Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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Natural History of Schwannomatosis-Related Pain

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Response Evaluation In Neurofibromatosis Schwannomatosis
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Goals / Objectives / Endpoints

- To longitudinally assess self-reported pain intensity, pain interference, physical function, and other patient-reported constructs in an international cohort of schwannomatosis patients
- To identify the proportion of schwannomatosis patients with neuropathic or nociceptive components to chronic pain
- To review patterns of pain medication use in schwannomatosis patients

Patient Population (Eligibility)

- Age: Adults 18+
- Clinical manifestations to be followed: Pain and related PROs
- Diagnosis: Physician-verified clinical or genetic diagnosis of non *NF2*-related schwannomatosis
- Disease severity requirement: None
- Treatment Status: No restrictions on prior or current pain treatments
- *Clinical trial population requires moderate to severe pain (NRS-11 ≥ 5) and may exclude patients receiving certain treatments based on drug-specific contraindications*

Study Design

- Prospective, longitudinal, online-only study
- Phase 1: Prior to comparator intervention trials (2015-present);
  Phase 2: Concurrent with comparator trial (STARFISH)
- Multi-institutional recruitment; single site oversight
- No patient advocacy involvement in Phase 1 design;
  Phase 2 will include input from REiNS patient representatives, including suggestion to move to mobile app for data collection
- Planned Duration of Study: Phase 1: 5+ years; Phase 2: 6 months

Study Evaluations

- Self-reported demographic, clinical, and PRO data only
  - Phase 1: Every 6 months
  - Phase 2: Weekly (with daily NRS-11 for limited duration)
- *Phase 2 PRO measures identical to STARFISH, but collected more frequently*

(Trial will collect NRS-11 weekly, other PROs once every 12 weeks)

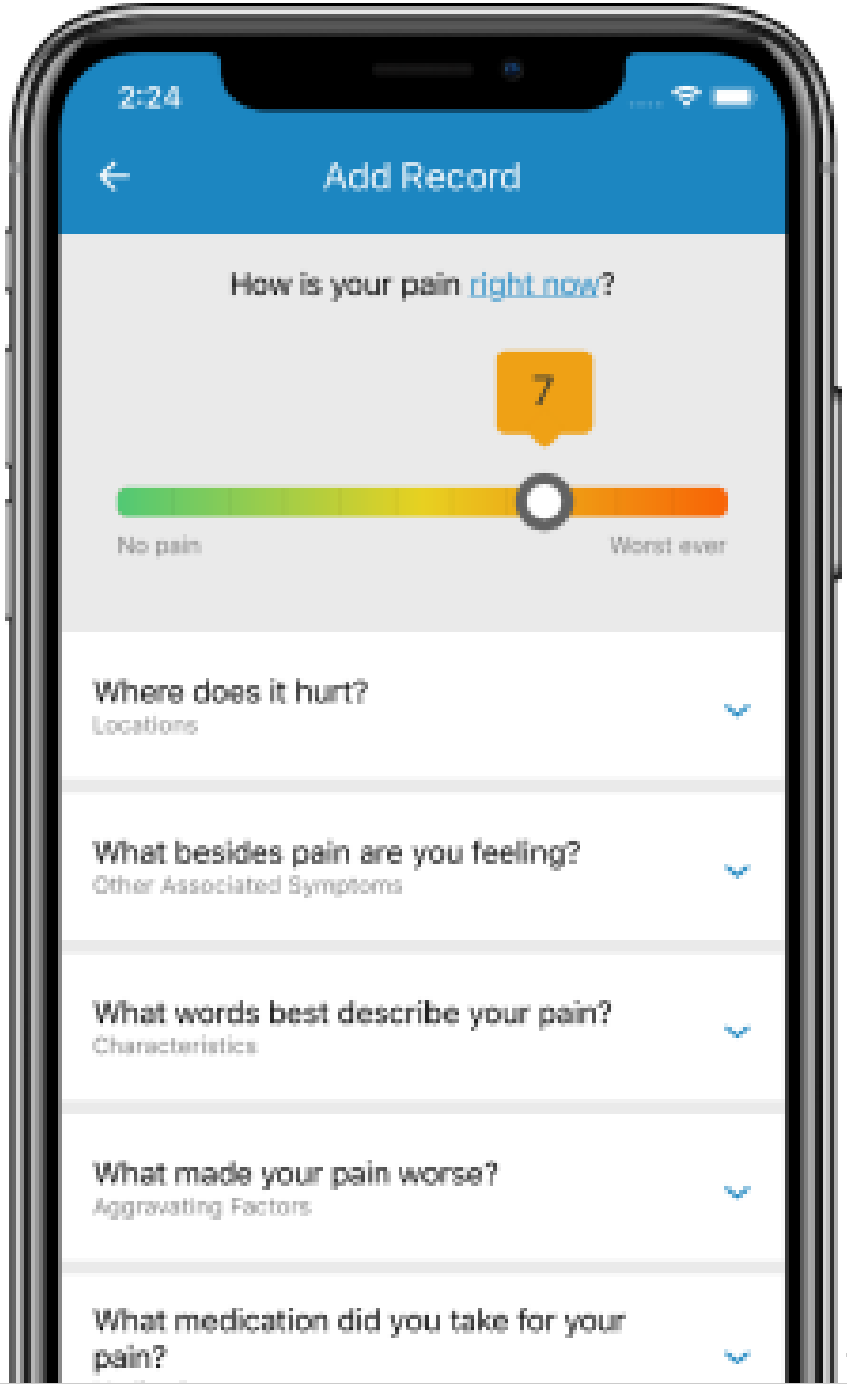
	Phase 1	Phase 2
Pain Intensity*	NRS-11	
Pain Interference*	PROMIS	
Physical Function*	PROMIS	
Depression	PROMIS	
Pain Quality	ID-PAIN	PROMIS + PQAS-R
Anxiety	PROMIS	PASS-20
Self-efficacy	PSEQ-2	PROMIS Self-Efficacy Managing Symptoms
Social Roles	N/A	PROMIS
Change Over Time	N/A	GIC

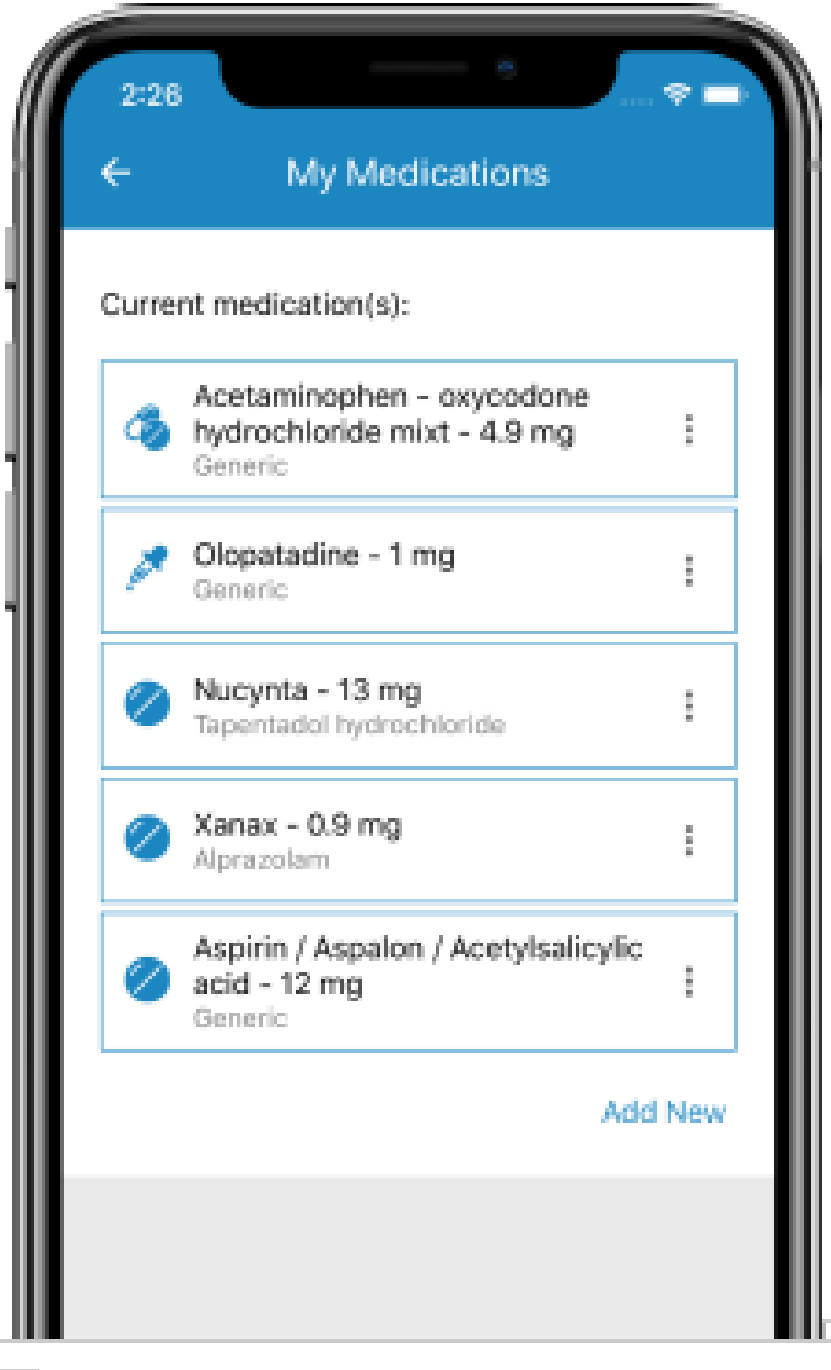
Data Collection and Analysis

- Data directly entered by patients
  - Phase 1: RedCap (website)
  - Phase 2: Manage My Pain (mobile app)
- REDCap and ManageMyPain both allow for real-time monitoring and keep audit trail of changes; data stored within program and can be exported for analysis
- Need to establish prospectively defined statistical analysis plan and determine how to drop-outs/missing data
- Analysis will focus on:
  - Look for patterns in PRO measures to look for phenotypic subgroups
  - Determine the proportion of patients who improve/decline in each PRO over time

Regulatory Aspects

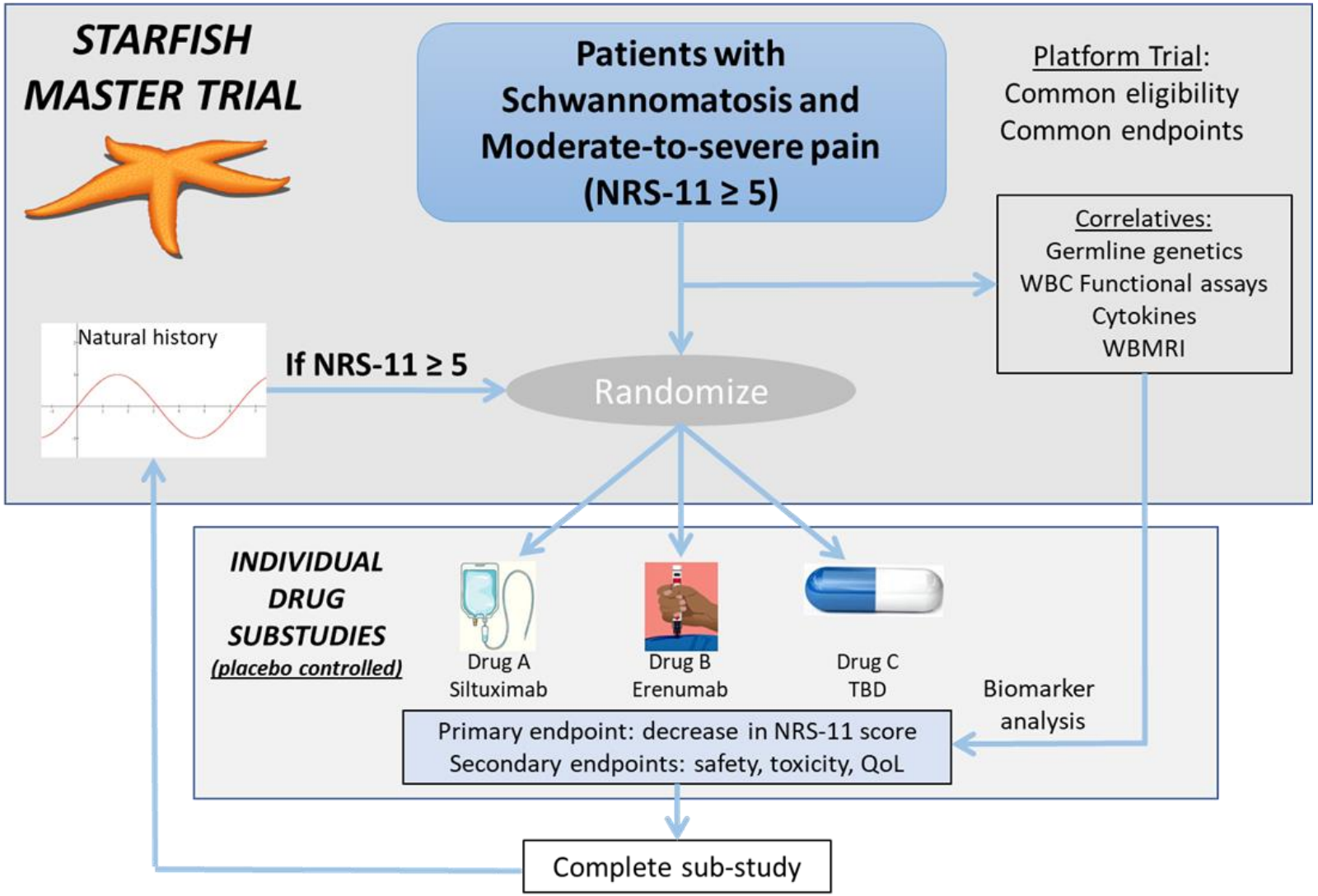
- Informed consent:
  - All participants consented to participate in International Schwannomatosis Registry via local, IRB-approved procedures
  - All participants read a short fact sheet about the study online, and check a box indicating their consent to participate in survey
- Participant confidentiality
  - Patient contact information retained to enable longitudinal follow-up
  - All data stored with participant ID only


2:24
Add Record
How is your pain right now?
7
No pain
Worst ever
Where does it hurt?
Locations
What besides pain are you feeling?
Other Associated Symptoms
What words best describe your pain?
Characteristics
What made your pain worse?
Aggravating Factors
What medication did you take for your pain?

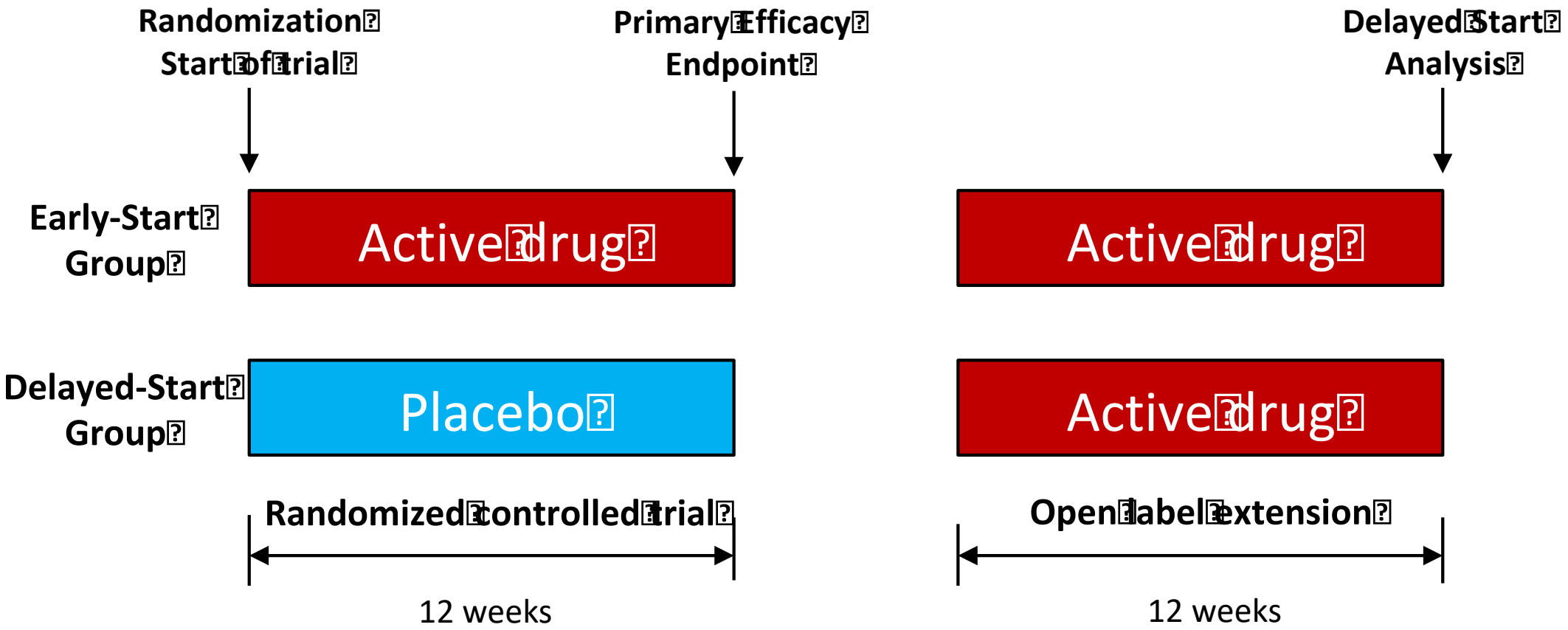

2:26
My Medications
Current medication(s):
Acetaminophen - oxycodone hydrochloride mixt - 4.9 mg
Generic
Olopatadine - 1 mg
Generic
Nucynta - 13 mg
Tapentadol hydrochloride
Xanax - 0.9 mg
Alprazolam
Aspirin / Aspalon / Acetylsalicylic acid - 12 mg
Generic
Add New


2:25
Records
INSIGHTS
CHARTS
RECORDS
55/55 records shown
Last 30 days
Pain Intensity
Pain Records: 36 4
Average: 4.6 0.8
10
9
8
7
6
5
4
3
2
1
0
14 Dec 2018
22 Dec 2018
30 Dec 2018
7 Jan 2019
13 Jan 2019

How does Natural History Study Compare to Interventional Trial?



How is Natural History Study and Population Similar / Different from Interventional Trial?



How is Natural History Study and Population Similar / Different from Interventional Trial?

- Natural history study will enroll a broader population, but sub-analyses could be matched to interventional trial
  - Interventional trials focused on people with moderate to severe pain (NRS-11 ≥ 5)
  - Interventional trials may exclude patients receiving certain treatments based on drug-specific contraindications
- PRO measures identical to comparator trial; trial will also collect baseline WBMRI, blood biomarkers, and archival tumors
- Limitations: Single-site protocols which may not represent all research priorities

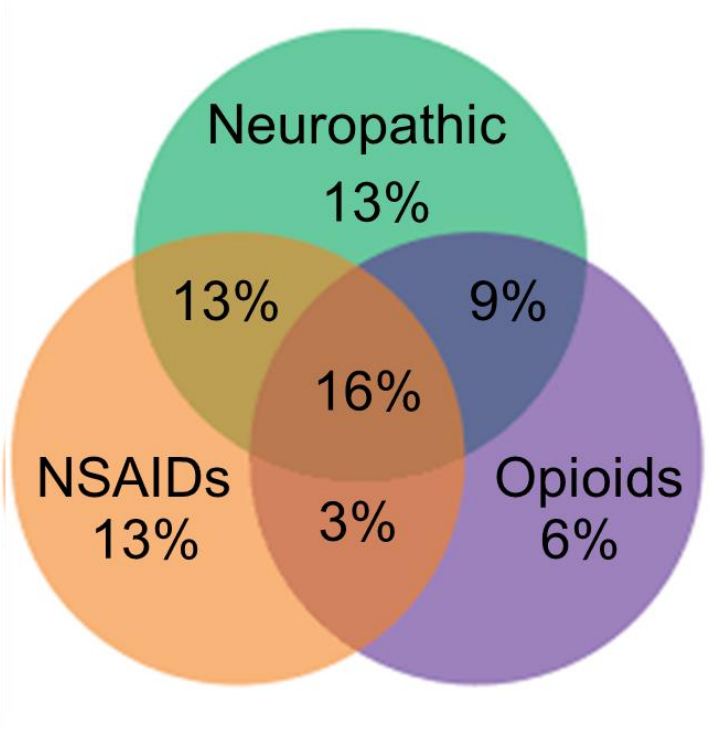
Preliminary results (Phase 1)

- Recruitment ran from November 2015 – November 2019 at 4 ISR sites: Mass General, New York University, Johns Hopkins, University of Manchester
- 79 adult patients enrolled
  - 58% female
  - Median age = 51 years (range, 30-78 years)
  - 16% had familial schwannomatosis
- Survey completion rates ≥75% over 3 years
  - Includes drop-out and missing data

Timepoint	Completion Rate
Baseline	79 (100%)
6 months	69 (87.3%)
12 months	63 (79.7%)
18 months	65 (82.3%)
24 months	63 (79.7%)
30 months	59 (74.7%)
36 months	60 (75.9%)

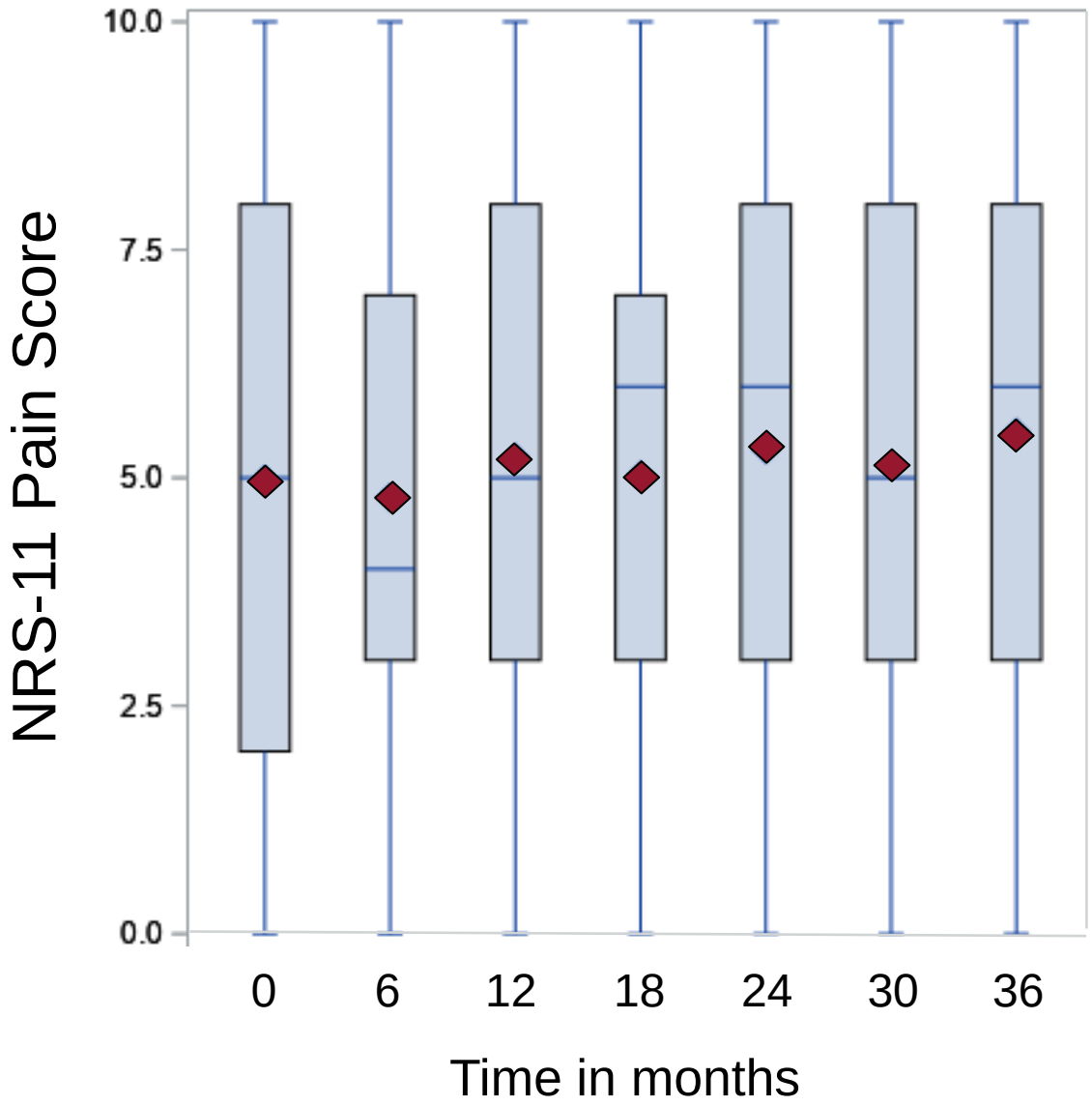
Study Participants: Baseline Characteristics

77% of patients were using pain medication



Patient Reported Outcome	Mean (Range)
NRS-11 Worst Pain Intensity	5 (range: 0 – 10)
PROMIS Pain Interference	56.0 (range: 40.7 – 77.0)
ID-Pain (Pain Quality)	2.3 (range: -1 – 5)

Group-Level Stability in Pain Intensity (NRS-11) Over Time



Mean NRS-11 = 4.8 to 5.5

Individual Improvements in Pain Intensity Using REiNS Criteria

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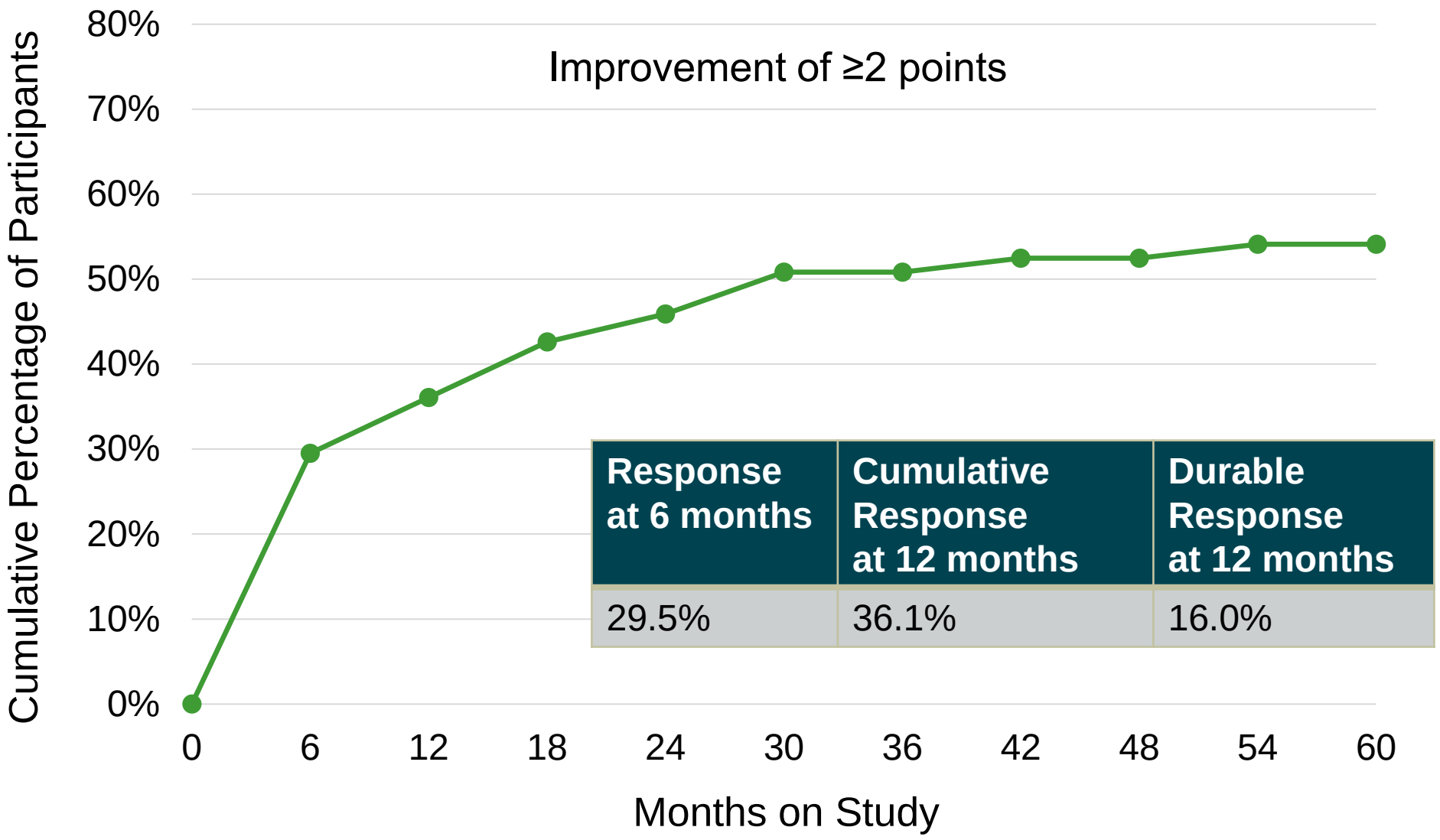
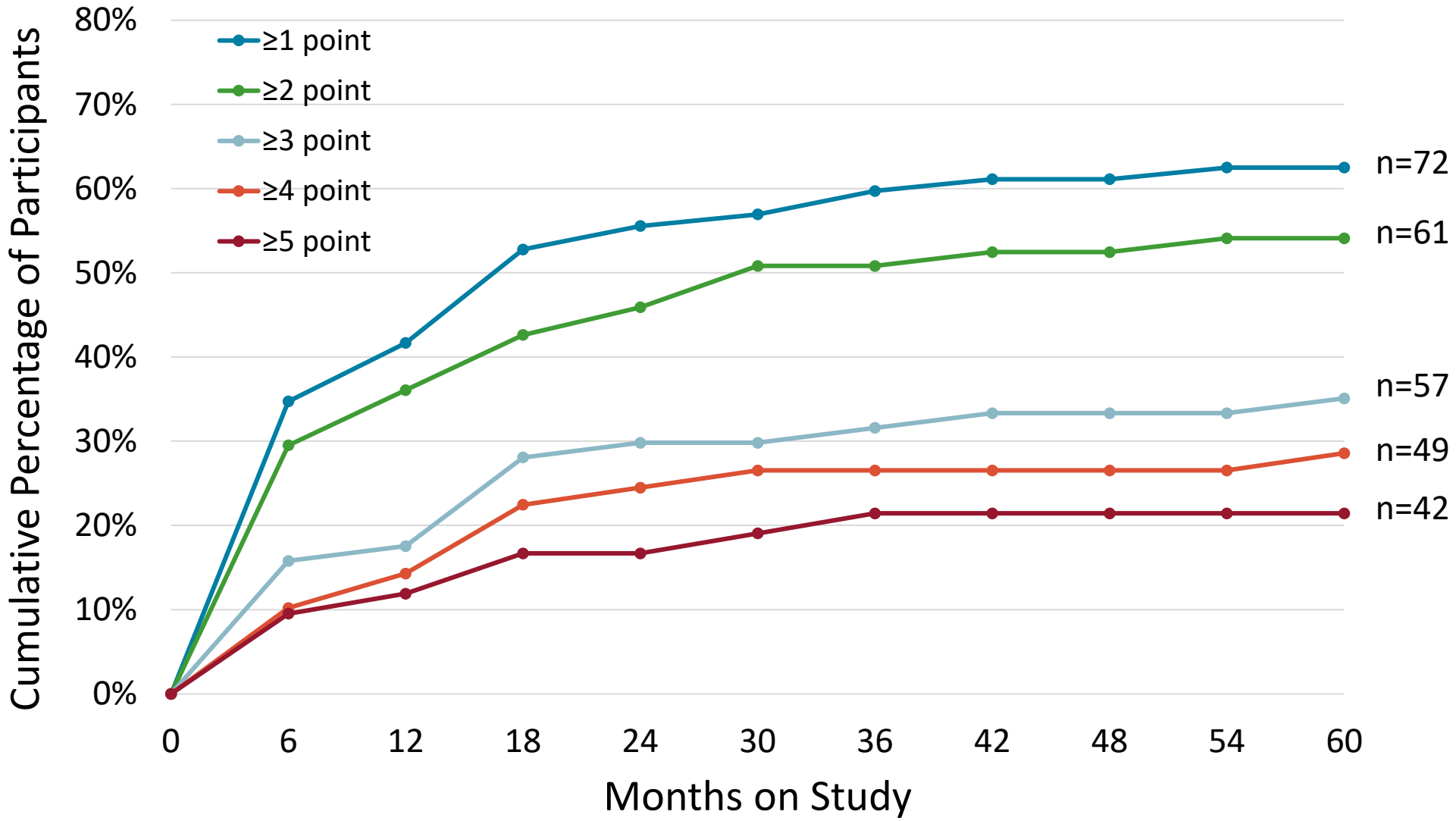


Response at 6 months	Cumulative Response at 12 months	Durable Response at 12 months
29.5%	36.1%	16.0%

N=61 patients
with baseline NRS-11
between 2 and 10

Cumulative Frequency of Pain Improvement with Alternate Thresholds



Eligible Baseline NRS-11 Scores
1 – 10
2 – 10
3 – 10
4 – 10
5 – 10

Other Pain-Related Constructs

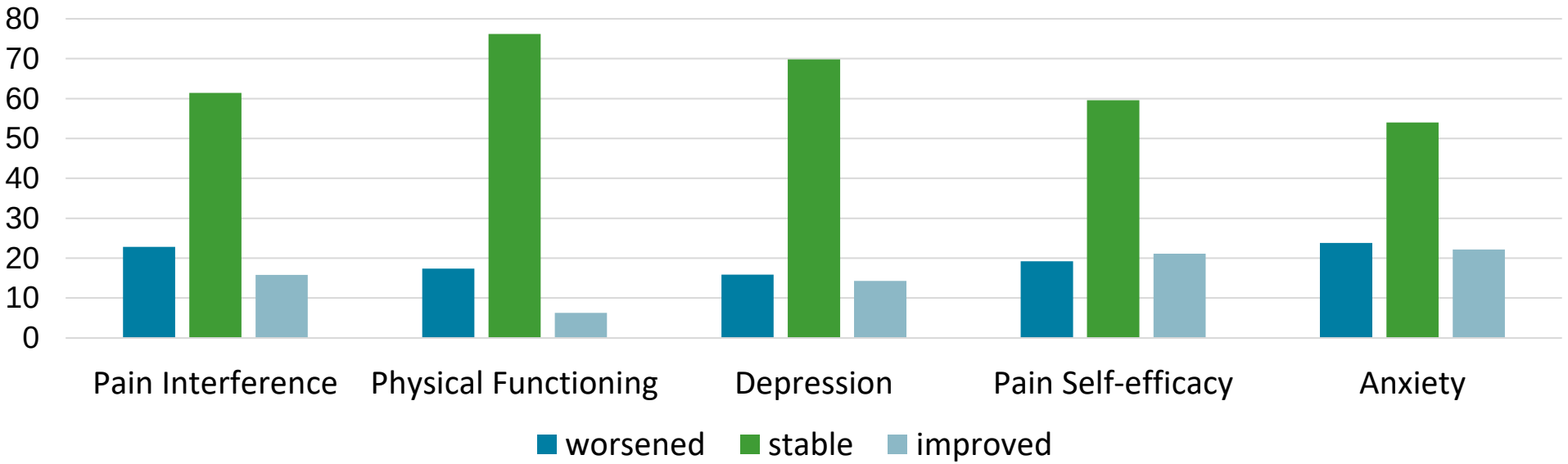
MASSACHUSETTS GENERAL HOSPITAL

Pain Intensity was associated with:

Pain Interference	Physical Function	Pain Self-Efficacy	Pain Quality	Depression	Anxiety
R = 0.78***	R = -0.65***	R = -0.46***	R = 0.44***	R = 0.35**	R = 0.2

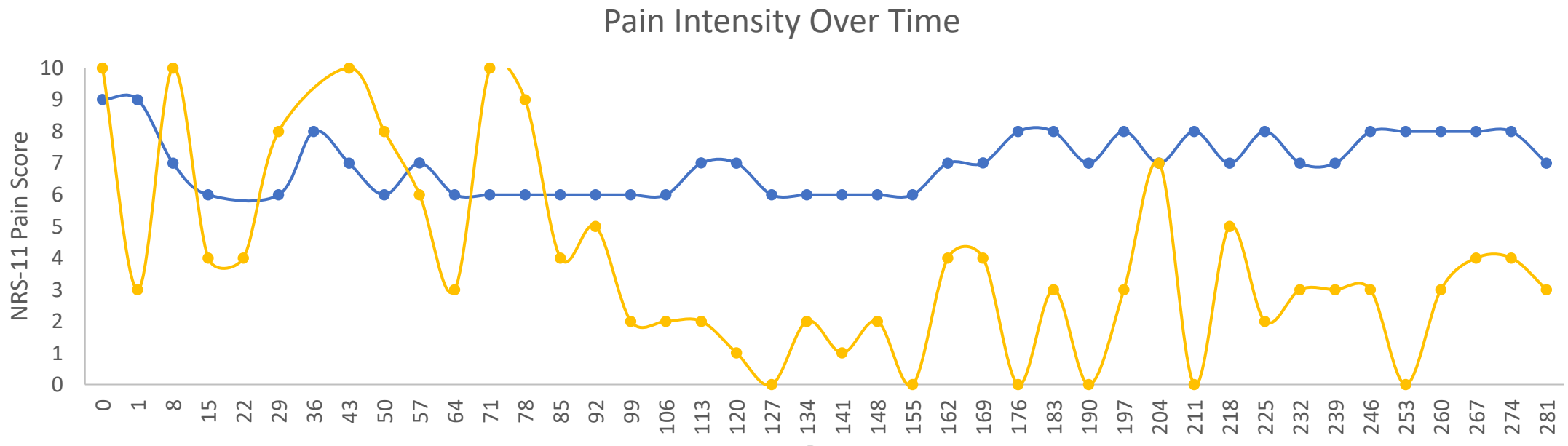
*	P < 0.05
**	P < 0.01
***	P < 0.001

Majority of patients are stable at 1 year:



Lessons learned from existing studies

- Need for more frequent data collection
  - To provide comparable data to clinical trials
  - To understand pain fluctuations and determine appropriate measurement intervals
  - Increases need for more user-friendly data collection platform
- More cognitive testing of PROs necessary for SWN-specific pain



Questions for next phase of the study

- Are there any regulatory concerns with using a commercial mobile app for data collection?
- Are PROs enough for drug approval for pain indication, or are other correlative studies (imaging, biomarkers) needed?
- Is 6 months sufficient follow-up?
  - More distal PROs may take longer to improve
  - How much durability of response will be necessary for approval?
- Are weekly PROs too burdensome?
- How to handle participant drop-out and missing data?
- Are we missing any important PRO constructs?

Checklist for Use of External Control Groups

The Use of External Control Design is Most Persuasive When: (Note: In many cases not all of these themes will be met and FDA will consider the totality of evidence)	**FDA Guidance**	**ICH E10**
• It is not possible and/or ethical to run a placebo control[1,2,4]	✓	✓
• There is no available therapy for comparison (usually the case for rare diseases)	✓	
• The disease progression is well understood or predictable[1,4,9]	✓	✓
• The outcome measure is objective[1,3,4–9,11]	✓	✓
• The treatment effect - is large/dramatic[1–4,9,11]	✓	✓
- is not affected by patient or investigator motivation or choice of subjects for treatment[3]	✓	
- has a strong temporal association with administration of the investigational product[3,4]	✓	
- is consistent with the expected pharmacological activity based on the target and perhaps shown in animal models[3]	✓	
- is measured in a manner that reasonably manages and minimizes bias[3]	✓	
• The control population closely resembles the treatment group including setting for and manner of treatment (i.e. standard of care)[1,2,4,8,10,11]	✓	✓
• Covariates influencing the outcomes of the disease are well characterized[1]		✓
• The control group is a well-documented population with access to individual patient records[1]		✓
• The results provide compelling evidence of a change in the established progression of disease[2]	✓	

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