

# REiNS Functional and PRO Recommendations Applied in NF1 Trials: From Theory to Practice

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REiNS Winter Meeting 2019

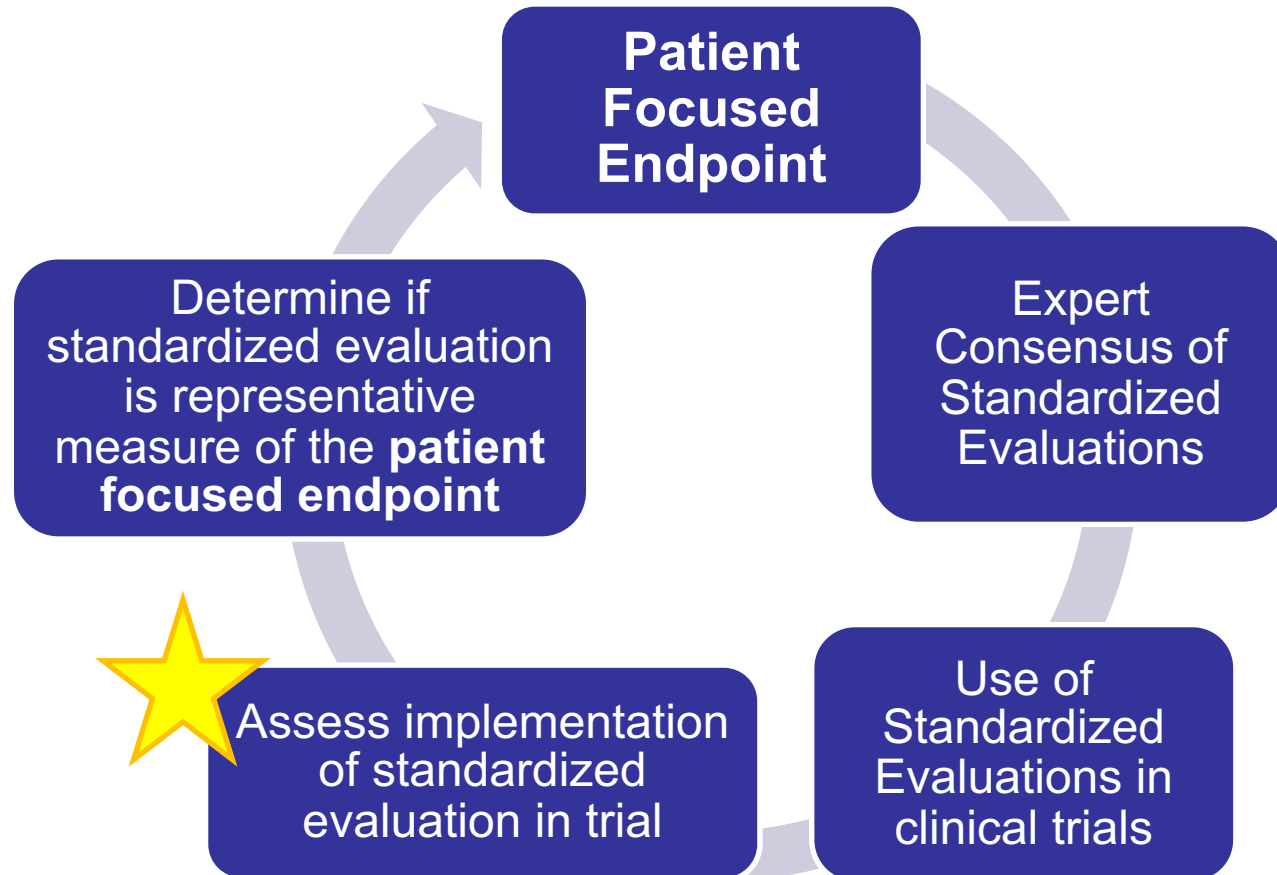
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Response Evaluation In Neurofibromatosis Schwannomatosis  
INTERNATIONAL COLLABORATION

# Background: Clinical Trial Design

- “Standard” endpoints used in cancer studies (e.g. survival, tumor response) not sufficient for Neurofibromatosis/ Schwannomatosis
- How to develop *clinically meaningful* endpoints?



# REiNS Clinical Trial Recommendations



- 2013 Neurology Supplement:

Clinical Trial Endpoint	Recommended Primary Outcome Measure(s)	Recommended Secondary Outcome Measure(s)
<b>Pain</b>	Numeric Rating Scale-11	
<b>Visual Acuity</b>	Teller Acuity Cards	HOTV; Visual Quality of Life PRO
<b>Hearing</b>	Maximum Word Recognition Score	Pure tone average
<b>Facial Function</b>	SMILE analysis	House-Brackmann Scale
<b>Tumor Response</b>	Volumetric MRI	



# REiNS Clinical Trial Recommendations



- 2016 Neurology Supplement

Clinical Trial Endpoint	Recommended Primary Outcome Measure(s)	Recommended Secondary Outcome Measure(s)
<b>Pain Interference</b>	Pain Interference Index (Age 6-24) PROMIS-PI (Age ≥ 18)	
<b>Physical Functioning</b>	PROMIS-Physical Functioning (Self report/Parent Proxy)	
<b>Sleep</b>	Apnea-Hypopnea Index	SpO <sub>2</sub> , End Tidal CO <sub>2</sub> , Arousal Index
<b>Pulmonary</b>	FEV <sub>1</sub> (FEV <sub>0.75</sub> for preschoolers) R <sub>10</sub>	FVC, PEF, Forced Expiratory Flows R <sub>5</sub> , R <sub>20</sub>
<b>Attention</b>	Digit Span WISC-IV (performance-based) Conners Scale (observer-rated)	



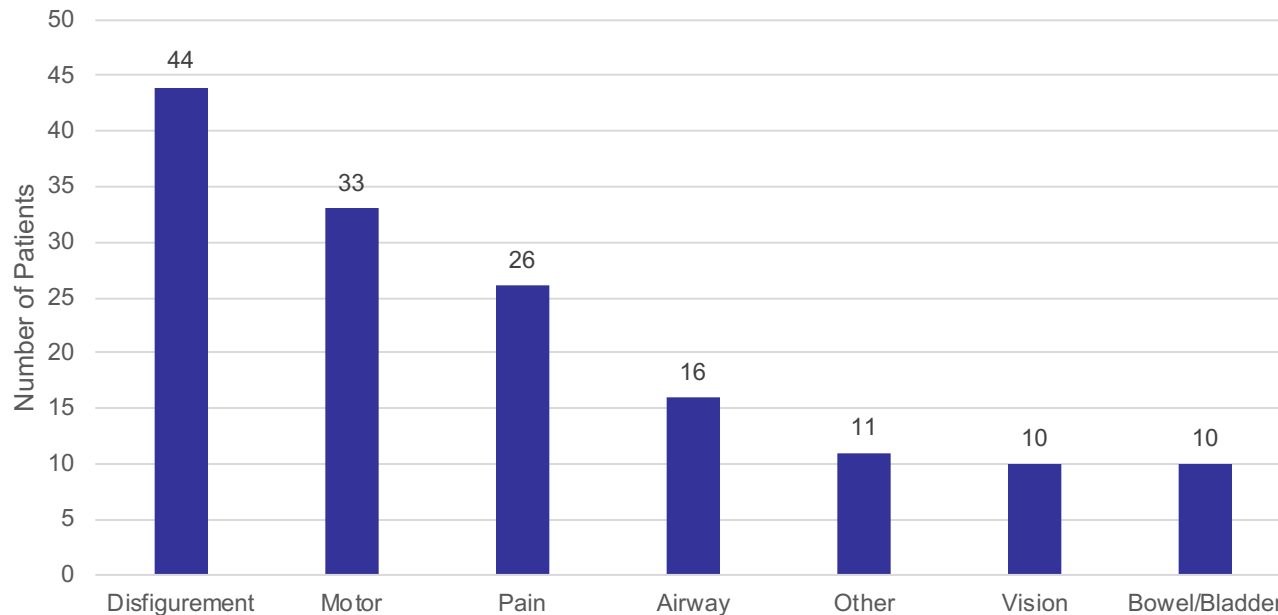
\*Additional publications on whole-body MRI and biomarkers also included in this supplement

# Implementation of REiNS Recommendations in NF1

- Phase 2 Trial of Selumetinib in Inoperable Plexiform Neurofibromas
- Study initiated in 2015
- 50 Pediatric patients enrolled
- Wide variety of PN-related morbidities



PN Related Baseline Morbidities



# Challenge #1: Who gets what tests?

- Not all patients need all of the functional and PRO measures
- For SPRINT: PN Location and Morbidity Form

To be completed by the Site PI prior to starting treatment

- Assess PN location(s) by clinical exam and imaging studies (target PN and up to 2 non target PN)
- List morbidities present using numbers below (see list)
- If no morbidity present, list potential morbidities based on PN site(s)
- Assign patient to Stratum 1 or 2 based on the presence/absence of PN-related morbidity

PN Location	PN Associated Morbidities					
	R	L	B/L	Pain (Y/N)	Present PN Morbidities (using numbers listed below)/ Comments	Potential Morbidities
Orbit						
Face						
Ear canal						
Tongue						
Anterior neck/upper airway						
Posterior neck (cervical paraspinal)						
Mediastinum						
Intra-thoracic						
Thoracic/paraspinal/chest wall						

What about morbidities related to non-target PN?

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Morbidity:			
1- Vision loss	4- Difficulty swallowing	8- Bladder dysfunction	12- Sensory deficit
2- Facial motor dysfunction	5- Abnormal speech	9- Bowel dysfunction	13- PN related Disfigurement/ appearance
3- Auditory loss	6- Airway obstruction	10- Motor weakness	
	7- Respiratory compromise	11- Decreased range of motion	
14- Other (please describe):			

Site PI Morbidity Assignment:  Motor  Airway  Vision  Disfigurement  Bowel/Bladder  
 Other (please specify): \_\_\_\_\_



# Example: Complexity of Functional Evaluations

8 y/o with left neck, arm, airway PN



## 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  $\geq 5$  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 Assessment



# Challenge #2: Implementation of PROs

	PN Morbidity Category	Baseline Evaluation	Timepoint (Exam prior to cycle(s) listed, 1 cycle = 28 days)
★ Pain Intensity (NRS-11)*	All ≥ 8 years	X	3, 5, 9, 13 then every 12 cycles
★ Pain Interference index (PII)*	All ≥ 5 years	X	
PedsQL QOL Scales*	All	X	
Global Impression of Change (GIC)*	All ≥ 5 years		
★ PROMIS Mobility & Upper Extremity	Motor	X	

★ REiNS Recommended Measure

- Required training of all outside sites who were performing the tests
- Completed forms needed to be carefully checked for errors in real time
- Ability to update the form based on patient feedback (e.g. NRS-11)





# NRS-11

- Rating pain on scale from 0-10
- REiNS Endorsed Measure

1. Please circle the one number that best describes your overall pain at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

2. Please circle the one number that best describes your overall tumor pain at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

3. We would like you to pick one tumor and tell us how much that one tumor hurts throughout the whole study.

Where on your body is that tumor? \_\_\_\_\_

Please circle the one number that best describes the pain in that one tumor at its **worst** during the past 7 days.

0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine



- Ongoing focus groups during the study found that patients could differentiate between different tumor pains and some patients found it helpful to have the tumor selected for them to rate

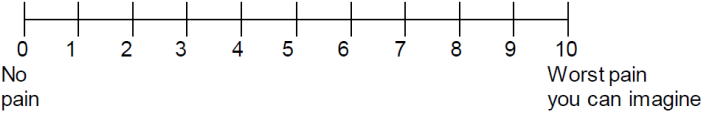
# NRS-11: Revised

- Allowed patients to pick their own tumor which caused the worst pain and then ALSO rate the target PN if it was a different location

1. Please pick your most important plexiform neurofibroma tumor pain. We will ask you to tell us about that same tumor pain at each study visit.

Where on your body is that tumor pain? \_\_\_\_\_.

Please circle the one number that best describes that tumor pain at its **worst** during the past 7 days.



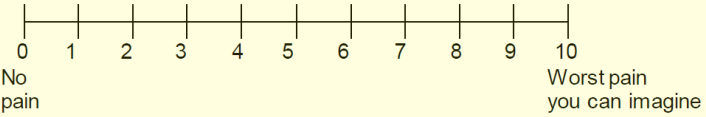
0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

2. The doctor's have picked the plexiform neurofibroma tumor in your \_\_\_\_\_ to measure for this study. We call this the "target tumor."

Is this the same tumor as the one you picked in the 1<sup>st</sup> question?  Yes  No

If yes, skip this question and continue to question #3.

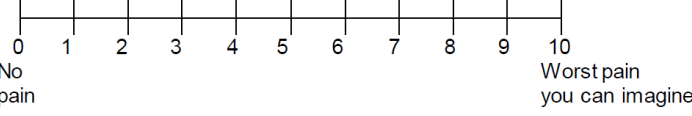
If no, please circle the one number that best describes the pain from your target tumor at its **worst** during the past 7 days.



0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

3. Do you have tumor pain in more than one place on your body?  Yes  No

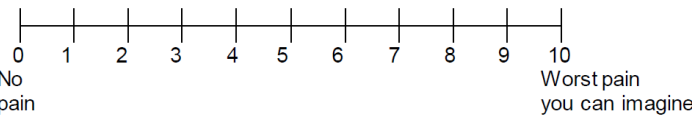
If yes, please circle the one number that best describes your overall tumor pain at its **worst** during the past 7 days.



0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

4. Do you have other kinds of pain (for example, headaches or back pain)?  Yes  No

If yes, please circle the one number that best describes your overall pain at its **worst** during the past 7 days (including tumor pain and any other kinds of pain.)

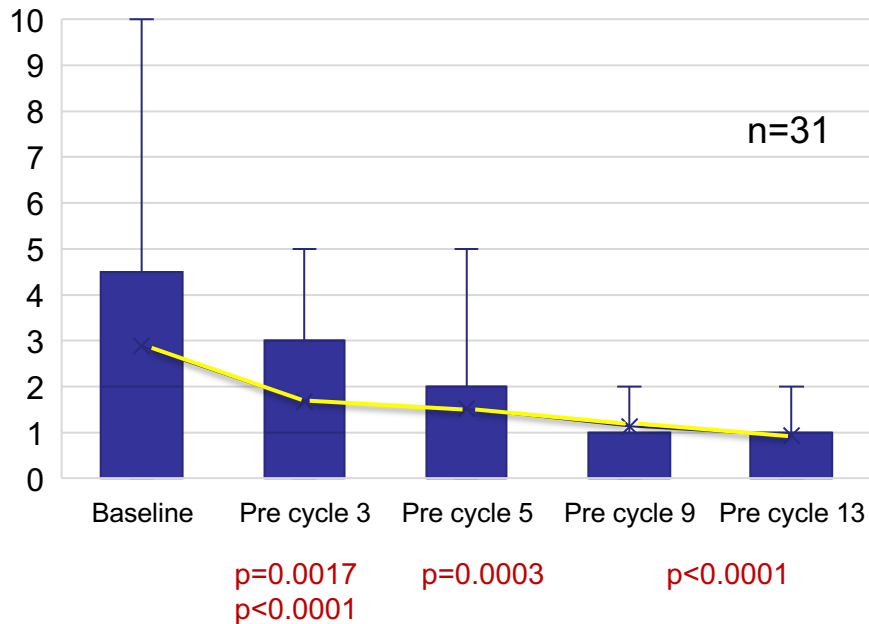


0 1 2 3 4 5 6 7 8 9 10  
No pain Worst pain you can imagine

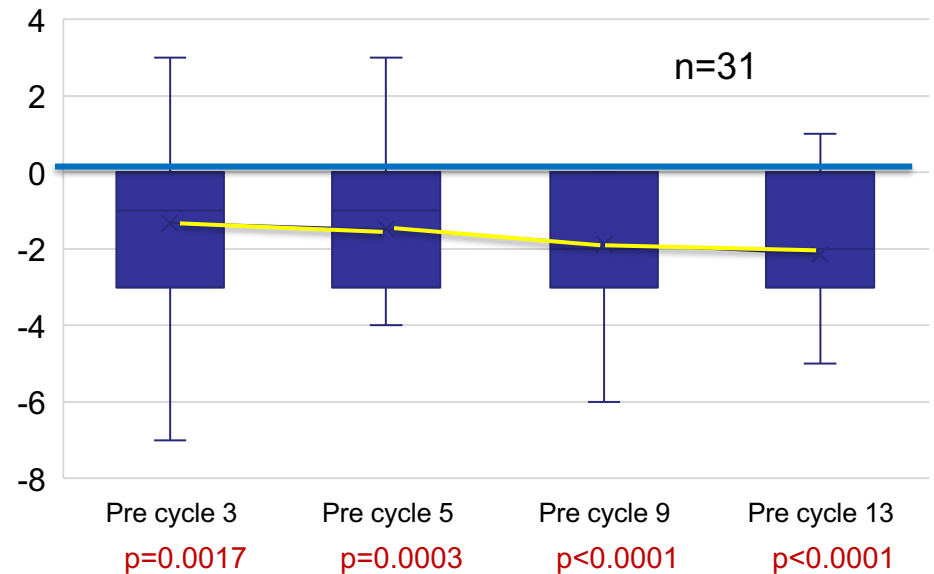


# NRS-11 Self-report of Tumor Pain Intensity

Overall Decrease in Tumor Pain Intensity

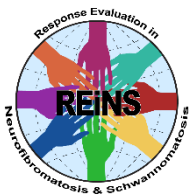


Change from Baseline in Tumor Pain Intensity



- Includes 5 patient's ratings of 0 (no pain) at baseline
- Excludes 2 patients with only baseline ratings

- By pre-cycle 13, 52% of NRS-11 tumor pain intensity ratings decreased  $\geq 2$  points



# Challenge #3: Implementation of Functional Evaluations

	PN Morbidity Category	Baseline Evaluation	Timepoint (Exam prior to cycle(s) listed, 1 cycle = 28 days)
Photography/Videography	All visible PN	X	5, 9, 13 then every 12 cycles
Strength Evaluation (Manual Muscle Test (MMT) using MRC scale)	Motor	X	
Range of Motion	Motor	X	
Leg Length Evaluation, Grooved Pegboard	Motor	X	
6-Minute Walk Test	Motor, Airway	X	
Polysomnography	Airway	X	
Pulmonary Function Tests (Spirometry, Impulse Oscillometry)	Airway	X	
Exophthalmometry	Orbital	X	
Visual Acuity	Orbital	X	
Bowel/Bladder Questionnaire	Bowel/Bladder	X	
Audiologic & Otolaryngology Exam	Other	X	
Speech evaluation/Swallow Study	Other	X	

# Airway Assessments

REiNS PROPOSED	TRIAL IMPLEMENTATION
Impulse Oscillometry: $R_{10}$	
Spirometry: FEV <sub>1</sub> (absolute)	
Sleep Study: Apnea-Hypopnea Index	



# Airway Results

Airway Morbidity (n = 16)	MedNian (range)	Median (range)	Median Ratio of PreC13: Baseline (range)
FEV <sub>1</sub> (liters) (n=11)	1.32 (0.64–3.84)	1.36 (0.72–4.08)	<b>1.15**</b> <b>(0.98–1.97)</b>
FEV1 % Predicted (n = 11)	84 (35–110)	92 (41–131)	1.021 (0.88–1.75)
Impulse Oscillometry (cmH <sub>2</sub> O)			
R <sub>5</sub> (n = 10)	7.01 (2.96–15.5)	6.08 (2.51–10.76)	<b>0.78*</b> <b>(0.61–1.17)</b>
R <sub>20</sub> (n = 10)	3.76 (2.54–5.81)	3.56 (2.54–5.17)	0.95 (0.76–1.62)
Impulse Oscillometry % Predicted			
R <sub>5</sub> (n = 10)	124 (80–317)	110 (73–194)	<b>0.83*</b> <b>(0.61--1.17)</b>
R <sub>20</sub> (n = 10)	84.5 (45–133)	82 (54–118)	0.95 (0.72–1.64)

\* p<0.05; \*\* p<0.01; \*\*\* p<0.001; using Wilcoxon signed rank test, testing difference of pre-C13 to baseline ratio from 1.0 (no change) or comparing median difference between baseline and pre-Cycle 13 scores

- REiNS Clinically Meaningful Thresholds:

- FEV<sub>1</sub>:

- 7/11 patients had >12% improvement in FEV<sub>1</sub>
- 3/11 patients had >12% improvement FEV<sub>1</sub>% pred

- Impulse Oscillometry

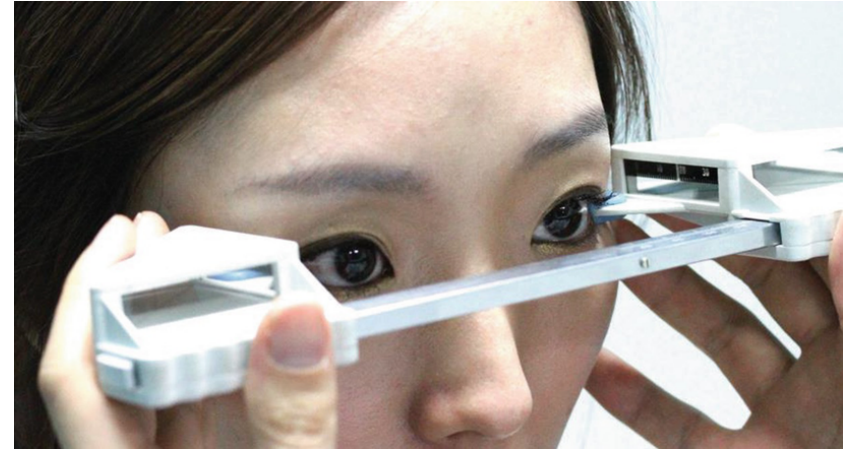
- 5/10 patients had > 20% improvement in R5 absolute and R5 % pred 14



# Orbital Plexiform Disfigurement: Exploratory (Not REiNS Recommended)

## • Exophthalmometry

- Need to measure from the SAME baseline position everytime
- With facial PN, difficult to get consistent measurements
- Cooperation issues with young children



**AFFECTED Side (n = 10)**

Study ID	Baseline	PreC13	Change (PreC13 - BL)
1019001	24	Not measured	N/a
1019002	15.67	Not measured	N/a
1019005	14.33	15.33	1
1019007	7	8.67	1.67
1019010	Not measured	13	N/A
2019001	33	37	4
2019008	16	16	0
3019001	Enucleated	Enucleated	N/a
3019007	Enucleated	Enucleated	N/a
3019009	Not measured	24	N/a

**UNAFFECTED Side (n = 10)**

Study ID	Baseline	preC13	Change (PreC13 - BL)
1019001	10	8	-2
1019002	14	Not measured	N/a
1019005	14	15.67	1.67
1019007	8	8.67	0.67
1019010	Not measured	13	N/a
2019001	10	20	10
2019008	11.67	15	3.33
3019001	Not measured	Not Measured	N/a
3019007	Not Measured	Not Measured	N/a
3019009	Not measured	15	N/a

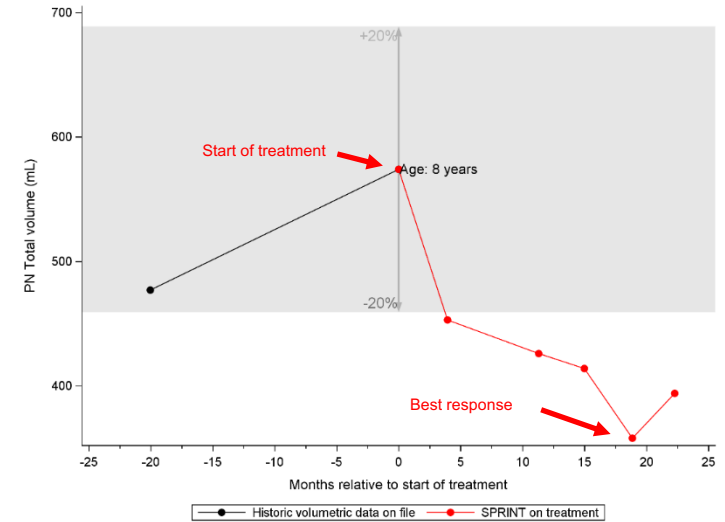
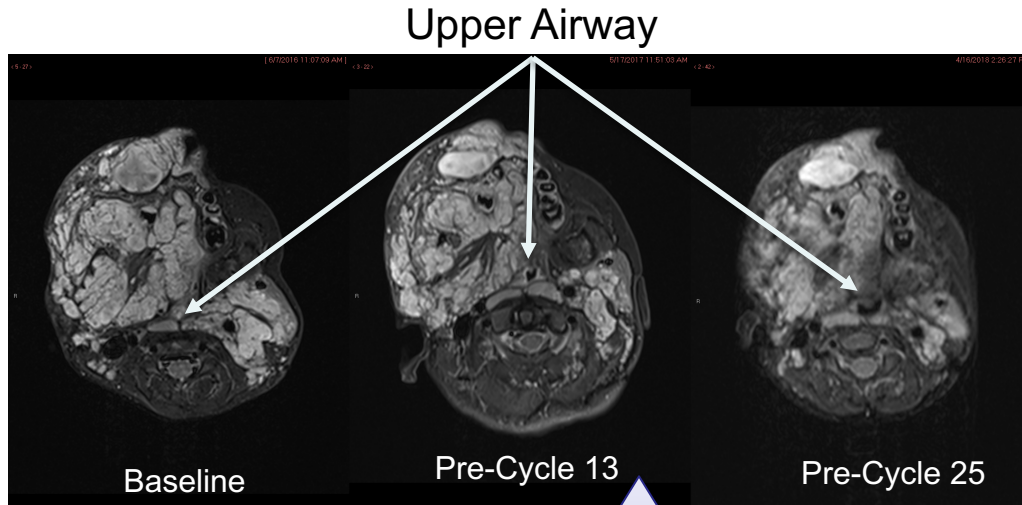
# Challenge #4: “Other” Morbidities

- Disfigurement: MOST COMMON morbidity
  - No current validated rating scale
  - Have standardized photography – developing a scale to evaluate
- Speech/Swallow
  - Narrative reports
  - Need to establish standardized measures
- Tracheostomy patients
  - Unable to undergo standard pulmonary function testing
- Orbital PN causing Enucleation
  - Shrinkage of tumor CAN'T improve vision
  - Importance of PREVENTION





# Limitations of Standardized Functional Evaluations: Patient 3019009



Baseline

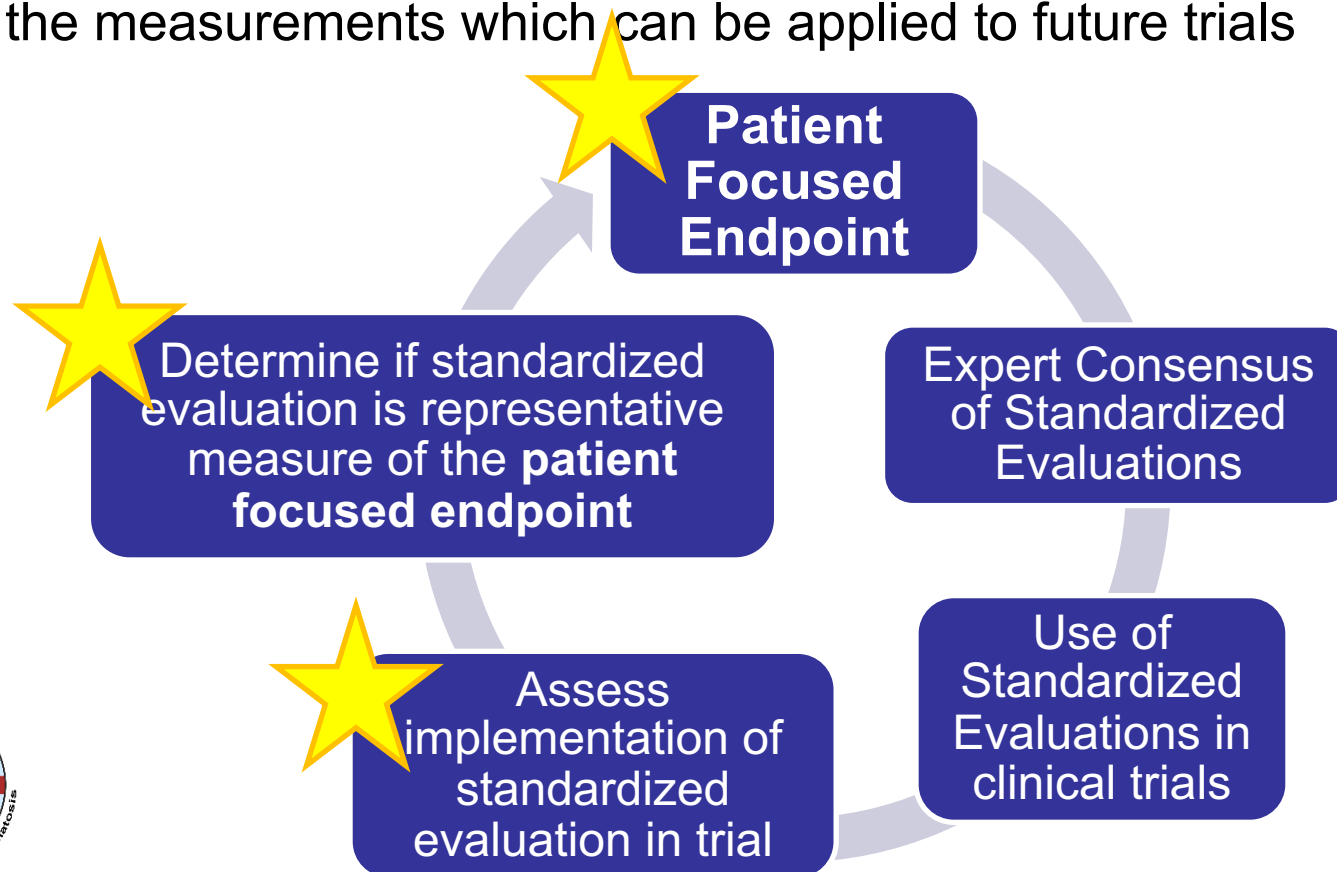
Patient  
Decannulated!



Pre Cycle 25

# Key Conclusions

- REiNS toolbox = essential framework for evaluating functional and PRO endpoints in clinical trials
- REiNS Measurements in SPRINT Study:
  - Able to demonstrate clinically meaningful improvement
  - ALSO learned important lessons about practical implementation of the measurements which can be applied to future trials



# Next Steps...

- Reassessing Current Recommendations
- Expand the current toolbox!
- Recommended Tools Needed For:

- Disfigurement
  - PN related, cNF related, orbital PN
- Skeletal endpoints
- Motor Function
- Bowel/Bladder dysfunction
- Speech/swallow endpoints

Work ongoing in  
REiNS and  
elsewhere!



# Any Questions?

