procedures, with the exception of muscle biopsies.

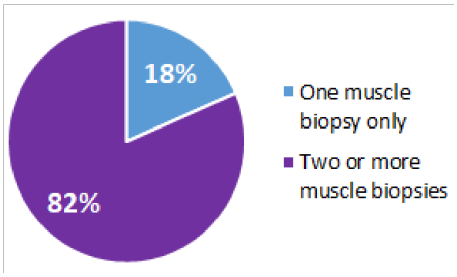
Less than 50% of participants would be willing to undertake a muscle biopsy. In the 'other' responses, some participants mentioned that having adequate anaesthetic or sedation might persuade them. Participants also noted that they would be more likely to take part in a muscle biopsy if time was taken to inform them on the necessity of the procedure and why no alternative was available.



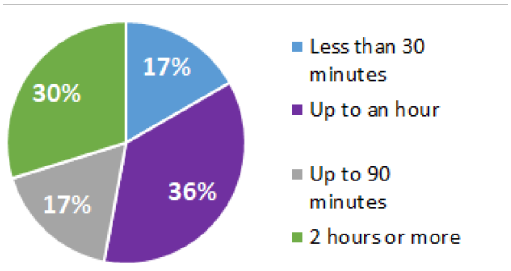
For those who responded they would be willing to undergo a muscle biopsy, 82% of people would be willing to undergo two or more muscle biopsies during a clinical trial.

For those who responded that they would be willing to undergo an MRI scan, participants indicated how long they would be willing or able to lie down in an MRI machine.

Number of muscle biopsies participants would be willing to have during a clinical trial



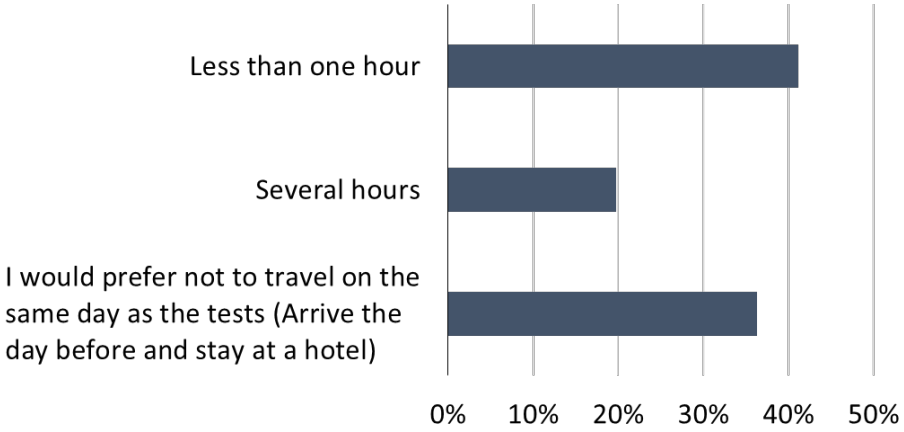
Time participants would be willing/able to spend in an MRI machine



Traveling with a neuromuscular condition such as FSHD can be strenuous, particularly for those with more severe symptoms. Participants indicated how long they might need to recover after travel, before taking part in a clinical trial.

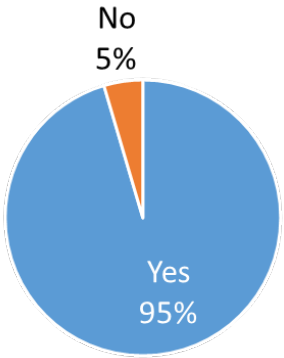
It is important that trial sites are aware of this to minimise discomfort and enhance safety and outcomes during trial procedures. For instance, if a participant was taking part in a strength test, it is better to allow them recovery time to ensure the best results are achieved.

How long a participant would need to recover after travel.

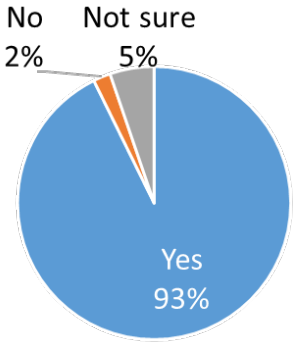


Participants reported that they would be able to take part in remote assessments, such as over the phone. The majority were also willing to complete self-monitoring assessments at home, and send the results back electronically.

Phone assessments

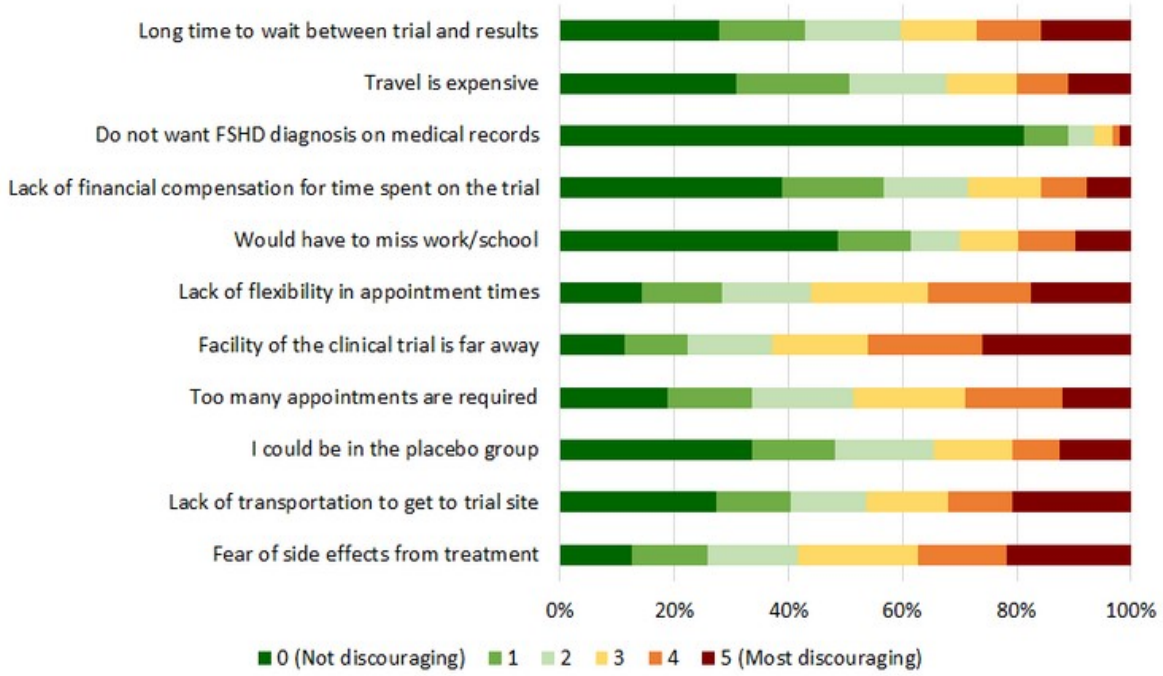


Self-monitoring assessments



What would discourage participation in a clinical trial

Participants were asked what would discourage them from participating in a clinical trial from 0 (not discouraging) to 5 (most discouraging).



The most discouraging factor for patients was if the facility conducting the trial was far away, followed by fear of side effects of treatment.

Participants could also note other factors not included in the list above, which are condensed into the bullet points below.

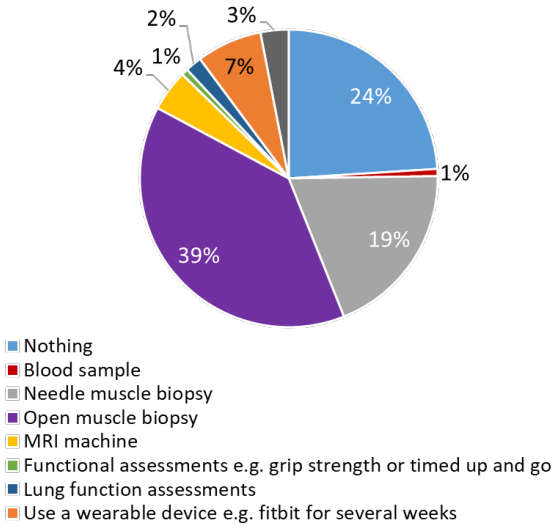
- Participants want to be well informed of what the aims of the trial are and what is expected from them as participants. Participants would also like to be well informed on the progress or the results of the trial.
- Trials should offer support to participants, especially if adverse events are experienced or if the trial is paused or ended unexpectedly.
- Lack of flexibility around work schedules or compensation for missed work could discourage clinical trial participation.
- Several uncertainties of participants were also noted, such as fear of painful or invasive tests, placebo or additional deterioration of their condition.

Participants were asked about which specific tests or side effects they may be concerned about experiencing and may discourage them from participating in a clinical trial.

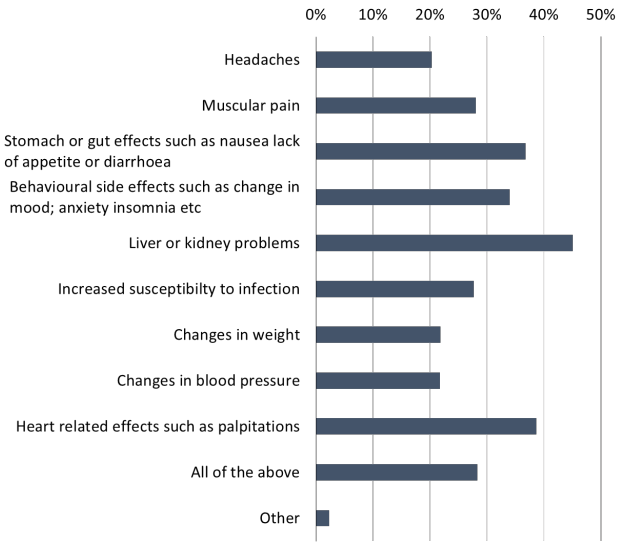
Muscle biopsies were again shown to be the procedure that participants found to be most discouraging for them taking part in a clinical trial. However, several participants noted that they may be more willing to participate with adequate and thorough explanation of the procedures and trial processes.

Participants were most concerned about experiencing side effects causing liver and kidney related problems. However, this does not take into account the level of risk that a person might be willing to take for a specific procedure or therapy. 24% of participants said that no procedure would discourage them from participation in a clinical trial at all.

Procedures discouraging clinical trial participation



Side effects that participants would be concerned about experiencing



Understanding what procedures and side effects are most discouraging for patients should help inform how health care professionals approach conversations about their use in a clinical trial.

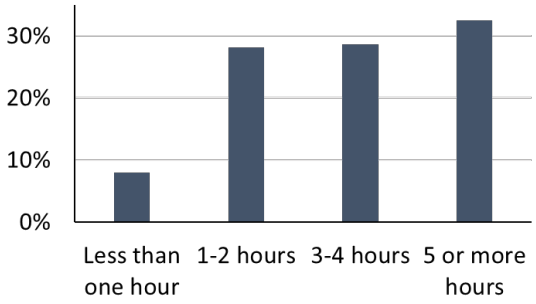
Participants have access to a wide variety of information sources online. However, it is important that they are informed of any risks from procedures or potential side effects of therapies using reliable, rational information provided by the experts in the trial themselves.

Travelling to take part in a clinical trial

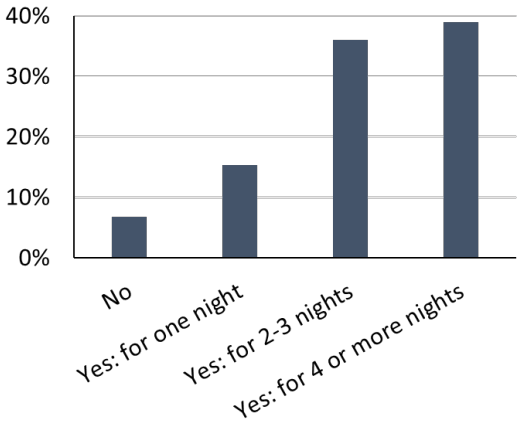
Despite the distance of a trial facility being a discouraging factor for trial participation, the majority of participants would be willing to travel to take part in a clinical trial, and stay overnight in a hotel that was suitably equipped to meet their needs.

Overnight stays should be clearly indicated when advertising for a clinical trial – travel with limited mobility can be difficult and participants may need to arrange childcare for example.

How long participants would be willing to travel to take part in a clinical trial



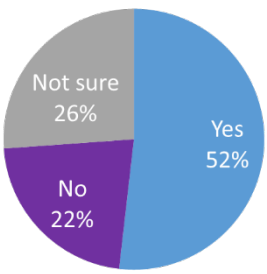
How long participants would be willing to stay away from home



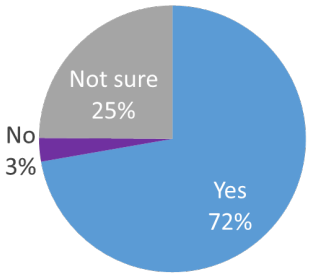
Over half of patients reported that they would be willing to travel to a different country to take part in a clinical trial. Of those, the majority would be willing to travel to a country with a different language to their own.

Adequate help in organising travel, reimbursement of travel costs or the possibility to be seen by a local clinic or remotely could encourage greater participation in clinical trials.

Participants that would be willing to travel abroad for a clinical trial



Participants that would travel to a country with a different language for a trial



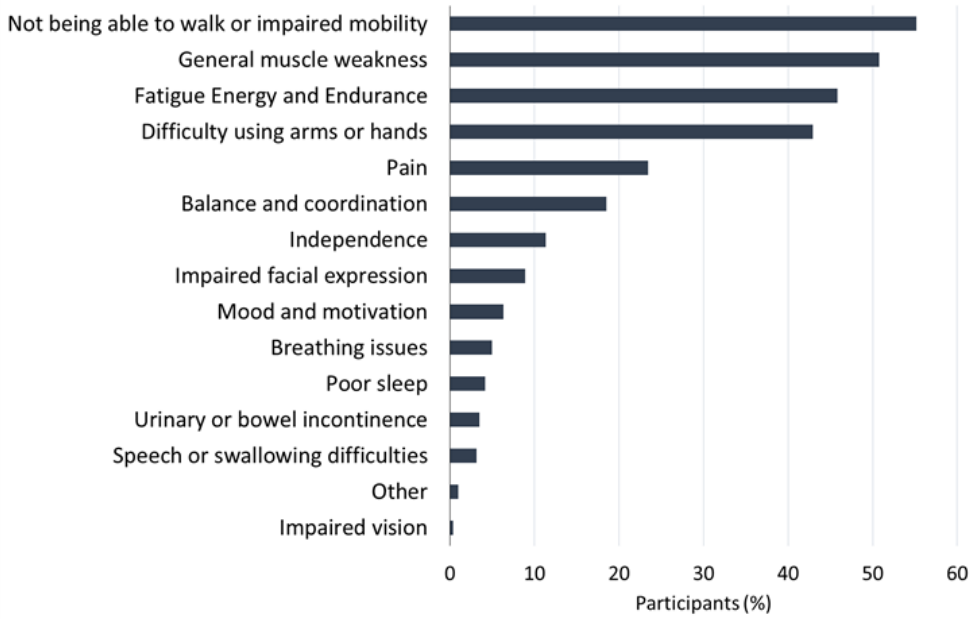
Expectations of a clinical trial

Potential benefits of clinical trials

The symptoms causing the most difficulty in daily life reflected were mainly due to the progressive muscle weakness that is experienced by people with FSHD.

This was reflected in the symptoms that patients would like to be improved first when designing clinical trials. Participants noted that impaired mobility and general muscle weakness were the symptoms that they would like to be improved first through a new therapy.

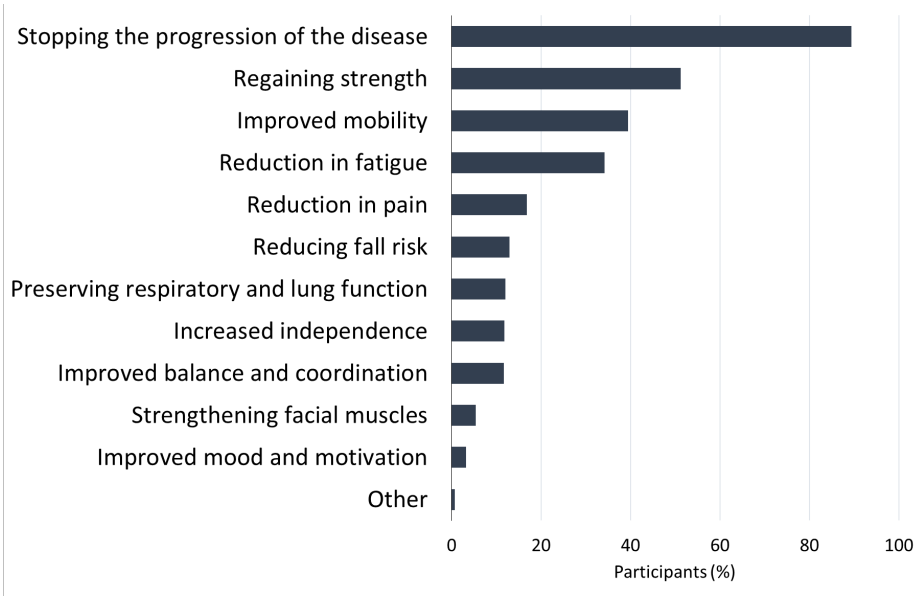
Which symptom participants would like to be improved first



Stopping the progression of the disease was ranked most highly by participants (31%), followed by regaining strength (18%) and improved mobility (14%) for what is the most important outcome when trialling a new therapy.

Mobility and muscle strength are clearly important to FSHD patients and should be considered when designing therapies as well as meaningful endpoints for clinical trials in FSHD.

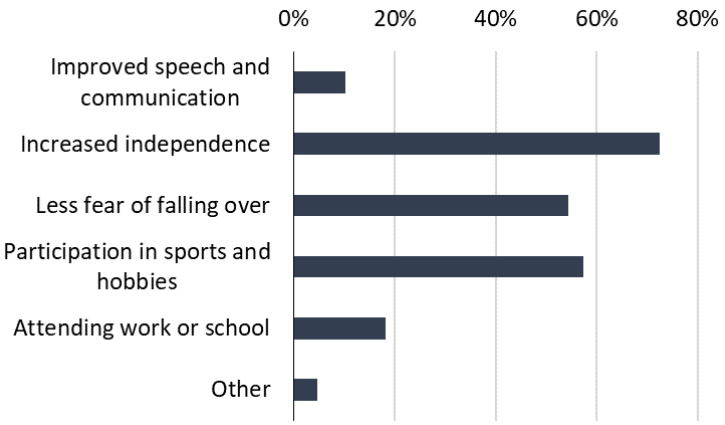
The most important outcome of a new therapy



Increased independence was considered to be the most important social benefit for participants. Participants could also note other factors not included in the list in the graph below, which are condensed into the following bullet points:

- Increased ability to take part in social activities and events, such as going for a walk with friends or family, looking after children and grandchildren as well as generally being more active were considered important
- Improved mood, confidence and energy, as well as easing pain were also noted.
- Some symptoms were directly mentioned, such as improvements in swallowing/eating, cardiac problems and weight.

Social benefits that participants consider most important



Expectations of communications

Several participants noted that they had taken part in trials before and not received any results. We suggest that an open and clear communication and information provided to current and prospective trial participants could potentially increase trial recruitment and improve participant experiences.

The expectations of participants should be managed to understand the timelines of the trial and results, and support provided in case of trial termination.

Trial sponsors, sites and patient organisations can contribute to ensure that information is widely available and accessible. Further funding in patient education initiatives as well as communication for healthcare professionals could also help to bridge this gap.

Conclusions

We would like to take this opportunity to thank all of the participants of this survey, without whom this research would not have been possible.

A total of 1147 participants responded to the survey representing 26 countries across Europe. This survey provided an opportunity to understand patient preferences from a broad range of the FSHD community, for instance from differing disabilities (mild, moderate and severely affected patients), ages (from aged 2 to 86) and diagnoses (FSHD type I and II).

This study highlighted the key symptoms causing concern for FSHD patients including muscle weakness and mobility issues, both of which scored highly when asking about symptoms that caused difficulty to participants in their daily lives. These symptoms were also reflected when asked what participants would like to be targeted first in future clinical trials.

The expectations and opinions of people with FSHD and their caregivers about clinical trials were also explored. Participants highlighted the need for clear information and communication throughout their participation in a clinical trial, as well as the importance of feedback of the results of a trial.

The factors that participants found most encouraging for clinical trial participation included access to new investigational therapy, access to trial results and benefits for the FSHD community.

The factors that participants found most discouraging for clinical trial participation included distance to trial site, fear of side effects and lack of transportation to get to the trial site.

The results from this study should provide researchers and industry with areas of therapeutic research that would be meaningful to people with FSHD. It could also be used to help develop and design clinical trials to ensure they maximise patient involvement and participation. The study provides an insight into symptoms that are most important to patients, as well as gaps in therapies that are currently offered to people with FSHD.