clinical trial readiness

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Clinical Trial Readiness?

• We as a community are stakeholders in the process of drug development
  • We need to facilitate therapeutic development not just for the trials which are active now, but for all drugs that may benefit people with FSHD

• We need the tools in place, so we can be confident
  • We do not throw out drugs which might work
  • We do not approve drugs that will not help

• Ensure all stakeholders take part in the conversation
  • Industry
  • Academia
  • FSHD advocacy groups
  • People with FSHD, and their family members
Why Plan Now

• From a practical POV there’s a lot of work that needs to be done
  • Ensure standard techniques for how we measure things
  • Address gaps in understanding of what happens clinically over time
  • Develop tools for clinical trials, and make sure results are consistent when implemented across multiple locations
  • Figure out what features predict how fast the disease changes: e.g. mutation, age, gender

• Advocate nationally (internationally) for resources to pursue research and cures

• Without people volunteering for studies we cannot make progress
  • Your participation means a lot!!!!
Innovation and Collaboration

• Early on we need people working independently
  • Thinking of new ways to measure the disease
  • Thinking of new avenues for treatments
  • Thinking outside the box
• But ultimately we need people to then come together to test these new ideas in large groups of people (we need to prepare)
  • We want things that work for all people with FSHD
  • To ensure our assumptions about what our tools measure and how they measure it are true
• If we can agree on common approaches we can accelerate drug development
  • Examples: Duchenne Muscular Dystrophy, Spinal Muscular Atrophy
  • By joining together as a community they were able to hasten overall drug development
Getting Ready for Clinical Trials: Tools

• We’ve made advances in our clinical trial tools, but for each there is work that needs to be done

• Biomarkers: blood, tissue, other
  • Proof a drug is reaching its target

Chen et al. *Molecular Therapy* (2016); 24 8, 1405–1411.
Getting Ready for Clinical Trials: Tools

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• Biomarkers: blood, tissue, other
  • Proof a drug is reaching its target
  • Monitoring disease activity

MRI Can Measure:
  Inflammation
  Fat
  Fibrosis

Serological Proteins
Which Might Track with Disease Activity
Getting Ready for Clinical Trials: Tools

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• Biomarkers: blood, tissue, other
  • Proof a drug is reaching its target
  • Monitoring disease activity
  • Monitoring physiological changes

• Biomarkers important for early studies: as early signals, before we see changes in strength or function

• But before we can use them:
  • Need to standardize the technique
  • Show we can get consistent results from multiple centers
  • Understand how they naturally change in people with FSHD over time
Getting Ready for Clinical Trials: Tools

• Strength and Function
• There are many techniques for measuring individual muscle strength
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• Standard functional tasks include things like how fast you can go 30 feet, get out of a chair, climbing 4 stairs, or how far you walk in 6 minutes
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• Can combine tasks into a composite

North Star Ambulatory Assessment
Hammersmith Motor Ability Scale
Performance Upper Limb Module
Motor Function Measure
FSHD – Composite Measure
Getting Ready for Clinical Trials: Tools

- **Strength and Function**
- There are many techniques for measuring individual muscle strength
- Standard functional tasks include things like how fast you can go 30 feet, get out of a chair, climbing 4 stairs, or how far you walk in 6 minutes
- Can combine tasks into a composite
- Can instrument a functional task
- There is still work that needs to be done:
  - We need to standardize our equipment and procedures
  - Train our evaluators
  - Ensure we understand the relationship to genetics, age, gender, baseline functional status

<table>
<thead>
<tr>
<th>Get Up and Go Motion Metrics</th>
<th>Normative Mean n=84 (SD)</th>
<th>FSHD Total n=17 (SD)</th>
<th>Number Outside Normative 95% CL (%)</th>
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<tbody>
<tr>
<td>Total Duration (seconds)</td>
<td>16.6 (2.2)</td>
<td>27.4 (7.1)</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td>Stride length (%stature)</td>
<td>84.8 (5.8)</td>
<td>77.4 (8.1)</td>
<td>12 (70.6)</td>
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<td>Stride velocity (%stature/s)</td>
<td>80.3 (8.9)</td>
<td>58.6 (12.8)</td>
<td>17 (100)</td>
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<td>Cadence (steps/min)</td>
<td>113.4 (8.7)</td>
<td>90.1 (13.7)</td>
<td>16 (94.1)</td>
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<td>Double support (%)</td>
<td>22.2 (4.1)</td>
<td>31.5 (7.5)</td>
<td>16 (94.1)</td>
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<td>RoM Knee (degrees)</td>
<td>57.6 (3.7)</td>
<td>61.2 (7.4)</td>
<td>13 (76.5)</td>
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<tr>
<td>RoM Knee Assymetry (</td>
<td>Diff R-L</td>
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<td>ROM Trunk Horizontal (degrees)</td>
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<td>ROM Trunk Sagital (degrees)</td>
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<td>RoM Arm (degrees)</td>
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<tr>
<td>RoM Arm Assymetry (</td>
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<td>Turn: Duration (seconds)</td>
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<td>3.2 (1.9)</td>
<td>15 (88.2)</td>
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</table>
Getting Ready for Clinical Trials: Tools

- Patient-reported outcomes
- Ask the question how a treatment impacts someone’s life
- These can be standard instruments like: the Short-Form 36, the Individualized Neuromuscular Quality of Life Scale, the PROMISE scales
- Or disease specific
- Still need to:
  - Establish common instruments which cover full range of disability
  - Understand the normal variability from year to year
  - Determine if there are differences from region to region, culture to culture

The FSHD Health Inventory

- Problems with shoulders or arms
- Limitations with mobility or walking
- Inability to do activities
- Back, chest, or abdomen weakness
- Changed body image due to disease
- Fatigue
- Pain
- Decreased performance in social situations
- Problems with hands or fingers
- Decreased satisfaction in social situations
- Emotional issues
- Problems eating
- Difficulty thinking
- Communication difficulties

Survey sent to > 300 people with FSHD

Ranked symptoms by prevalence and impact on their lives

Developed by Chad Heatwole, MD
Getting Ready for Clinical Trials: Understanding disease progression

• The ability to understand the normal progression of FSHD and how it impacts the types of tools we choose for measurement can:
  • Help prevent us from rejecting a drug or therapy when it may actually work (example: DMD)
  • Help us design more efficient clinical trials
  • Reduce the burden on individuals participating, by allowing us to reduce the number of people required for early phase studies
  • Help us design confirmatory trials

• There are still several gaps in our understanding which need to be addressed:
  • How does genetics, baseline functional status, demographics influence rates of progression?
  • Are there simple tools we can use to ‘predict’ how someone might do over the next year?

Getting Ready for Clinical Trials: How big a change is meaningful

• Ultimately understanding how big a change would be meaningful can help make the argument for approval of a drug
• Short of hard outcomes like mortality, or time to requiring a wheelchair, or non-invasive ventilation we need other ways to determine how big a change would be meaningful
• This will depend on what the treatment is for
  • For example a drug designed to help with pain does not need to improve how you walk
• We can try and understand this using statistical techniques, by using questionnaires, or by relating a change in one measurement to a change in another
• Your voice / your opinion is important!!!
Future Directions

• We have collaborated with 7 large academic centers across the US, the FSH Society, and private funding to form an FSHD Clinical Trial Research Network
  • Our goal: to hasten therapeutic development for FSHD
  • We plan to work with drug companies, researchers, advocacy groups, and people with FSHD
  • To address gaps in our understanding of the natural history of FSHD, or the tools we use to measure changes in FSHD
  • To make large clinical data sets available to anyone with an interest in developing therapies for FSHD

• This network is getting started now and your participation can make a difference – you can contact me, my coordinator, or the FSH Society to find out how to take part