

clinical trial readiness

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Collaborator: Rabi Tawil, MD, UPMC

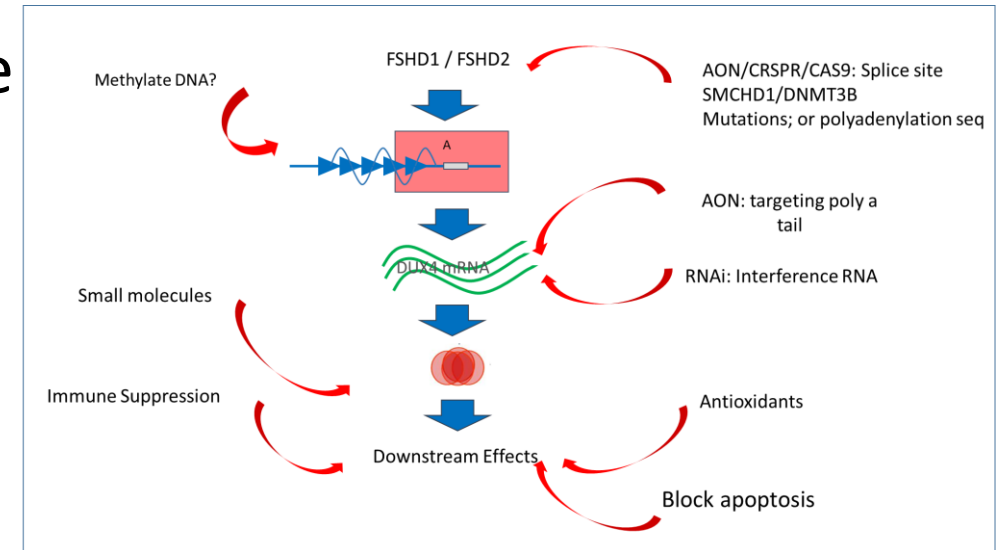


Support:
Private donors
FSH Society
Friends of FSH Research
MDA
Industry

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)

WHY NOW?

- 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





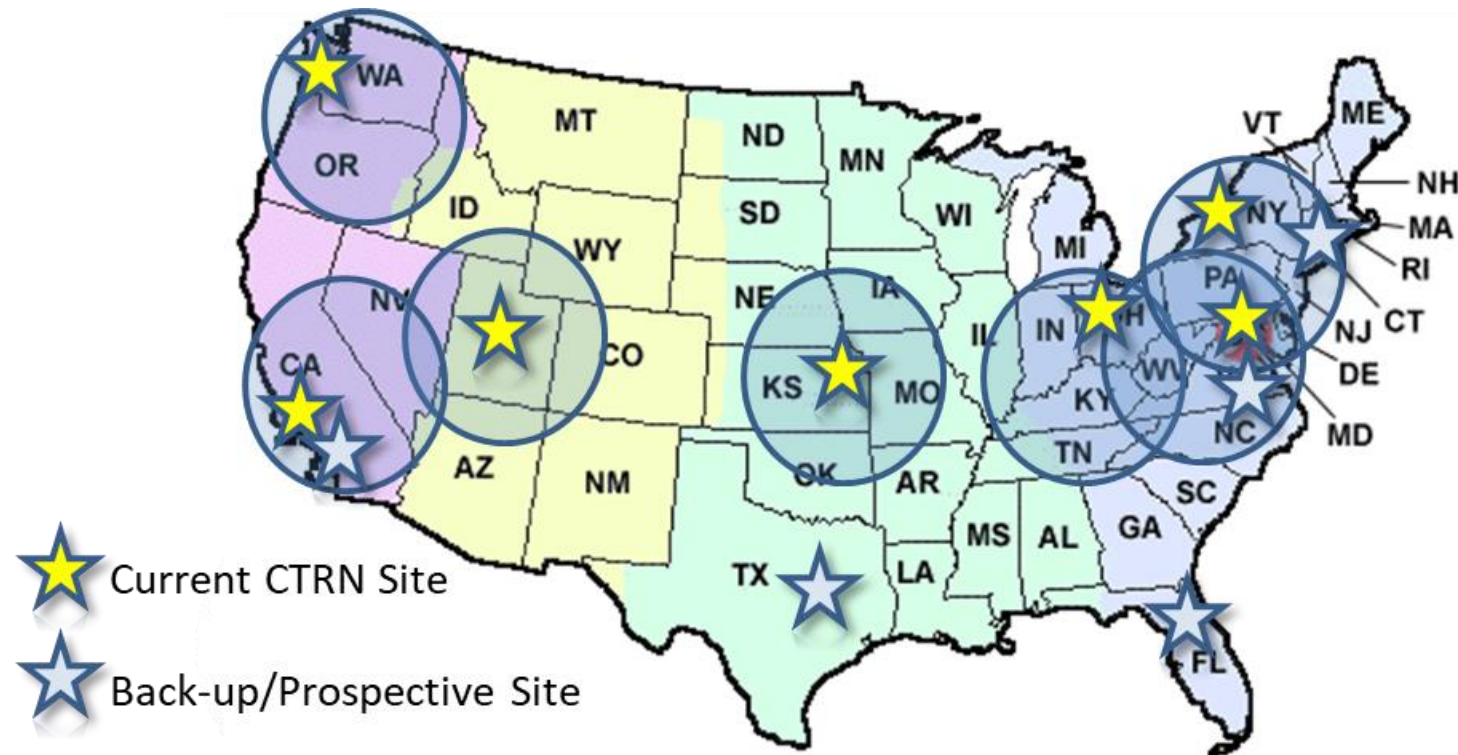
What is a clinical trial research network?

- 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

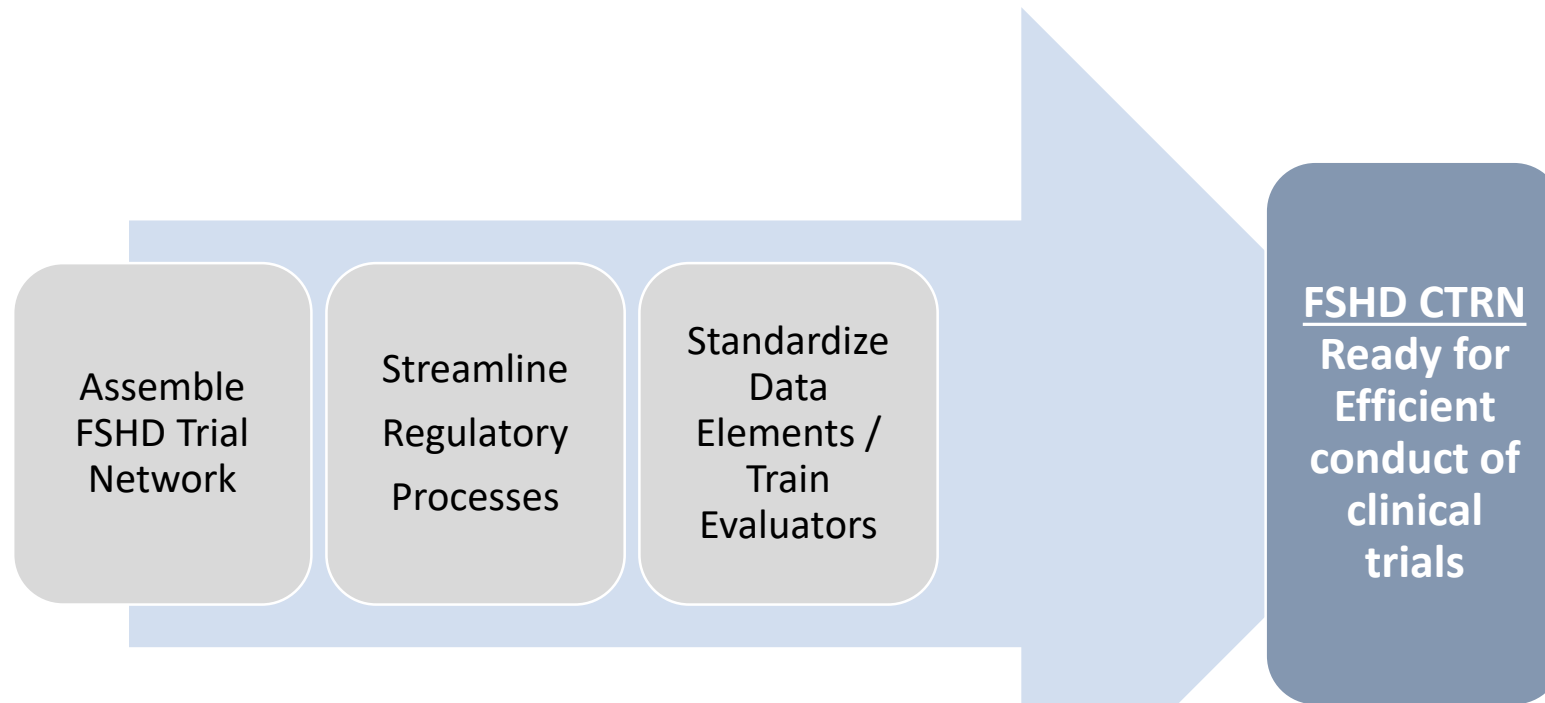
FSHD Clinical Trials Research Network (CTRNN)

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

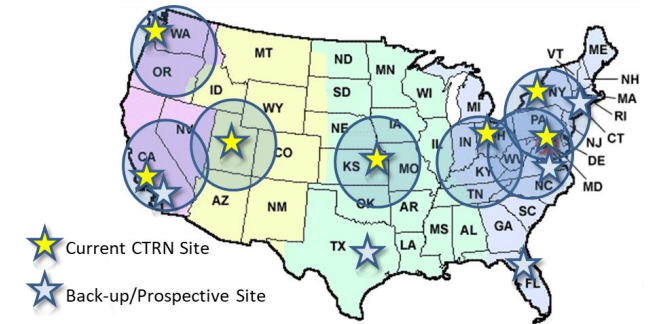


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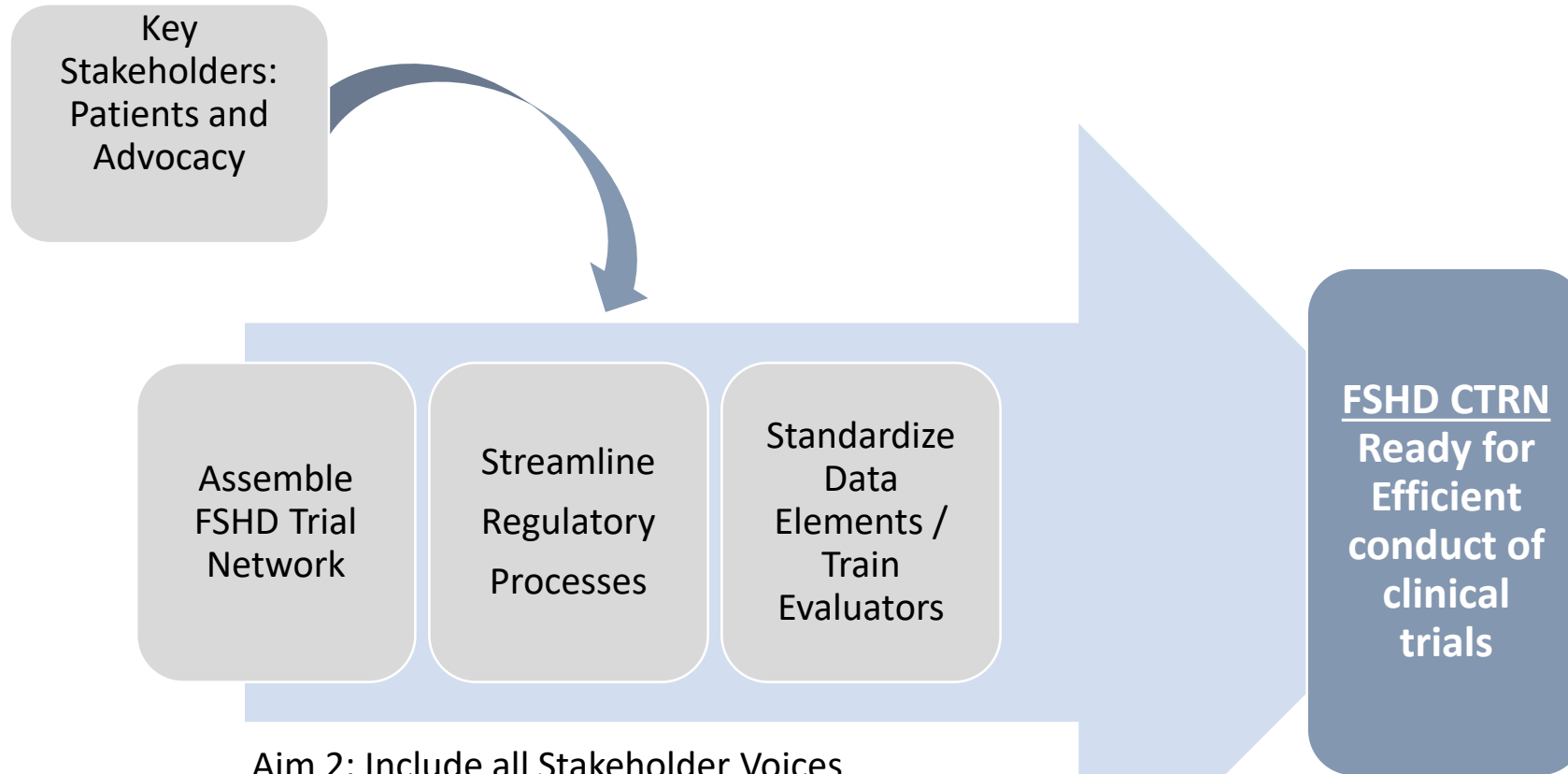


Aim 1: To streamline infrastructure

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

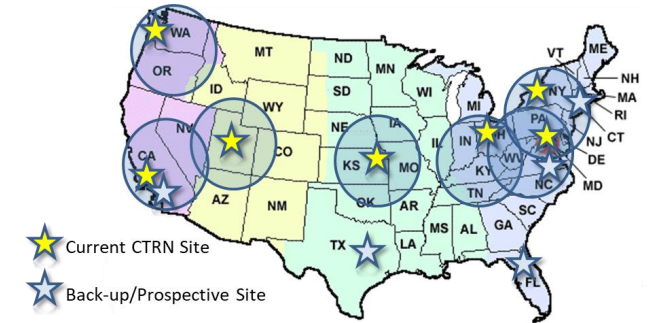


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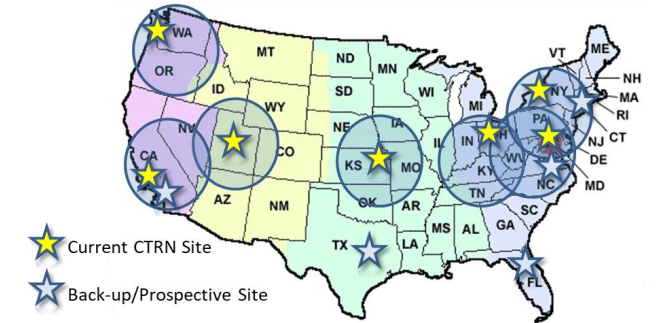
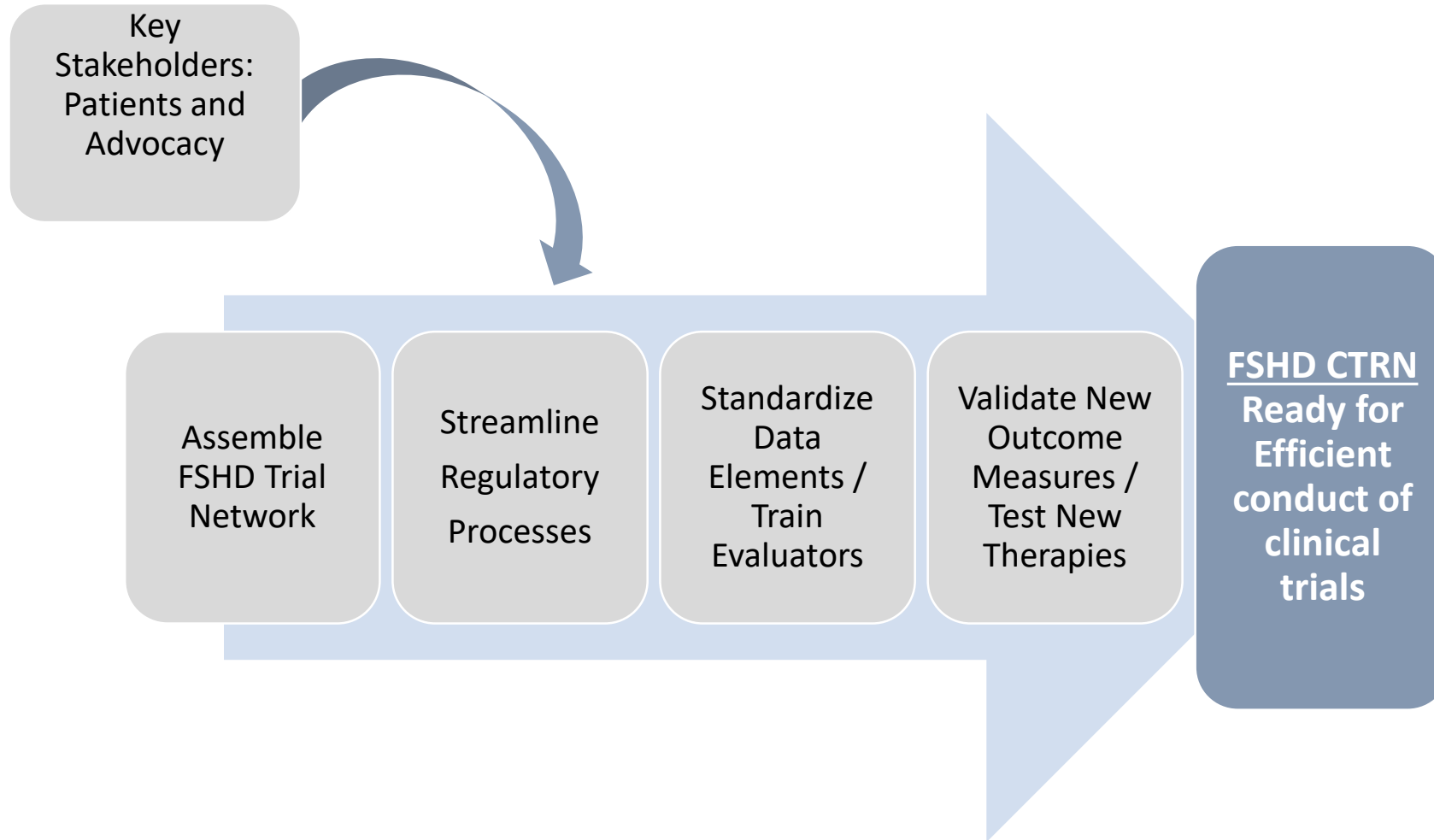


Aim 2: Include all Stakeholder Voices

- 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, and dissemination
 - Outreach to industry



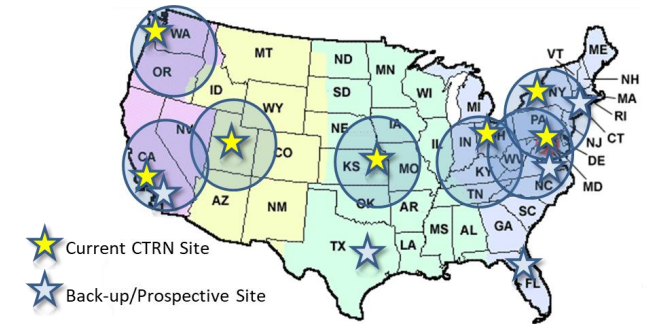
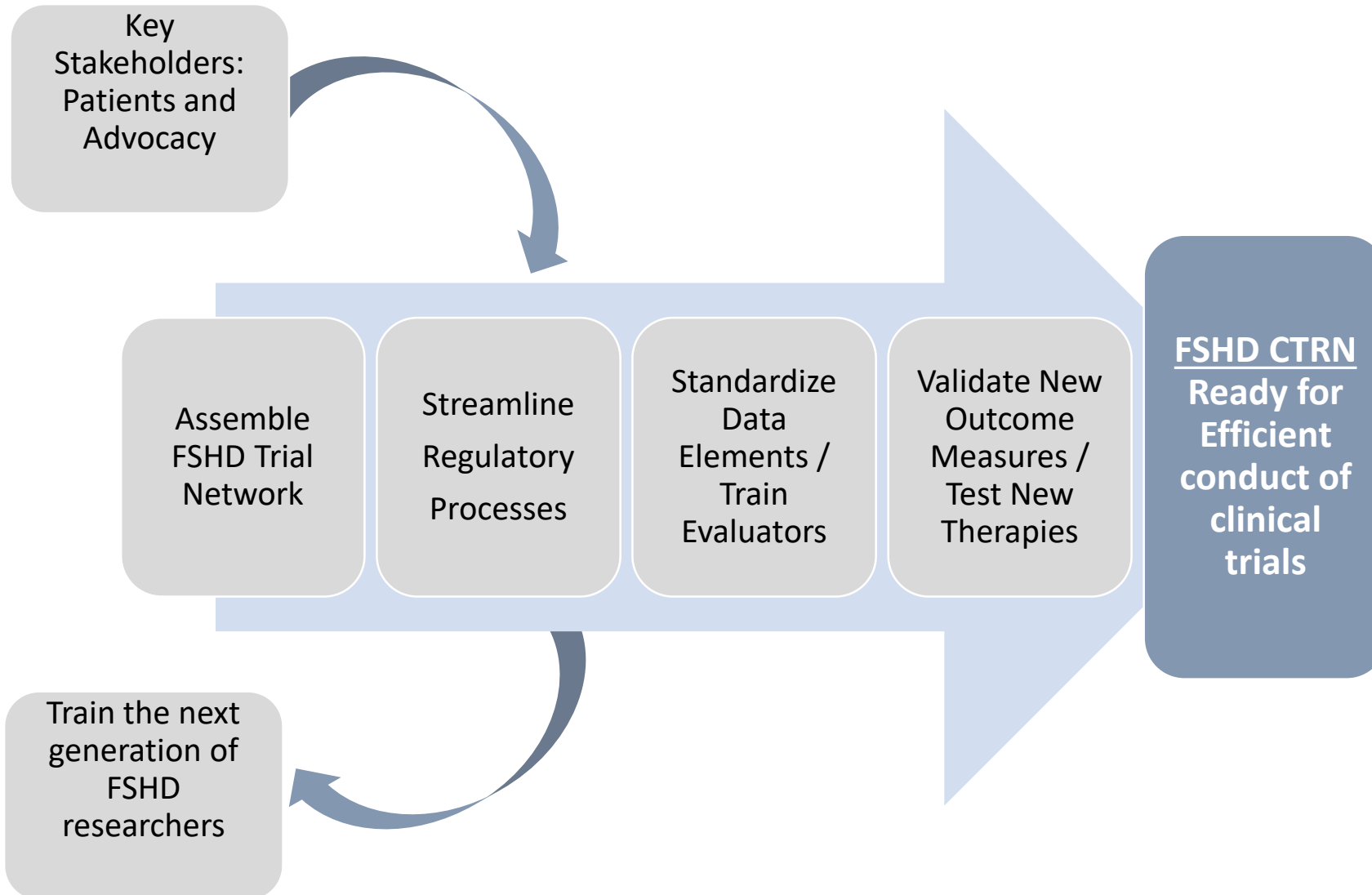
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Aim 3: Refine clinical trial strategies

- Address gaps in our understanding of the natural history of FSHD
- Develop the tools we use to measure changes in FSHD
 - Test new therapeutics

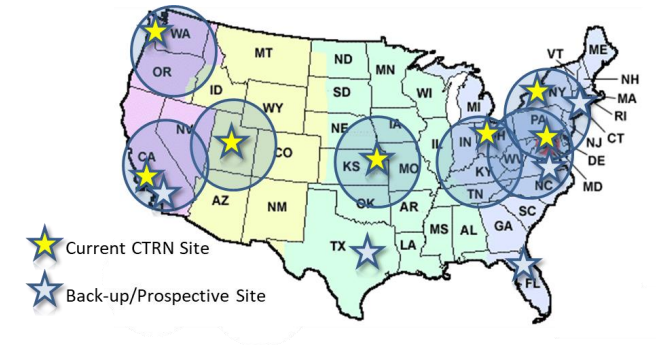
FSHD Clinical Trials Research Network (CTRn)



Aim 4: Train the next generation of FSHD clinical researcher

- Can be clinician, basic scientist, statistician, epidemiologist, etc

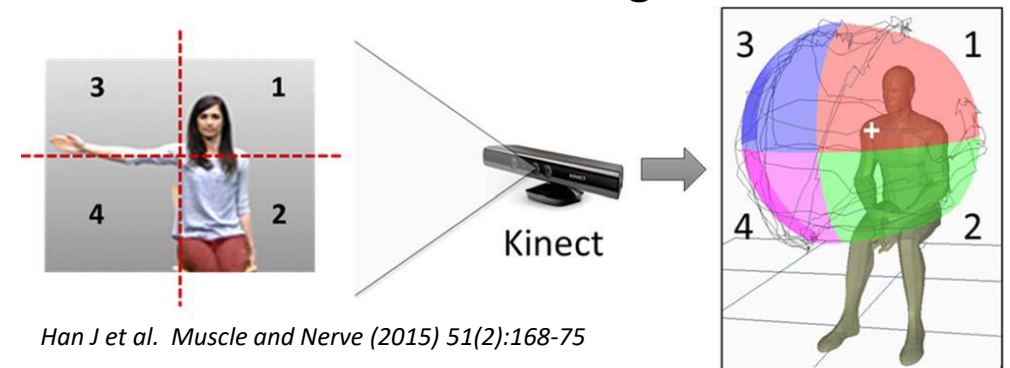
FSHD Clinical Trials Research Network (CTRN)



- 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 (ReSolve)

- 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

N=388	Very much	Moderately	Slightly	Not at all
Foot/leg weakness	58%	22%	14%	7%
Arm/shoulder weakness	53%	35%	11%	1%
Core/abdominal weakness	51%	30%	13%	6%
Fatigue	35%	39%	21%	4%
Pain	19%	34%	33%	15%
People's lack of understanding	19%	25%	33%	24%
Having to keep my FSHD secret	10%	8%	16%	67%
Loss of facial expression	9%	20%	35%	38%
Breathing issues	6%	16%	28%	50%
Hearing loss	5%	11%	25%	59%
Speech impairment	2%	6%	28%	64%

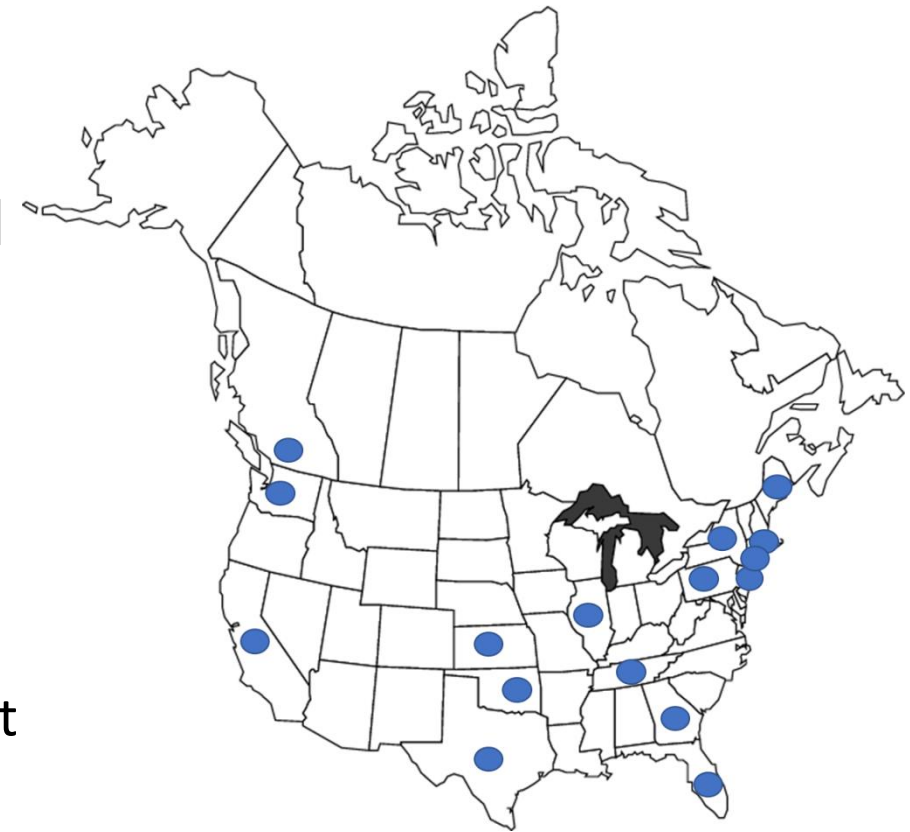
Example: FSHD-COM

- 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

Region	Item
Leg function	Sit to stand
	without hands
	6 Minute Walk
	Self-selected gait speed
	Go 30'
	Ascend/ descend stairs
Shoulder / Arm function	Shoulder Abduction (R/L)
	Shoulder Forward Flexion (R/L)
	Elbow Flexion (R/L)
	Don/doff Coat
Trunk function	Pick up a penny from floor
	Sit up with feet held
	Supine to sit
Hand function	Hand Grip Force Men
	Hand Grip Force Women
Balance	TUG: Timed up and Go

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

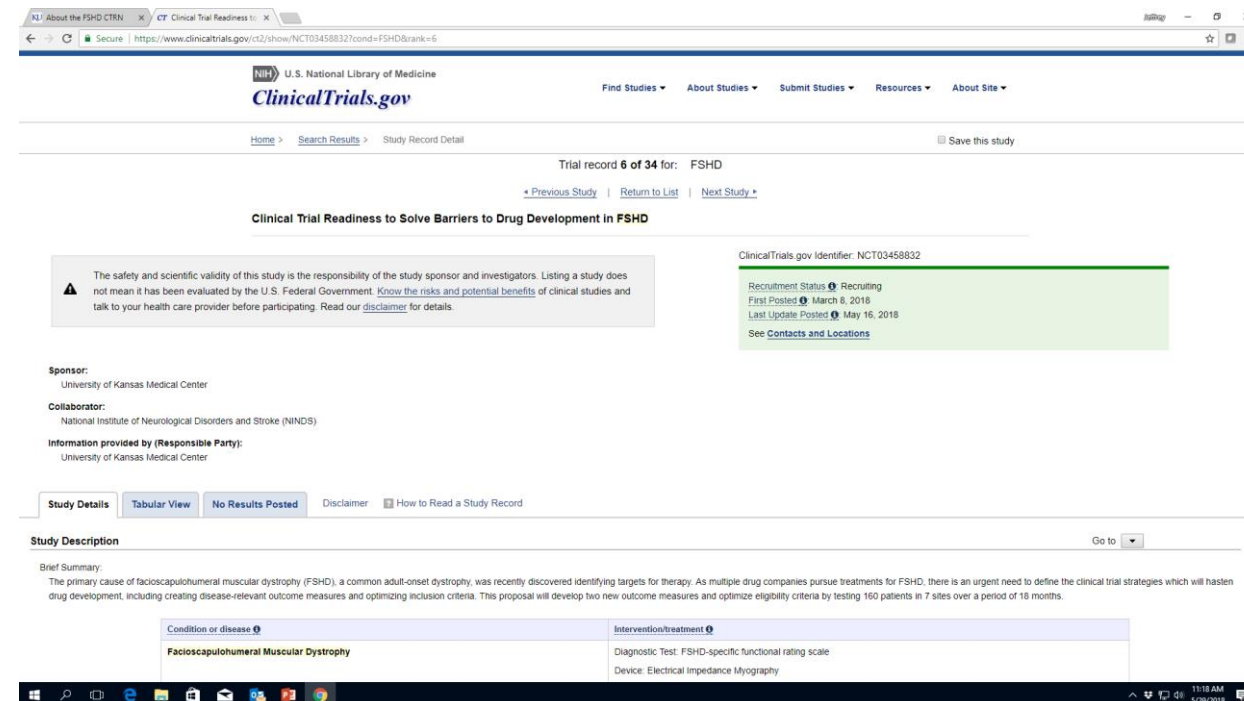
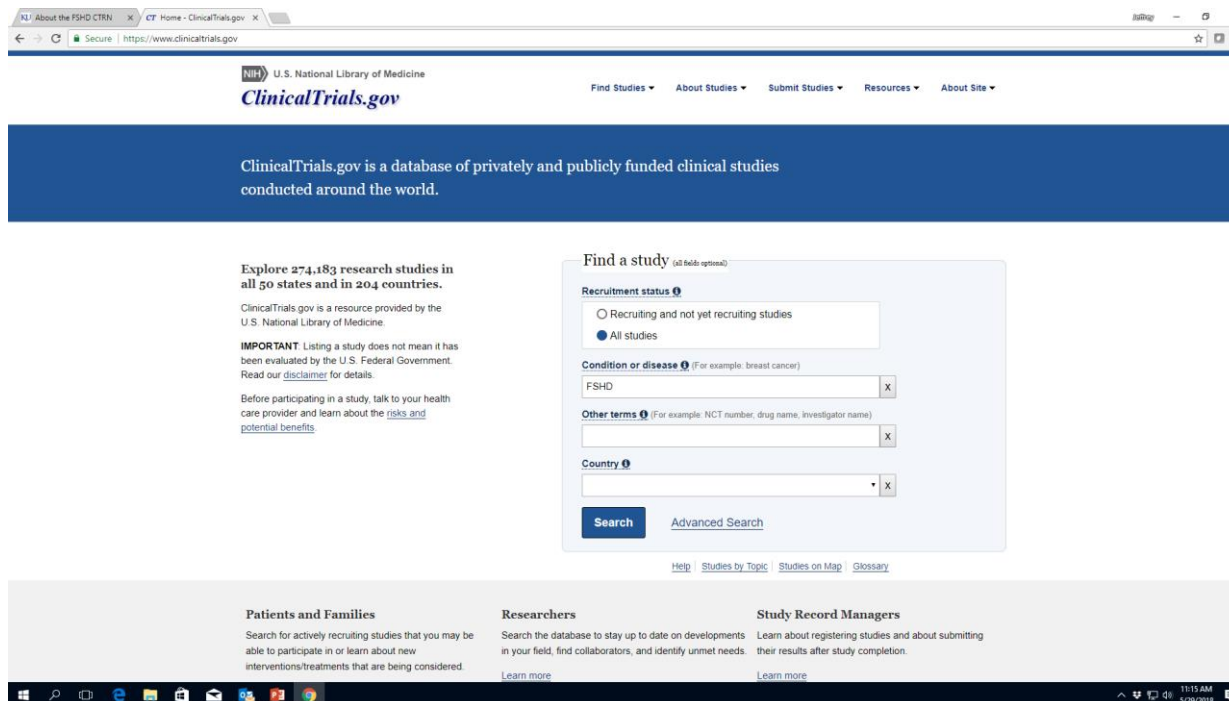
- But we still need to understand how the FSHD-COM changes over time
 - How does genetics, baseline functional status, demographics influence rates of progression?
 - How does the FSHD-COM compare to other functional composites (e.g. motor function measure)
 - How big a change in the FSHD-COM will be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

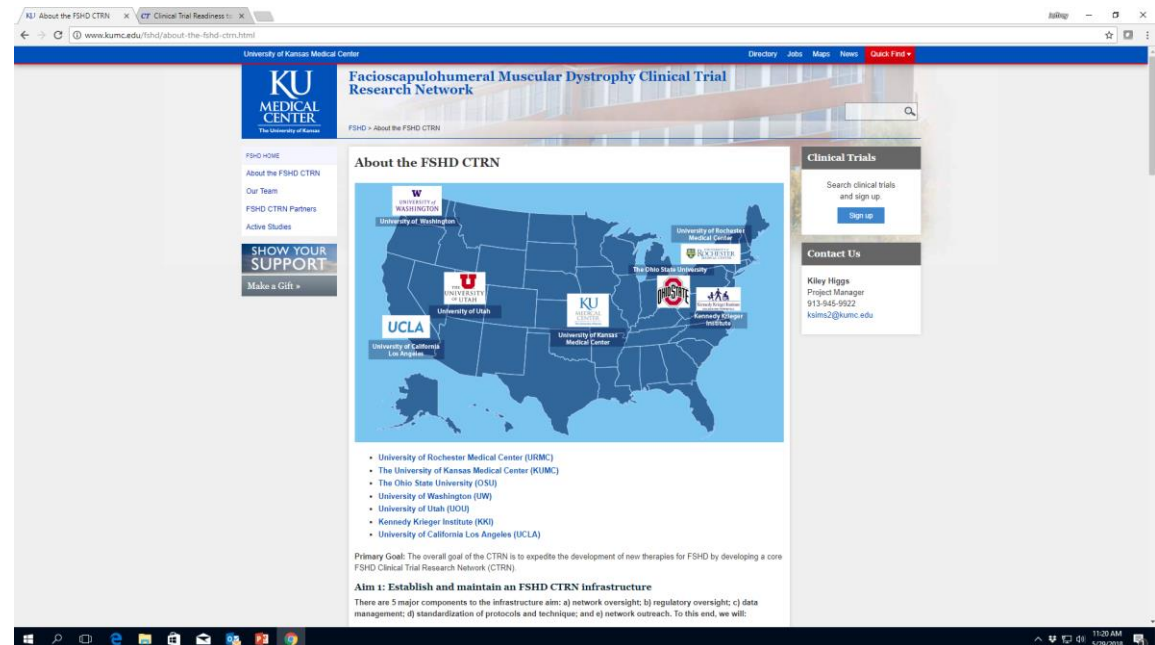
Conclusions: many ways to participate

- Can contact us directly: project manager Kiley Higgs 913-945-9922
ksims2@kumc.edu
- Can find studies at www.clinicaltrials.gov : NCT03458832



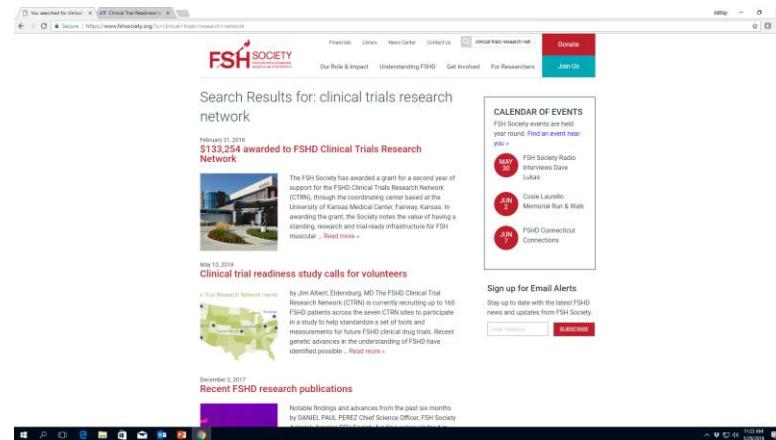
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- Can go to the FSH Society website: <https://www.fshsociety.org/>



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- 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>

FSHD patients and family members!!

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!