- If sharing any data or information from these slides generated by the REiNS International Collaboration, please acknowledge the authors, group chairs, and specific working group.
- If using any information presented with a citation, please reference the primary source.

Inching toward decentralized trials for NF1 and SWN

Scott Plotkin, MD, PhD

Mass General Hospital / Harvard Medical School

December 3, 2023

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking forward: a REiNS perspective

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking forward: a REiNS perspective

Barriers to participation in clinical trials

- Contributing factors vary by indication and patient populations
  - Disease-specific (ovarian cancer vs. COVID-19 vs. lupus)
  - Race and ethnicity
  - Gender
  - Geography (rural vs. urban)
  - Age

Selected structural barriers to enrolling cancer patients to clinical trials: Physician and staff perspectives

	Total (n=120) N (%)	Physician (n=47) N (%)	Staff (n=73) N (%)
Administrative			
Difficult to keep track of eligibility	74 (73.3%)	38 (84.4%)	36 (64.3%)
Enrolment process is too time consuming	48 (49.0%)	26 (56.4%)	22 (42.3%)
Patient-related			
Patients refuse placebo	43 (51.8%)	20 (50.0%)	23 (53.5%)
Patients frequently miss appts	35 (35.7%)	14 (32.6%)	21 (38.2%)
Process related			
Communicating complex information very difficult	56 (57.1%)	26 (56.5%)	30 (57.5%)
Making time during visit	47 (50.5%)	31 (67.4%)	16 (34%)
Few eligible patients	45 (46.9%)	22 (51.2%)	23 (43.4%)

Hillyer et al, Clin Trials, 2020

[redacted]

Barriers to enrollment in clinical trials which can also exacerbate inequity

- Cost/financial
  - Working patients may not have the ability to travel, miss work, or to pay for an extra day of parking to participate in clinical trials
  - Persons with annual income below $50,000 are 27% less likely to participate
- Insurance
  - Insurance may not cover costs associated with clinical trial
  - Patients require assistance with insurance issues which may not be available
- Mistrust of medical research
  - Historical (Tuskegee syphilis trials, 1932-1972)
  - Use of placebo controls
- Health literacy
  - Lack of literacy can leave patients fearful of the unknown

Roy et al, Int J Rad Onc Biol Phys, 2022

[redacted]

Barriers to enrollment in clinical trials which can also exacerbate inequity

- Eligibility criteria are also often used to exclude patients from participation
  - Higher rates of comorbidities can be linked to different social determinants of health
  - Exclusion of patients with psychiatric history can reduce enrollment to pain trials
- Poor knowledge about clinical trials
  - Patient factors:
    - **Awareness**: 85% of patients are not aware that they could participate in a clinical trial
    - **Health literacy**: Patients with low health literacy are less likely to enroll
  - Physician factors:
    - **Mismatch** between site of clinical trials (high-resource institutions) and where most patients are seen (community health clinics)
    - **Lack of awareness** of ongoing clinical trials
    - Perceived **lack of time** to refer patients

Roy et al, Int J Rad Onc Biol Phys, 2022

[redacted]

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking forward: a REiNS perspective

Rarity of NF1/SWN limits pool of patients for trials

- Regional prevalence
  - NF1: 1 in 4,088
  - *NF2*-SWN: 1 in 50,500
  - non-*NF2*-SWN: 1 in 126,315
- Birth incidence
  - NF1: 1 in 2,000
  - *NF2*-SWN: 1 in 27,956
  - non-*NF2*-SWN: 1 in 68,956

Kallionpaa et al., Genet Med, 2017
Evans et al., J Neurol Neurosurg Psychiatry, 2018

[redacted]

Few specialty NF clinics in the United States

- NF Clinic Network was created in 2007 by CTF to recognize clinics with expertise in caring for persons with NF1 and SWN
- In 2015, 50 specialty clinics with patient volume 10,245 (13% of estimated NF population)
- Only 43% of patients in CTF Registry receive care at NF specialty clinic
- Travel distances to specialty clinic
  - Average patient travels 50 miles to nearest clinic
  - 25% of patients travel more than 125 miles to nearest clinic
  - Adults travel further than children (300 vs. 68 miles) to high volume clinics
  - SWN patients travel further than NF1 patients (>300 miles vs. 160 miles) to high volume clinics

Merker et al., BMC Health Serv Res, 2018

[redacted]

NF specialty clinics are not evenly distributed across US leading to unequal access to services and clinical trial opportunities

Merker et al., BMC Health Serv Res, 2018

[redacted]

Capacity for specialized NF care varies widely among US regions

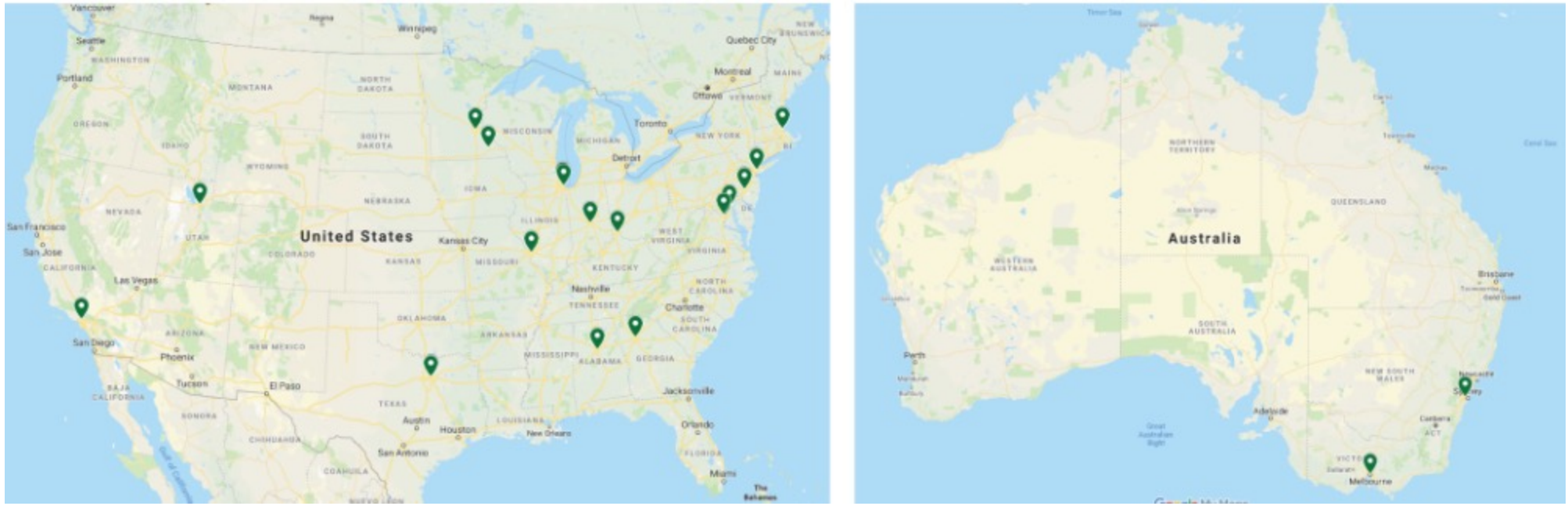
Plains:	1 clinic for 855 patients
Mideast:	1 clinic for 1085 patients
Great Lakes:	1 clinic for 1136 patients
New England:	1 clinic for 1192 patients
Rocky Mountains:	1 clinic for 1423 patients
Southeast:	1 clinic for 1814 patients
Southwest:	1 clinic for 3261 patients
Far West:	1 clinic for 3357 patients

Merker et al., BMC Health Serv Res, 2018

[redacted]

Even fewer centers that offer clinical trials

DOD Neurofibromatosis Clinical Trials Consortium



24 sites across US and Australia

Health literacy among NF1-SWN patients at Mass General

- Health literacy is “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions”
- Assessed using 2 scales
  - Adapted FCCHL: self-reported perceptions of functional, communicative, and critical health literacy
  - Health LiTT: performance-based health literacy.
- Participants had moderate levels of health literacy by FCCHL
- Lower health literacy scores for
  - Less educated than more educated
  - Learning disability than no learning disability
- Diagnosis, gender, race were not significant predictors

Merker et al., J Neuro-oncol, 2018

[redacted]

Financial issues for NF1 patients

- Many persons with NF1 in Denmark are not employed, mainly due to health reasons
- Reduced disposable income compared to controls (14%)
- Less likely to be employed in high skilled occupations

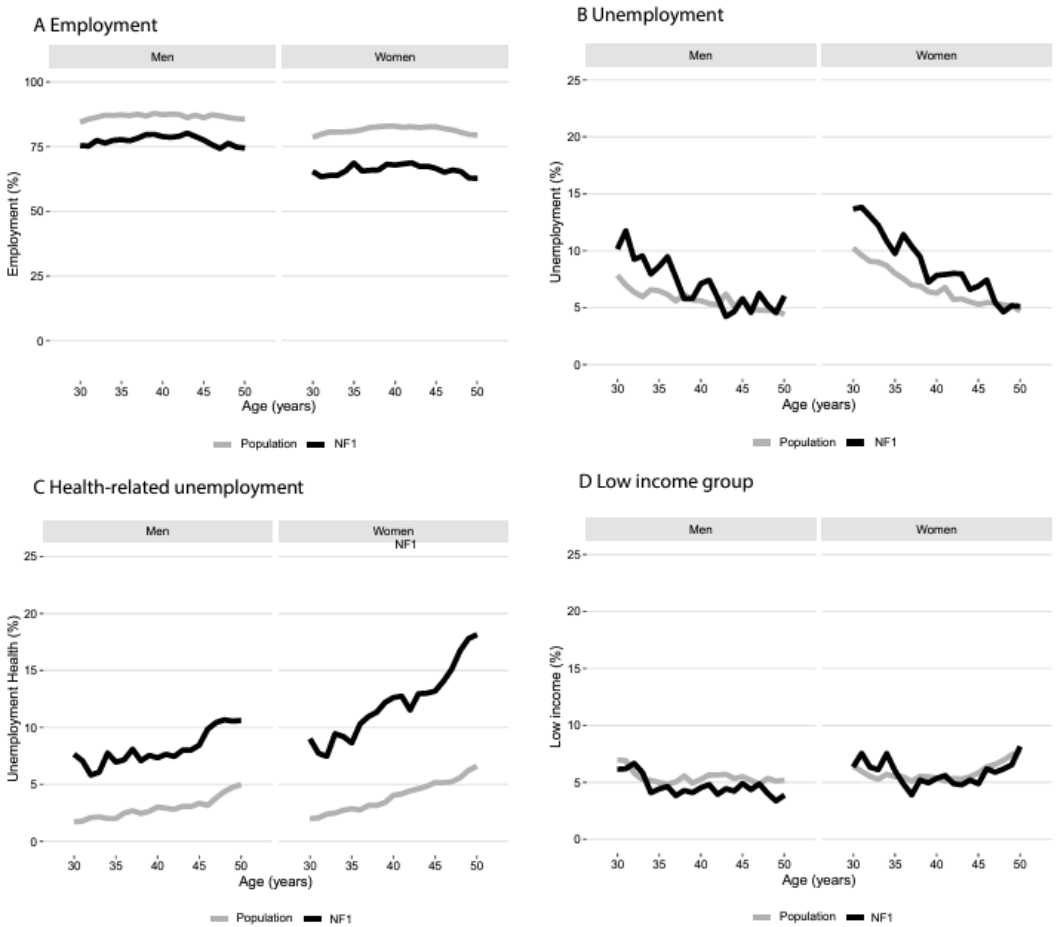


Fig. 1 Employment (**A**), unemployment (**B**), health-related unemployment (**C**) and low income (**D**) by ages 30 to 50 years for adults with NF1 and population comparisons

Kenborg et al., Orphanet J Rare Dis, 2023

Summary of features of NF1/SWN that may hinder clinical trial participation and slow progress for new treatments

Patient-related

- Rarity of NF1/SWN
- Reduced SES (disposable income, travel, missed work)
- Insurance coverage
- Reduced health literacy due to learning disability

Structural

- Few specialty clinics, even fewer clinical trial sites
- Restrictive trial eligibility criteria

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking ahead: a REiNS perspective

Rationale for decentralized trials in NF1/SWN

Barrier to trial participation	Potential benefit for decentralized trial
Rarity of NF1/SWN	Improve accrual by lowering distance and financial barriers
Reduced SES (disposable income, travel, missed work)	Reduce costs for participants who will travel less frequently to clinic sites
Insurance coverage	No obvious benefit
Reduced health literacy due to learning disability	Incorporation of virtual educational tools
Few specialty clinics, even fewer clinical trial sites	Can open trials to patients not seen as specialty clinics
Restrictive trial eligibility criteria	Can accommodate more liberal eligibility criteria

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking forward: a REiNS perspective

A “game changing” clinical trial: SPRINT

The National Cancer Institute Model

Children (patient reported outcomes):

- Pain intensity (Numeric Rating Scale; NRS-11)
- Interference of pain in daily functioning (Pain Interference Index; PII)
- Health-related quality of life (QOL; PedsQL Generic Core Scales)
- PROMIS Mobility and Upper Extremity functioning
- Global Impression of Change (GIC) Scale

Parents (observer reported outcomes (ObsRO):

- PII for children ≥5 year
- PedsQL for all ages
- PROMIS Mobility and Upper Extremity functioning
- Global Impression of Change (GIC) Scale

Gross et al., NEJM, 2020

Specific Evaluations Based on PN Location/Morbidity:

Orbital PN
- ☐ Ophthalmologic functional evaluations

Airway PN
- ☐ Sleep study
- ☐ PFTs/Oscillometry
- ☐ Endurance evaluation: 6-Minute Walk-Run Test

Motor PN (Lower Extremity)
- ☐ Strength evaluation
- ☐ ROM evaluation
- ☐ Leg length evaluation
- ☐ Endurance evaluation: 6-Minute Walk-Run Test
- ☐ PROMIS

Motor PN (Upper Extremity)
- ☐ Strength evaluation
- ☐ ROM evaluation
- ☐ Grooved Pegboard Test (Age ≥5 years)
- ☐ PROMIS

Bowel/Bladder PN
- ☐ Bowel/Bladder Questionnaire

Visible PN, Disfigurement (or Potential Disfigurement)
- ☐ Photography
- ☐ +/- Video

Other PN
- ☐ PN affecting speech/swallow: Speech Pathology Assessment
- ☐ PN affecting auditory system: Audiology and/or ENT

SPRINT trial was partially decentralized (a “hidden” feature of NCI trials to improve participant convenience)

Table 1. Trial Evaluations.*

Evaluation	Category of Plexiform Neurofibroma–Related Complications	Baseline	Time Point after Baseline†
Safety and disease evaluations			
* History taking and physical examination, safety laboratory studies	All	Yes	Before cycles 2, 3, 4, 5, 7, 9, 11, 13, 17, 21, and 25, then every 6 cycles
* Echocardiography, plexiform neurofibroma disease evaluation (MRI)‡	All	Yes	Before cycles 5, 9, 13, 17, 21, and 25, then every 6 cycles
* Ophthalmologic examination	All	Yes	Before cycles 5 and 13, then every 12 cycles
Patient diary and capsule count	All	No	Before cycles 3, 5, 9, 13, 17, 21, and 25, then every 6 cycles
Pharmacokinetics and pharmacodynamics			
Selumetinib and N-desmethyl selumetinib	All	Yes	Before cycle 2 or 3
Cytokines and bone marrow–derived precursor cells	All	Yes	Before cycles 3, 5, 9, and 13 and at the time of progression

* Some of these evaluations (non-restaging visits) were performed by local providers/local labs throughout the trial

* Some of these evaluations were done by local providers during COVID19 travel restrictions

Gross et al., NEJM, 2020

[redacted]

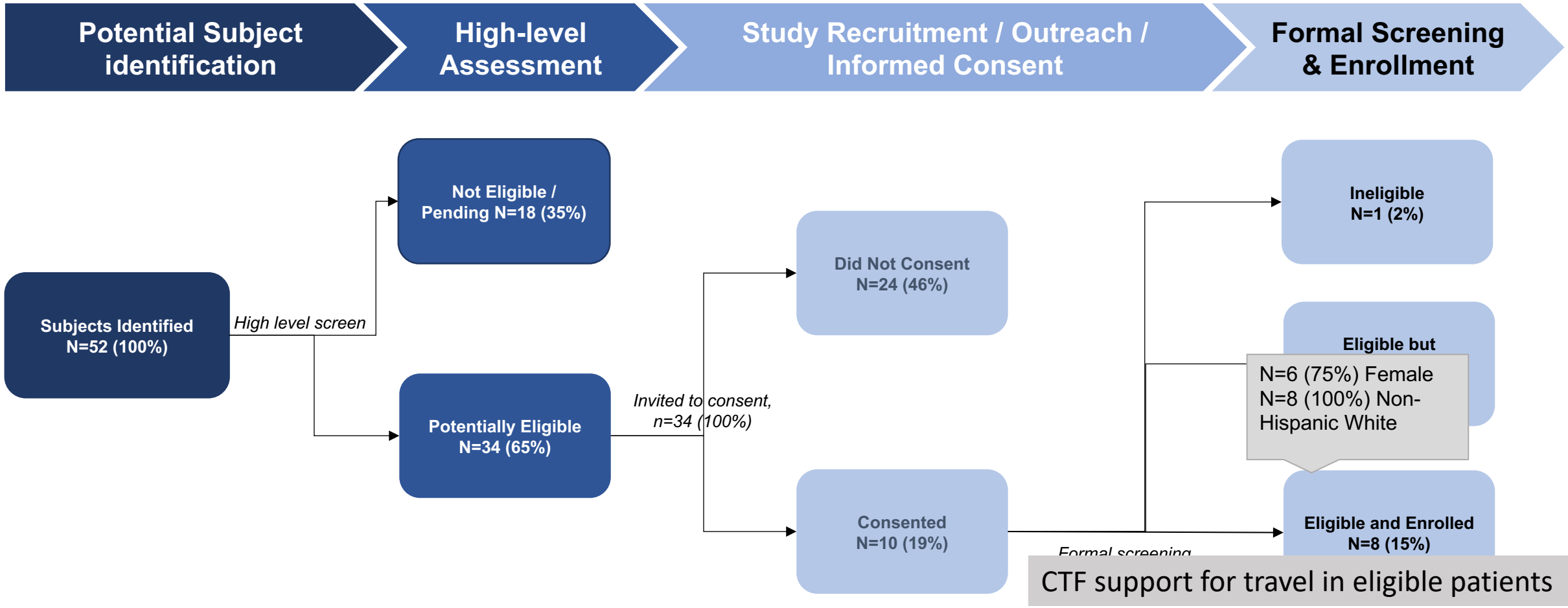
A missed opportunity: under-enrollment for pain study in SWN

- There is significant unmet need for pain therapies to treat SWN-related pain
  - Chronic pain is a common symptom of schwannomatosis
  - No medications are approved to treat schwannomatosis-related pain
- NCT04163419 is the first therapeutic clinical trial in schwannomatosis-related pain
  - Phase 2 clinical trial at Massachusetts General Hospital (single site)
  - Open during COVID-19 pandemic
  - Investigates safety and efficacy of tanezumab (anti-NGF antibody) for moderate-to-severe non-*NF2*-SWN pain
- Experience from this clinical trial has helped us identify and address barriers to participation in clinical trials for SWN-related pain

[redacted]

Results of recruitment and enrollment process

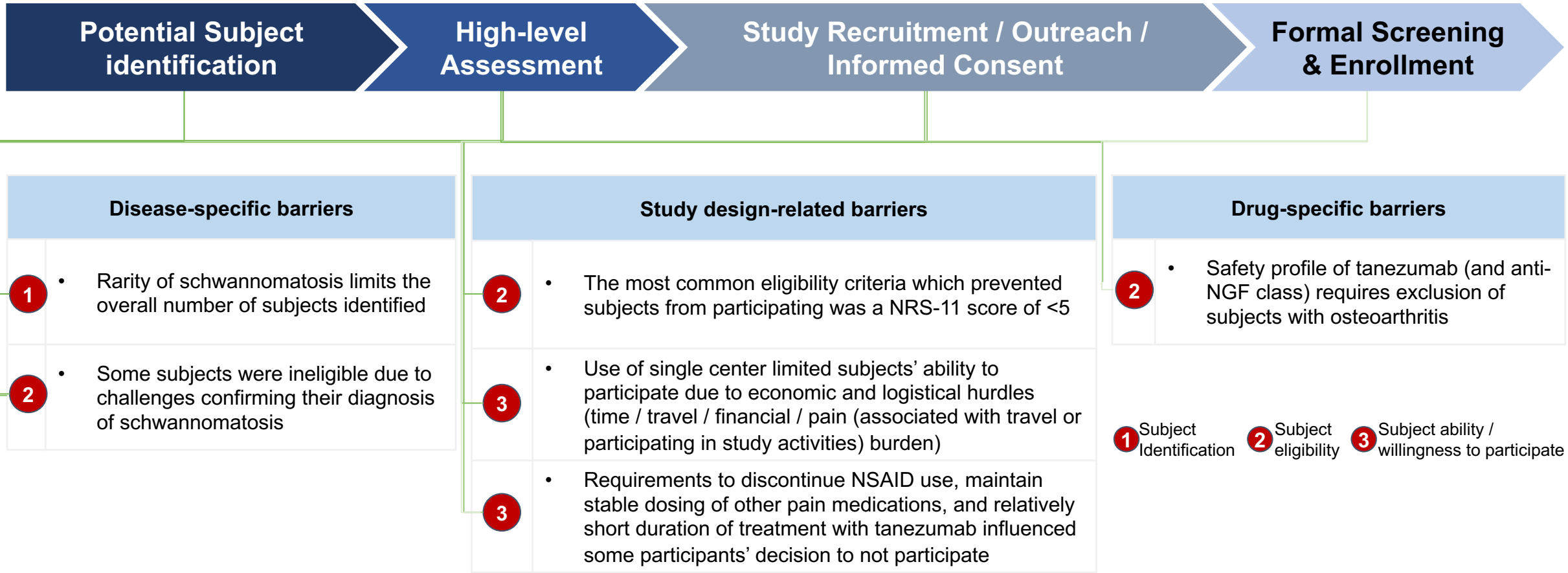
Recruitment Process



[redacted]

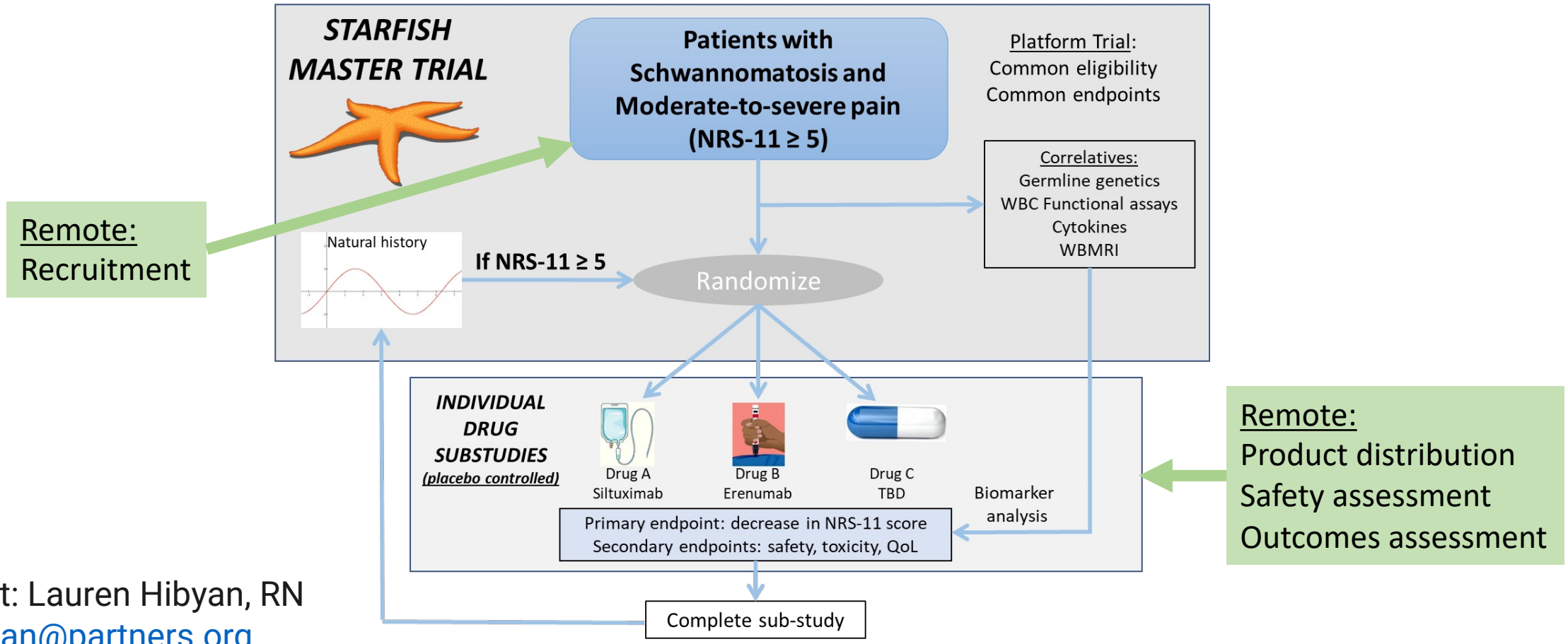
Lessons learned from the tanezumab study

Recruitment Process and Barriers Mapping



[redacted]

STARFISH is a partially decentralized trials for SWN pain



Contact: Lauren Hibyan, RN
lmhibyan@partners.org

Clinicaltrials.gov NCT05684692

[redacted]

JAMA Network Open

Original Investigation | Neurology

Effect of Mind-Body Skills Training on Quality of Life for Geographically Diverse Adults With Neurofibromatosis
A Fully Remote Randomized Clinical Trial

Ana-Maria Vranceanu, PhD; Heena R. Manglani, PhD; Nathaniel R. Choukas, BS; Millan R. Kanaya, BS; Ethan Lester, PhD; Emily L. Zale, PhD; Scott R. Plotkin, MD, PhD; Justin Jordan, MD, MPH; Eric Macklin, PhD; Jafar Bakhshaie, MD, PhD

- 993 patients responded to flyer → 371 screened (37%) → 286 eligible (28%) → 228 signed informed consent (23%)
- Intervention: 8 weekly virtual group session, 90 min each, with instruction using 3RP-NF or active control
- Primary outcome: Physical health and psychological QOL

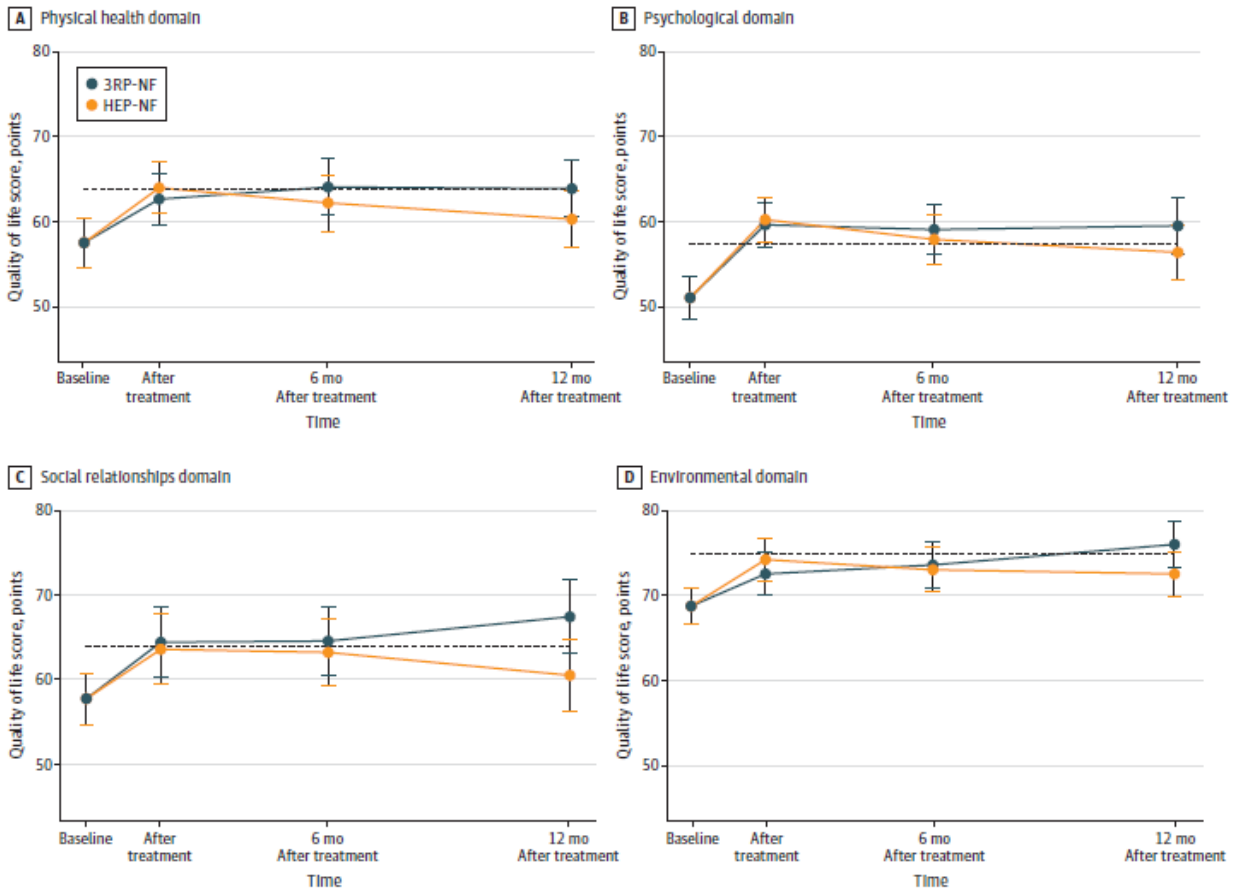
[redacted]

Results

- 228 participants
- 166 (73%) with NF1
- 32 (14%) with *NF2*-SWN
- 30 (13%) with non-*NF2*-SWN
- 217 (95%) attended 6 or more of 8 sessions and provided posttest data

→ Successful completion of fully decentralized psychosocial trial in NF1-SWN

Figure 2. World Health Organization Quality of Life Brief Version Domain Scores



Changes in mean scores at baseline, after treatment, and at 6- and 12-month follow-up. 3RP-NF indicates Relaxation Response Resiliency Program for Neurofibromatosis; HEP-NF, Health Enhancement Program for Neurofibromatosis.

Outline of talk

- Known barriers to clinical trial participation
- Features of NF1-SWN that hinder clinical trial participation
- Rationale for decentralized trials in NF1-SWN
- Completed/ongoing decentralized trials in NF1 and SWN
- Looking forward: a REiNS perspective

Inching toward (partially) decentralized trials in NF1-SWN

- Not all trials should be fully decentralized
  - Trials with investigational agents (unapproved drugs)
  - Trials of approved drugs with IV formulation, narrow risk/benefit profile
  - Build on success of NCI model (SPRINT trial)
- During trial design, consider:
  - What type of decentralization would improve recruitment (faster, more diverse), reduce costs, improve participant convenience?
  - Are virtual tools/endpoints currently available for NF1-SWN?
  - Can virtual tools/endpoints available for other conditions be adapted?
  - Can we convert current REiNS endpoints to virtual tools/endpoints?
- Next steps for REiNS
  - Working groups to adapt or create virtual endpoints for trial use

[redacted]

Acknowledgements

Massachusetts General Hospital

Vanessa L. Merker, PhD

Jennifer Da

Danielle Silverman, MS

Justin T. Jordan, MD, MPH

K. Ina Ly, MD

Alona Muzikansky, MA

Michael Parsons, PhD

Lei Xu, MD, PhD

Scott R. Plotkin, MD, PhD

Ana-Maria Vranceanu, PhD

National Cancer Institute

Andrea Gross, MD

Brigitte Widemann, MD

Pamela Wolters, PhD

Pfizer

Mark Brown, MD

Scot Styren, PhD

The case for decentralized trials in NF1/SWN

- Rare
- Few clinics, not evenly distributed
- Low diversity
- Access to trials is unfair (certain parts of the country)
- Cost –
- We are a roll model for rare diseases
- Affects everyone evenly
- Heterogenous manifestations – too burdensome to do this in clinic. NIH can do this but not everyone else.
- Many outcomes besides tumor size that are important – see STARfISH and ANA-MARIA trial.
- The road to partial decentralization

Future of decentralized trials in NF1/SWN

- Partial decentralization – bloods, imaging, PROs, central review
- Maybe good for natural history, for pregnant women/children (difficulty to travel)
- Good for equity, faster enrollment
- Can do more frequent sampling (high density data)
- Lead with PRO > functional > others
- Major challenges
  - Participant drop out
  - Missing data
- What are questions I want answered?

Opportunities to address these issues with DCT

- In addition, follow-ups needed for clinical trials can be performed while patients attend regular appointments, eliminating the need for extra visits.
- These measures can address socioeconomic barriers such as transportation costs and loss of income due to repeated leave from work.
- When clinical trial staff work alongside community clinic physicians, this reduces the extra burdens associated with referrals on physicians.
- Thus, this practice increases physician referral rates of the population of interes

What do (French) patients want?

- Involve local hospitals and health care providers for follow-up visits.
- Involve primary care doctors for informed consent and follow-up visits.
- Ensure close contact with investigators.
- Provide equipment (technology) suitable to patients' conditions.
- Apply technology to reduce the burden of data collection.

Nguyen, J. Med Internet Res, 2022