Jeffrey Statland, MD
University of Kansas Medical Center
Collaborator: Rabi Tawil, MD, URMC

Support:
Private donors
FSH Society
Friends of FSH Research
MDA
Industry

FSHD Clinical Trial Research Network Investigators: Kathryn Wagner, MD (Kennedy Krieger), John Kissel, MD (OSU), Nicholas Johnson, MD (University of Utah), Leo Wang, MD (University of Washington), and Perry Shieh (UCLA)
• Advances in our understanding of FSHD have identified potential targets for therapy

• Researchers and companies are developing molecularly targeted therapies

• Companies are also moving forward with therapies which may benefit FSHD but are not molecularly targeted

• Hand in hand with the work in the lab comes the work we as a clinical research community need to do to get ready for clinical trials
Innovation and Collaboration

• We need separate people from all over the world trying new things
  • Thinking outside the box
  • Thinking of new ways to measure the FSHD
  • Thinking of new avenues for treatments

• But ultimately we need people to then come together to test these new ideas in large groups of people
  • 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
What is a clinical trial research network?

• On its simplest level a group of academic or private research centers who agree to work together to accomplish common goals
• Create more efficient processes for running clinical studies
• There is power in numbers
  • By agreeing to pool resources we can answer lingering questions in natural history and outcome development for FSHD
  • Ensure findings at one site can be replicated at multiple sites
  • By including multiple sites across the country (the world) findings are more likely to represent the broader FSHD community
We have collaborated with 7 large academic centers across the US, the FSH Society, MDA, and private funding to form an **FSHD Clinical Trial Research Network** (PI: Rabi Tawil, MD and Jeffrey Statland, MD)

- **Our goal**: to hasten therapeutic development for FSHD
FSHD Clinical Trials Research Network (CTRN)

Aim 1: To streamline infrastructure

- Central IRB
- Central coordination and data management
  - Standard data elements and forms
  - Training key personnel – coordinators and evaluators

FSHD CTRN Ready for Efficient conduct of clinical trials
FSHD Clinical Trials Research Network (CTRN)

Key Stakeholders: Patients and Advocacy

Assemble FSHD Trial Network
Streamline Regulatory Processes
Standardize Data Elements / Train Evaluators

FSHD CTRN Ready for Efficient conduct of clinical trials

Aim 2: Include all Stakeholder Voices

- External advisory committee (clinical trialist, drug company, advocacy, and patient)
- NIH engagement officers to reach minority or underserved communities
- Patient advisory groups to help with recruitment, retention, dissemination
  - Outreach to industry
FSHD Clinical Trials Research Network (CTRN)

Key Stakeholders: Patients and Advocacy

- Assemble FSHD Trial Network
- Streamline Regulatory Processes
- Standardize Data Elements / Train Evaluators
- Validate New Outcome Measures / Test New Therapies

FSHD CTRN Ready for Efficient conduct of clinical trials

Aim 3: Refine clinical trial strategies
- Address gaps in our understanding of the natural history of FSHD
- Develop the tools we use to measure changes in FSHD
  - Test new therapeutics
FSHD Clinical Trials Research Network (CTRN)

Key Stakeholders: Patients and Advocacy

- Assemble FSHD Trial Network
- Streamline Regulatory Processes
- Standardize Data Elements / Train Evaluators
- Validate New Outcome Measures / Test New Therapies

FSHD CTRN Ready for Efficient conduct of clinical trials

Train the next generation of FSHD researchers

Aim 4: Train the next generation of FSHD clinical researcher
- Can be clinician, basic scientist, statistician, epidemiologist, etc
FSHD Clinical Trials Research Network (CTRN)

- Commitment to make large clinical data sets available to anyone with an interest in developing therapies for FSHD
Clinical Trial **Readiness to Solve** Barriers to Drug Development in FSHD (ReResolve)

- National Institute of Neurological Disorders and Stroke U01 (PI: Tawil and Statland): study of 160 individuals with FSHD followed for 18-24 months
  - Refine trial strategies (inclusion criteria, relation of genetics, demographics, baseline function to progression)
  - Validate new outcomes (functional composite, electrical impedance myography, FSHD-Health Inventory)
  - Collaborating to add two European sites! Nijmegen, the Netherlands, and Milan, Italy – *Thanks to Friends of FSH Research!*
    - Recruiting now!! – contact our project manager Kiley Higgs 913-945-9922, ksims2@kumc.edu
- Add on study of reachable workspace (in collaboration with Fulcrum Therapeutics)
  - Using a 3-D camera document the volume of space someone can reach as surrogate for upper extremity function
- New MRI/muscle biomarker study
  - Coming soon!
Example: Developing the FSHD Functional Composite

- An iterative process: meaning several cycles of development and testing

- First step is ask what we know about FSHD

- Occurs in the context of the disease
  - Expert opinion / Prior studies
  - Genetics / molecular pathology / MRI - anatomy

- Patient Experience
  - Treatments which improve mobility, arms and shoulder function, and core stability will be important

<table>
<thead>
<tr>
<th></th>
<th>Very much</th>
<th>Moderately</th>
<th>Slightly</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot/leg weakness</td>
<td>58%</td>
<td>22%</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Arm/shoulder weakness</td>
<td>53%</td>
<td>35%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>Core/abdominal weakness</td>
<td>51%</td>
<td>30%</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35%</td>
<td>39%</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>Pain</td>
<td>19%</td>
<td>34%</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>People’s lack of understanding</td>
<td>19%</td>
<td>25%</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>Having to keep my FSHD secret</td>
<td>10%</td>
<td>8%</td>
<td>16%</td>
<td>67%</td>
</tr>
<tr>
<td>Loss of facial expression</td>
<td>9%</td>
<td>20%</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>Breathing issues</td>
<td>6%</td>
<td>16%</td>
<td>28%</td>
<td>50%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>5%</td>
<td>11%</td>
<td>25%</td>
<td>59%</td>
</tr>
<tr>
<td>Speech impairment</td>
<td>2%</td>
<td>6%</td>
<td>28%</td>
<td>64%</td>
</tr>
</tbody>
</table>

N=388

Nguyen et al. MDA Clinical Conference 2017
Example: FSHD-COM

• We asked for expertise from PTs
• We picked the low-hanging fruit - for each functional domain we found existing functional motor tasks
  • Did not have to start from scratch – already data in other diseases
  • Some already had been used for drug approval with FDA
• Evaluator administered
• Yields total body score: 0-72
Outcome development is an iterative process

- We tested this in 30-40 individuals at 2 sites, to see if it was reliable and correlated to other measures we think are important in FSHD
- You go back and ask the researchers and people with FSHD how they feel about the measure and revise
- The CTRN performed a focus group to get feedback on the FSHD-COM
  - We received detailed feedback about the practical performance of each item
  - Adjusted how the evaluations were performed based on concerns
  - Incorporated recommendations regarding what might be missing into the design of our current study
Understanding disease progression

• But we still need to understand how the FSHD-COM changes over time
  • How does genetics, baseline functional status, demographics influence rates of progression?
  • How does the FSHD-COM compare to other functional composites (e.g. motor function measure)
  • How big a change in the FSHD-COM will be meaningful to people with FSHD?

• This is what the CTRN can help get an answer for!
Summary

• Clinical Trial Preparedness is a collaboration
  • Industry ↔ academics ↔ basic scientists ↔ advocacy ↔ people with FSHD

• Understanding the natural history and how we measure things
  • Can help gain approval for new drugs
  • Ensure we do not discard a treatment which might be beneficial (Or approve a drug which will not help)

• Having a network
  • Gets sites ready to participate in clinical trials
  • Creates a national group of trained coordinators and evaluators
  • Can help individual investigators or small companies take their drugs into clinical trials
Conclusions: many ways to participate

• Can contact us directly: project manager Kiley Higgs 913-945-9922
  ksims2@kumc.edu

• Can find studies at www.clinicaltrials.gov : NCT03458832
Conclusions: many ways to participate

• Can contact us directly: project manager Kiley Higgs 913-945-9922 ksims2@kumc.edu
• Can find studies at www.clinicaltrials.gov: NCT03458832
• Can find the network online: http://www.kumc.edu/fshd.html
Conclusions: many ways to participate

• Can contact us directly: project manager Kiley Higgs 913-945-9922
  ksims2@kumc.edu

• Can find studies at www.clinicaltrials.gov: NCT03458832

• Can find the network online: http://www.kumc.edu/fshd/about-the-fshd-ctrn.html

• Can go to the FSH Society website: https://www.fshsociety.org/
Conclusions: many ways to participate

• Can contact us directly: project manager Kiley Higgs 913-945-9922 ksims2@kumc.edu
• Can find studies at www.clinicaltrials.gov : NCT03458832
• Can find the network online: http://www.kumc.edu/fshd/about-the-fshd-ctrn.html
• Can go to the FSH Society website: https://www.fshsociety.org/
• Can register with the National Registry of FSHD Patients and Family Members: https://www.urmc.rochester.edu/neurology/national-registry/join.aspx
Organizations
NINDS
FSH Society
Friends of FSH Research
MDA
Fulcrum Therapeutics
External Advisory Committee
Robert Griggs, MD – clinical trialist
Laurie Mignon – Ionis Pharma
Dan Perez – FSH Society
Christopher Eklund – FSH Society
Susan Barclay – patient representative

LUMC – the Netherlands
Silvere van der Maarel - collaborator

CTRN:
University of Kansas Medical Center (Jeffrey Statland)
University of Rochester Medical Center (Rabi Tawil)
Kennedy Krieger Institute (Kathryn Wagner);
University of Utah/Virginia Commonwealth University (Nick Johnson);
Ohio State University (John Kissel);
University of Washington (Leo Wang);
UCLA (Perry Shieh)

Thank You!