UK FSHD Patient Registry Newsletter

Issue 3
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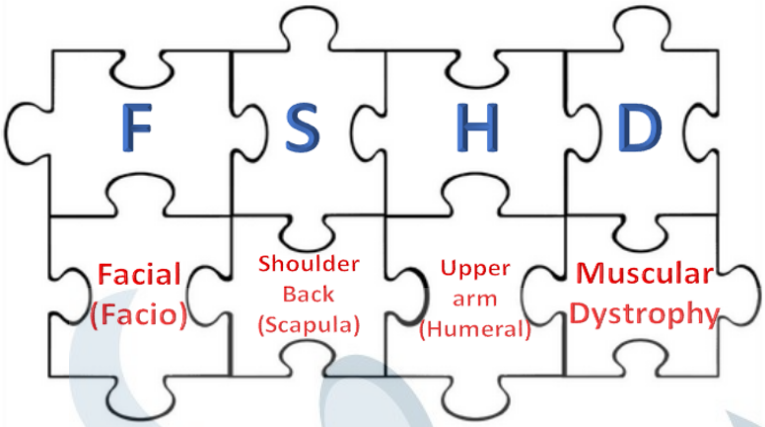
https://www.fshd-registry.org/uk/

The registry is only as useful as the information it contains
Remember to update your details!

We are pleased to see the registry is still growing and as of June 2017 we have over 770 active participants. We would like to thank you all for being involved. The registry has proved useful for a number of different research studies over the last few years. As research into FSHD continues to grow worldwide we would like to use the newsletter to explain more about clinical research, what that means, and how you can be involved.



What is Clinical Research?

Figure 1: Comments about Clinical research

Clinical research is what clinicians and researchers do to better understand, prevent, treat and diagnose diseases. Clinical research involves human participants and is the step in between basic research (done in labs) and clinical practice. An example of clinical research are the studies used to prove the safety and efficacy of a new drug, a new intervention or a new device. In this newsletter we want to introduce you to different types of studies under clinical research

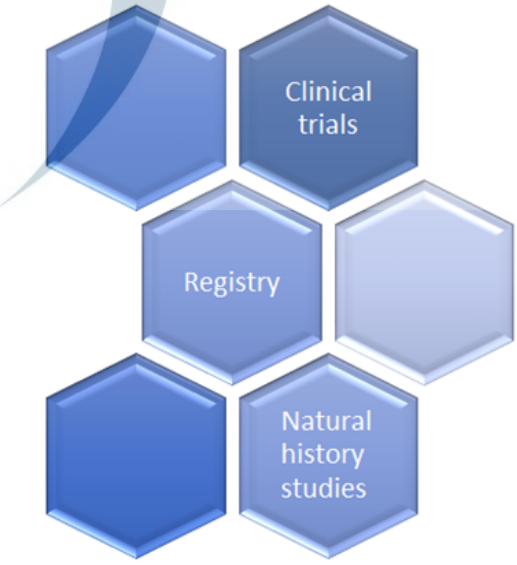
Different Types of Clinical Research

There are two main types of studies that we will be discussing here:

Natural history studies are a type of clinical research studies that involve observing the normal progression of a disease and measuring certain traits and functions. They typically involve a variety of tests repeated over a series of months or years. A natural history study does not involve any new treatments or therapies but can help with the design of clinical trials as they inform the researchers about the normal progression of a disease

Clinical trials typically involve the testing of a new treatment or therapy in people. This includes new drugs. These studies are used to determine how safe and how effective new medications and treatments might be. They are also referred to as interventional studies. At present clinical research in FSHD has shown a significant increase. A number of natural history studies are carried out and some pharmaceutical companies are in the early stages of clinical trials. Some of these studies are described later in this newsletter. All clinical research studies are carried out in carefully controlled conditions adhering to strict rules and regulations. It can involve lots of new words and phrases. You can obtain more information online at www.clinicaltrials.gov. You can discuss anything you read here with your doctor who might be able to answer any questions.

Figure 2: Types of Clinical Research



News!!! Recently, on 24th of March, Muscular Dystrophy UK held an information day for people affected by FSHD, which took place in London. We have attached a summary of the day and what was discussed in the FSHD workshop.

Natural History Studies:

One thing about FSHD that makes it hard for doctors, researchers and scientists to understand it is how it affects people differently even in the same familly. This will make it hard to know if a drug is working or not. Natural history studies follow large numbers of people with FSHD overtime to measure what is the same and what is different in people. This will help to identify patterns or groups of people who are affected in the same way. Natural history studies also look to see what changes over time and how long it takes, this is important if a drug is developed that slows down the progression of the disease.

A natural history study is like the control group of a clinical trial, it shows what is "normal" for people with FSHD. If something is changed, for better or worse, by a new treatment it is important to be able to identify that. Natural history studies often include lots of different tests and measurements, these are known as outcome measures. Natural history studies are often used so that we can test to see which outcome measures work best. More about outcome measures is described later in this newsletter.

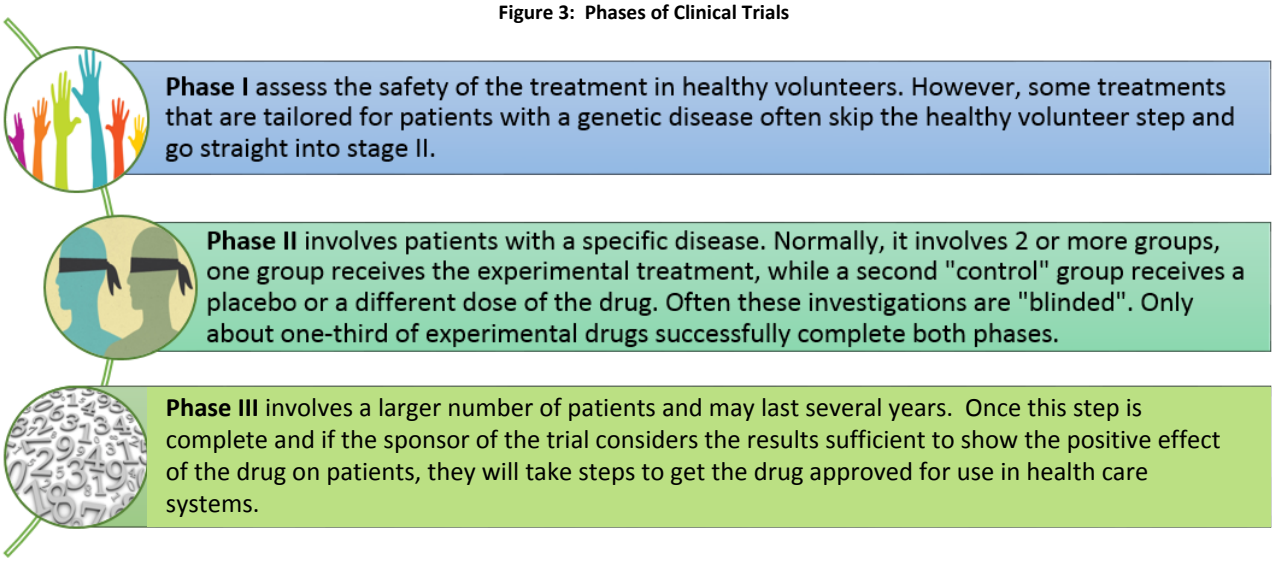
Clinical Trials

Clinical trials are designed to test new treatments and therapies both to see if they are safe and if they work as expected. It is important to understand, that just because a new treatment is in a clinical trial it does not mean that it will be safe or even effective. A clinical trial is a test to find that out.

What are the different phases of clinical trials?

Before a new treatment or therapy can be approved for general use it must go through a number of trials. These different trials are called phases. There are usually three phases (phase I, phase II, phase III) and each phase builds on the results of the previous step. Although positive results in an early phase may be encouraging, it does not guarantee that a new treatment or therapy works. As a treatment or therapy moves through these phases they require more people to be involved and the design can change depending on the research question. Below we describe the different phases in more detail.

Figure 3: Phases of Clinical Trials



The role of Pharmaceutical Companies in Clinical trials

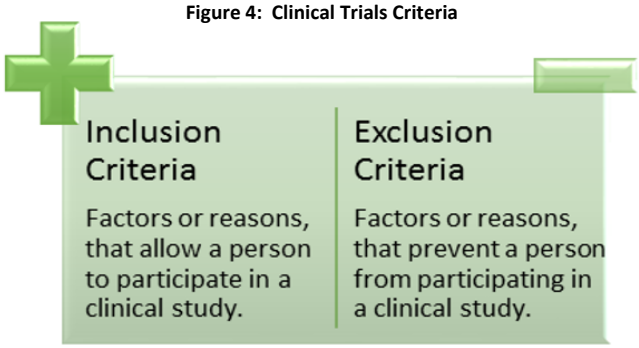
Normally a new treatment or therapy is developed by a pharmaceutical company. These companies usually provide the funding for clinical trials. They are in charge of the design of the trial and they decide if a trial is successful enough to move to the next phase. Pharmaceutical companies normally work closely with researchers and doctors to ensure the greatest chance of success.

Who can take part in clinical trials?

It is not possible for everyone to take part in a clinical trial. There are strict rules about who can and cannot take part, these are called inclusion and exclusion criteria. These criteria are often needed to ensure that the people taking part are put at as little risk as possible. These criteria are also put in place to make sure it will be possible to see if the drug is working. For example if it is proposed that a drug reduces pain, it would not be possible to test this in a group of people who do not experience pain. These criteria are often very detailed and complex, if you have questions about the criteria of a specific trial it is always best to discuss them with your doctor in the first instance.

The first time you visit any clinical trial site you will take part in a screening visit. These visits are an opportunity for the staff involved in the trial to check if you meet the criteria.

Figure 4: Clinical Trials Criteria



How are trials designed?

Every clinical trial is designed slightly differently this is because they are all answering different questions. The design of a study can depend on lots of different factors such as how many patients might be available to take part, or the type of treatment or therapy being developed (e.g. a tablet or an injection)

However, there are some common terms used when describing trials and some of these are listed on the side panel of this page.

Figure 5: Circle of New Treatment

Placebo

A Placebo is a "dummy" version of a drug. They are made to have the same appearance as the treatment being tested, however, do not contain an active substance. These are administered to what is called the control group in a trial. This is sometimes necessary so that researchers have a group of patients having exactly the same experience as those taking the drug to see if there is any difference. However, not all studies use a placebo. When placebo is not applicable, usual care will be the method of control.

Randomised study

When a study involves a placebo it is often related to a randomised controlled trial. This means that it is completely by chance if the person involved receives the active treatment or the placebo. The researchers involved have no control over which group their patients/participants are in. It is normally decided by a computer and there often is a 50/50 chance you will receive the placebo. Not all studies using a placebo are designed in this way.

Blinded study

When a placebo is involved in a study it is important that the research team do not know who is receiving the active drug and who is receiving the placebo. This prevents the researchers from acting differently around the participant, and stops them from making different decisions during assessments. This means that a study is blinded.

How do we know if a clinical trial is successful?

A crucial thing about a clinical trial is to be able to accurately measure if a drug or therapy is working or not. Not all drugs will reverse all symptoms so sometimes it might be a subtle change. When a clinical trial is being designed, you must choose one aspect of the disease to be your "primary outcome measure". This is the thing you are looking at for change, if this aspect of the disease improves then your drug works.

It is important that the outcome is easy to measure and sensitive to change. Some examples of outcome measures that can be included in trials are:

- **Time to walk 10 meters**
- **How many times you can sit and stand (30 sec.)**
- **A measure of pain**
- **A breathing test**

If the outcome measure that is chosen doesn't show change it will take longer to determine if it works or not, it could even mean that research into that drug will stop.

As you can see, there are many different steps involved in clinical research.

There is a lot of work being carried out to move things forward as fast as possible. In the rest of this newsletter we will discuss some of the clinical research studies that are ongoing in the UK and around the world at the moment.

Outcome Measures

An outcome measure is a test that is used to determine how well a new treatment or therapy is working. This is used at the start of a study and then at every visit so that changes can be measured. In diseases such as FSHD outcome measures are often functional and involve a physiotherapist. However, they can also be questionnaires or the results of blood tests and scans.

Biomarkers

Sometimes outcome measures are not measures of things you can or can't do or feel. Biomarkers are types of outcome measures that do not test functional change. They are changes in the body that can be measured; this could be a certain molecule in your blood, or the amount of muscle that is seen on a scan of your leg.

RESOLARIS

This phase 1/2b study is taking place in the USA and Europe. The first outcomes of safety and biological activity of Resolaris (ATYR1940) in patients with early onset Facioscapulohumeral Muscular Dystrophy (FSHD) are pending publication (Study completed in April 2017), while the results of evaluation of the long-term safety, tolerability, and biological activity of ATYR1940 in patients with Facioscapulohumeral Muscular Dystrophy (FSHD) estimated to be available in September of 2018. Both studies sponsored by Atryrpharma are ongoing, but they are not recruiting new patients.

In the preclinical part of this trial, they observed that Resolaris alters immune responses and the expression or release of immune-related proteins from cells in response to inflammation. They are currently evaluating Resolaris as a potential therapy in myopathies, such as FSHD, in which the muscle tissue itself and the blood clearly reflect immune dysregulation. In contrast to most current immunomodulatory or immunosupressor drugs, Resolaris is derived from a naturally occurring protein, HARS, which is believed to have the potential to reset the immune system in diseased tissue to a more normal state in a non-immunosuppressive manner.

Evaluate Safety and Biological Activity of ATYR1940 in Patients With Early Onset FSHD: https://clinicaltrials.gov/ct2/show/NCT02836418?term=ATYR1940&rank=2

Study to Evaluate the Long-Term Safety, Tolerability, and Biological Activity of ATYR1940 in Patients With Limb Girdle and FSHD: https://clinicaltrials.gov/ct2/show/NCT02836418?term=ATYR1940&rank=2

For more information: http://www.atyrpharma.com/programs/resolaris/

ACE-083 (Prototype Name)

This phase 2 study, to evaluate the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of ACE 083 in patients with FSHD, is running in different centres of the U.S. It is sponsored by Acceleron Pharma and is currently recruiting participants. It is estimated to have the first outcomes in the first part of 2019. ACE-083 is a product candidate in the neuromuscular therapeutic programme of Acceleron Pharma company. It is a locally active agent that may be useful for diseases with focal muscle loss such as Facioscapulohumeral Muscular Dystrophy (FSHD). ACE-083 is designed to increase strength and function in specifically targeted muscles and improve patient function and quality of life.

ACE-083 works by binding to and inhibiting select proteins in the TGF-β protein superfamily that negatively regulate (reduce) muscle growth, such as activins and myostatin (GDF8). This is believed to increase mass and strength in the muscle where the drug is administered. Untreated muscles or other organs are not affected, reducing the potential for systemic side effects.

In a Phase 1 study in healthy volunteers, ACE-083 produced substantial dose-dependent increase in muscle volume, with the highest dose generating an unprecedented 14.5% increase in muscle volume.

Study of ACE-083 in Patients With Facioscapulohumeral Muscular Dystrophy (FSHD): https://clinicaltrials.gov/ct2/show/NCT02927080?term=ACE-083&rank=2

For more information: http://acceleronpharma.com/product-candidates/ace-083/

APABETALONE

This drug is under investigation in Phase 3 clinical trials with patients at high-risk of cardiovascular disease with Type 2 diabetes and low high-density lipoprotein (HDL), is taking place in Israel, sponsored by Resverlogix Pharma company. Apabetalone (RVX-208) belongs to a group of compounds called BET bromodomain inhibitors that bind to a specific region of the BET proteins, inhibiting their activity.

Previous studies have shown that bromodomain inhibitors (BET), such as Apabetalone, suppressed the expression of the DUX4 gene, which is abnormally active in the muscles of FSHD patients, causing inflammation and muscle atrophy. , Researchers have also found that apabetalone switches off DUX4 gene activity (expression) without affecting the activity (expression) of other genes important for muscle cell maturation. These findings suggest that treatment of FSHD patients with apabetalone may become a promising therapeutic strategy to improve FSHD symptoms. Although these are promissing findings the company has to conduct a clinical trial with FSHD patients to proof these pre-clinical findings.

Effect of RVX000222 on Time to Major Adverse Cardiovascular Events in High-Risk T2DM Subjects With CAD (BETonMACE):
https://clinicaltrials.gov/ct2/show/NCT02586155?term=RVX-208&rank=5

https://musculardystrophynews.com/2017/02/17/apabetalone-toxic-gene-rare-muscular-dystrophy-fshd/

Although there is not an effective treatment yet available for FSHD, emerging therapies are under way and this calls for a better understanding of the natural history in this condition.

Exercise as always been seen as a matter of controversy in neuromuscular diseases. In recent years it is more and more consensual that physical activity is not deleterious in myopathies, including muscular dystrophies. In the last decade exercise has become the subject of numerous studies in the neuromuscular field, worldwide . In FSHD the following are ongoing or waiting publication of final results.

A MULTICENTRE COLLABORATIVE STUDY ON THE CLINICAL FEATURES, EXPRESSION PROFILING, AND QUALITY OF LIFE OF INFLANTILE ONSET FSHD

The purpose of this study is to establish a standardized functional testing protocol able to measure longitudinal changes in muscle strength and function among patients with infantile onset FSHD. The researchers also aim to describe the longitudinal changes in the clinical phenotypes, to evaluate the long-term impact of physical impairment, secondary health conditions, activity limitations and disability caused by FSHD on health-related quality of life and disability, and to discover genetic modifiers and biomarkers in infantile FSHD.

This study involves several centres around the world (*This study is ongoing, but not recruiting participants.*). The UK is represented by Newcastle University. This study is sponsored by FSH Society Inc., FSHD Global Research Foundation, and aTyr Pharma Inc.This study is listed on clinicaltrials.gov at:
https://clinicaltrials.gov/ct2/show/NCT01437345?term=FSHD&rank=10

ACCEPTANCE & COMMITMENT THERAPY FOR MUSCLE DISEASE (ACTMuS)

There has been limited research to evaluate interventions that may improve quality of life (QoL). The QoL of those with Muscular Dystrophy is not just affected by the severity of their Muscular Dystrophy but also by a variety of psychological variables. Based upon the knowledge of these psychological variables the investigators felt that a particular type of psychological intervention known as "acceptance and commitment therapy" (ACT) could potentially improve QoL in those with Muscular Dystrophy. FSHD is one of the diseases included in this study and part of the participants have been recruited through the UK FSHD registry. It is taking place in London and is currently recruiting patients. They have estimated primary completion date in July 2018.

For more information:
https://clinicaltrials.gov/ct2/show/NCT02810028?term=actmus&rank=1

In clinic FSHD patients are often asked to have a muscle MRI, the study bellow shows one more reason to continue to use MRI as a tool in the diagnostic and evolution of your disease.

Acceptance and commitment therapy (ACT) is a form of psychotherapy frequently described as a form of Cognitive behavioural therapy (CBT), which is a psycho-social therapy focused on the development of strategies that target solving current negative thoughts, feelings and behaviours.

SAFETY AND EFFICACY OF A 6 MONTH HOME BASED EXERCISE PROGRAM IN PATIENTS WITH FSHD: A RANDOMIZED CONTROLLED TRIAL

This study assessed the safety and efficacy of a 6-month home-based exercise training program on fitness, muscle, and motor function in FSHD patients.Training consisted of cycling 3 times weekly, for 35 minutes at home for a total of 24 weeks. The primary outcome measure was the change in peak oxygen uptake measured every 6 weeks. The main secondary outcomes were maximal quadriceps strength and local quadriceps endurance, 6-minute walking distance, and muscle characteristics from vastus lateralis biopsies taken pre- and post-intervention. Significant improvements with training were observed in the oxygen peak uptake and maximal aerobic power by week 6 and further to week 24. Muscle endurance, maximal quadriceps strength, and 6-minute walking distance increased and experienced fatigue decreased.

This study has been completed in France and it concluded that a combined strength and interval cycling exercise-training program compatible with patients' daily professional and social activities leads to significant functional benefits without compromising muscle tissue. Please, click here to read this more about this information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4979851/

For more information:
https://clinicaltrials.gov/ct2/show/NCT01689480?term=FSHD&rank=4

Peak oxygen uptake, is the maximal oxygen consumption, in other words, is a measurement, numerical one, of your body´s ability to consume oxygen.

EFFECTS OF NMES ON MUSCLE FUNCTION OF PATIENTS WITH FSHD: A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL (NEMS & FSHD).

One of the major problems of patients affected by FSHD is the limitation in performing daily activities induced by the progressive muscle weakness. This sedentary lifestyle can cause a "debilitative cycle," and neuromuscular deconditioning can even aggravate the muscular deficiencies.

Recent studies have indicated safety and effectiveness of moderate aerobic training programs in patients with FSHD. However, these training programs have limited applicability in patients with more severe muscular weakness. Artificial strength training by means of neuromuscular electrical stimulation (NMES) appears to be a promising rehabilitation strategy for FSHD patients suffering from neuromuscular disorders. Therefore, this study proposes to investigate the feasibility, safety, and effectiveness of NMES strength training to counteract quadriceps muscle weakness in patients affected by FSHD. This study is runnig at Montpellier University Hospital and it is estimated that this study will have finished by October 2017.

https://clinicaltrials.gov/ct2/show/NCT02861911?term=FSHD&rank=8

Neuromuscular Electrical Stimulation (NMES) is the action of provoking a muscle contraction using electric impulses.

MRI AS OUTCOME MEASURE IN FSHD: 1-YEAR FOLLOW-UP OF 45 PATIENTS

In this study (which is now closed), the researchers used quantitative MRI to assess yearly disease progression in patients with FSHD1. This first study to longitudinally monitor fat replacement in FSHD1 has showed that MRI provides an objective measure of disease progression, often before changes can be appreciated in strength and functional tests. The study indicates that quantitative MRI can be a helpful end-point in follow-up and therapeutic trials of patients with FSHD1.

Publication of results:
http://link.springer.com/article/10.1007%2Fs00415-016-8361-3

Thank you

For reading this newsletter and being part of the UK FSHD Patient Registry. If you have any questions then please get in touch, phillip.cammish@ncl.ac.uk