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Taking the REiNS: How REiNS Clinical Trial Recommendations Contributed to the FDA Approval of Selumetinib for NF1

REiNS Summer Meeting 2020

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Response Evaluation In Neurofibromatosis Schwannomatosis

INTERNATIONAL COLLABORATION

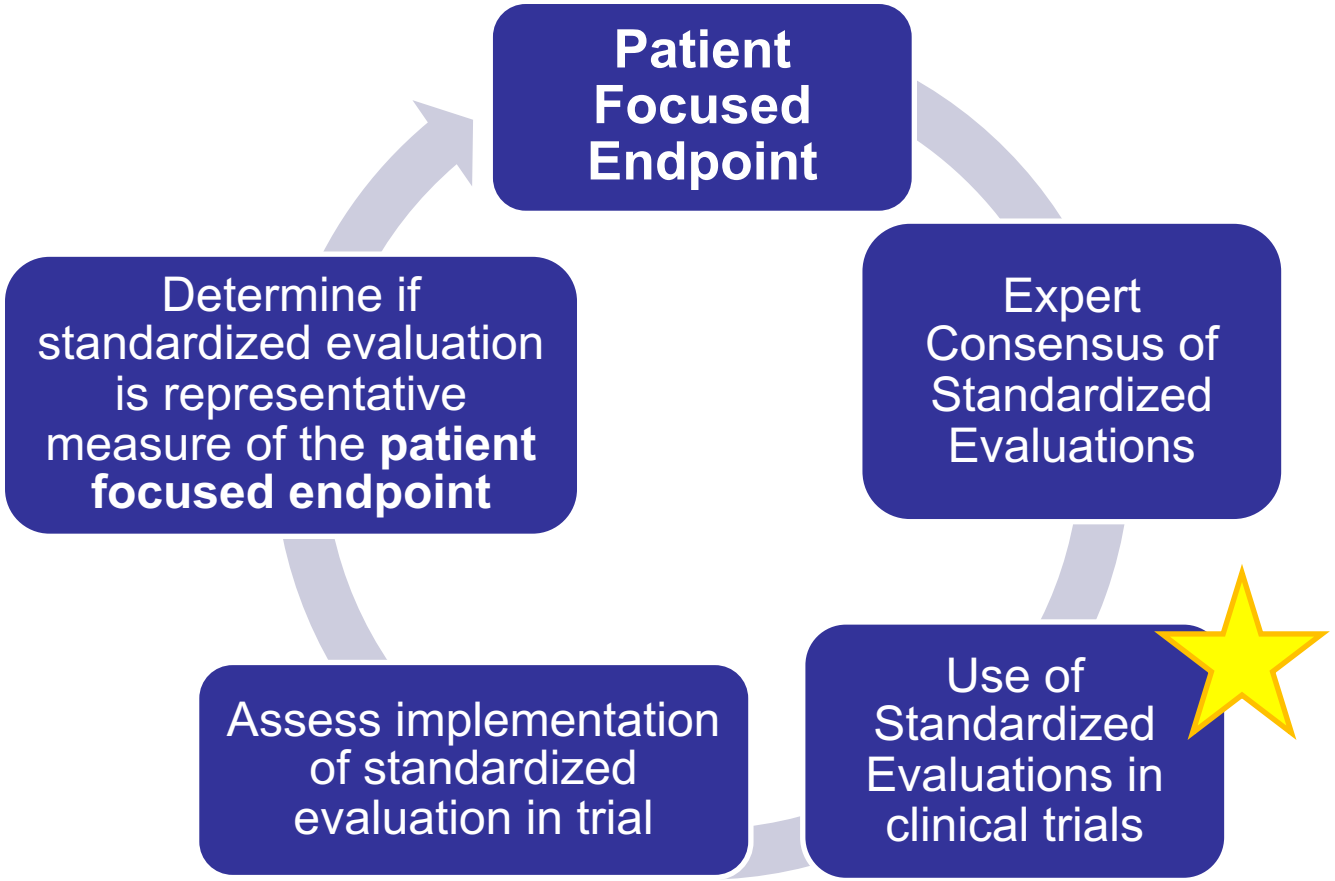
Background

- REiNS founded in 2011 by Drs. Plotkin and Widemann
- REiNS Mission Statement:

“To develop new standardized response criteria for determining treatment response in patients with NF1, NF2, and schwannomatosis.”

- Representatives from the FDA have been attending REiNS meetings since 2014

Development of Clinical Trial Endpoints



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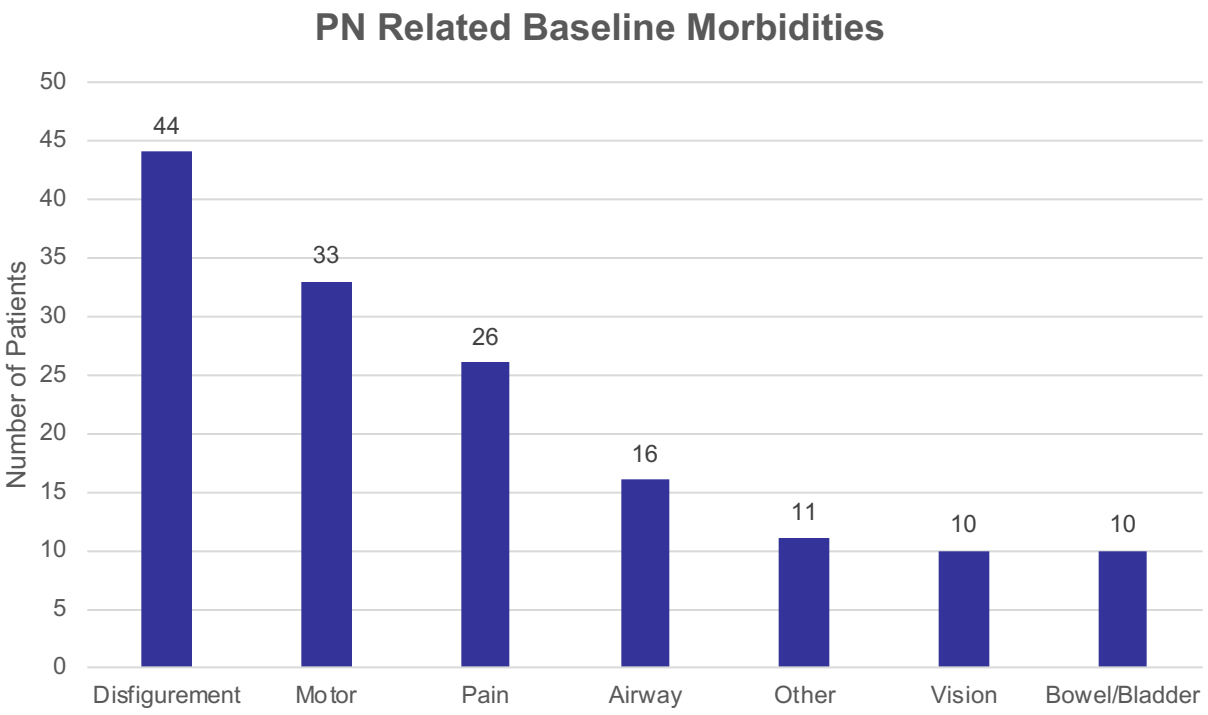
SPRINT Trial: Selumetinib for Children with NF1 and Inoperable Plexiform Neurofibromas (PN)

- Phase 1 opened to enrollment in 2011
- REiNS recommendations published in 2013 and 2016
- Phase 2 study began enrollment in 2015
  - Incorporated REiNS endpoints where available
- 50 patients enrolled 2015-2016:



REiNS Clinical Trial Recommendations

- 2013 Neurology Supplement:

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

REiNS Clinical Trial Recommendations

- 2016 Neurology Supplement

Clincial Trial Endpoint	Recommended Primary Outcome Measure(s)	Recommended Secondary Outcome Measure(s)
Pain Interference	Pain Interference Index (Age 6-24) PROMIS-PI (Age ≥ 18)	
Physical Functioning	PROMIS-Physical Functioning (Self report/Parent Proxy)	
Sleep	Apnea-Hypopnea Index	SpO_2, End Tidal CO_2, Arousal Index
Pulmonary	FEV_1 ($FEV_{0.75}$ for preschoolers) R_{10}	FVC, PEF, Forced Expiratory Flows R_5, R_{20}
Attention	Digit Span WISC-IV (performance-based) Conners Scale (observer-rated)	

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

REiNS Criteria in SPRINT

- Primary Endpoint: Tumor Volumetric Response
  - Using the response criteria from REiNS to define a partial response (≥ 20% tumor shrinkage) was ESSENTIAL to the FDA submission
- Secondary Endpoints:
  - Functional Evaluations
    - Airway (PFTs, sleep studies)
    - Visual Acuity
  - Patient Reported Outcome Measures
    - NRS-11 (Pain)
    - Pain Interference
    - PROMIS Physical Functioning

"REiNS" mentioned **138** times in the Phase 2 Case Study Report submitted to the FDA

Implementation of REiNS Criteria: Lessons Learned

Patient Reported Outcome Measures

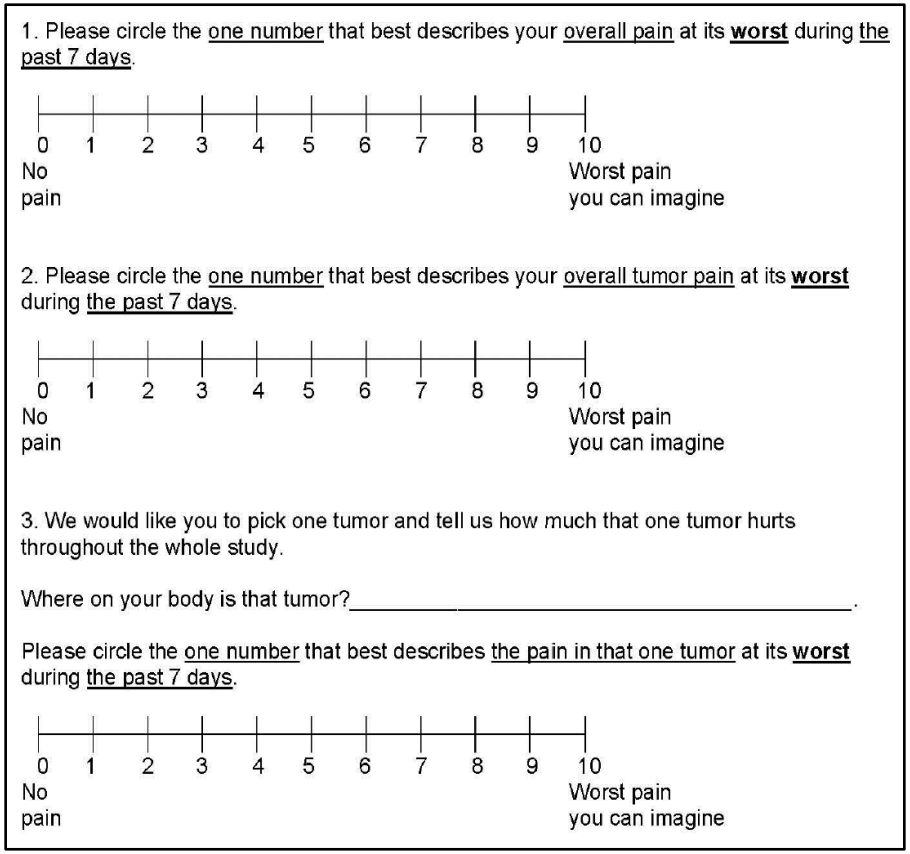
	PN Morbidity Category	Baseline Evaluation	Timepoint (Exam prior to cycle(s) listed, 1 cycle = 28 days)
★ Pain Intensity (NRS-11)*	All ≥ 8 years	X	3, 5, 9, 13 then every 12 cycles
★ Pain Interference index (PII)*	All ≥ 5 years	X	
PedsQL QOL Scales*	All	X	
Global Impression of Change (GIC)*	All ≥ 5 years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

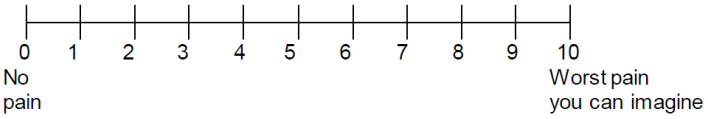
NRS-11: Revised

- 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.

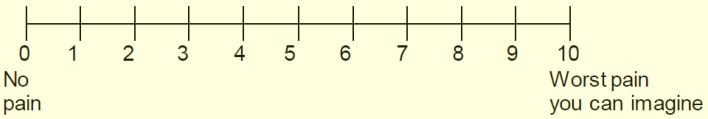


2. The doctor's have picked the plexiform neurofibroma tumor in your _____ to measure for this study. We call this the "target tumor."

Is this the same tumor as the one you picked in the 1st question? ☐ Yes ☐ No

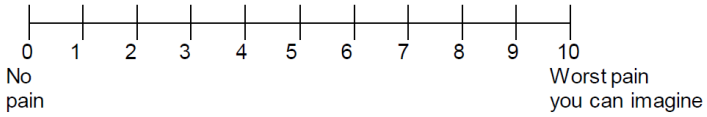
If yes, skip this question and continue to question #3.

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



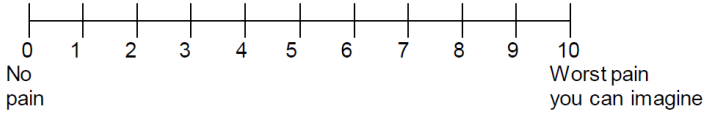
3. Do you have tumor pain in more than one place on your body? ☐ Yes ☐ No

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



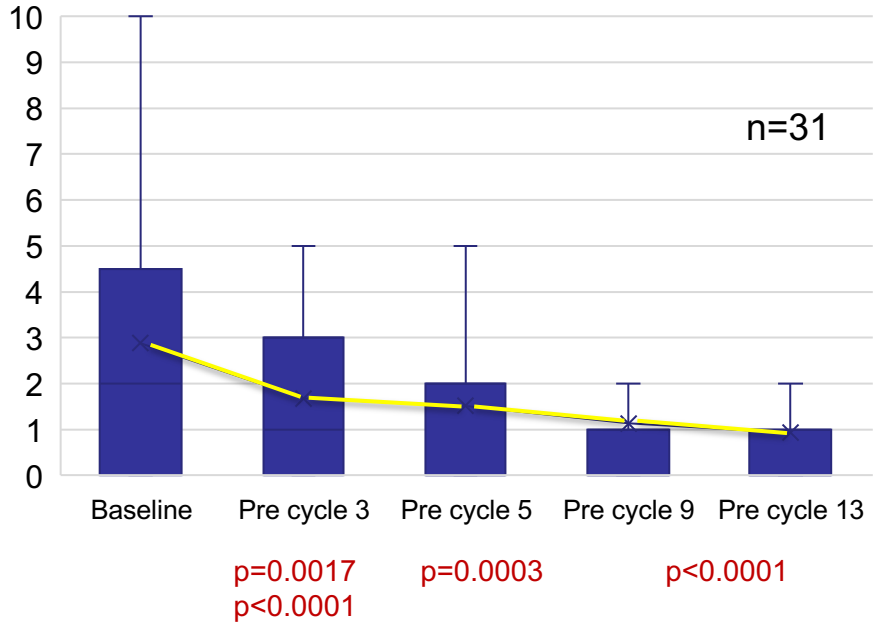
4. Do you have other kinds of pain (for example, headaches or back pain)? ☐ Yes ☐ No

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.)

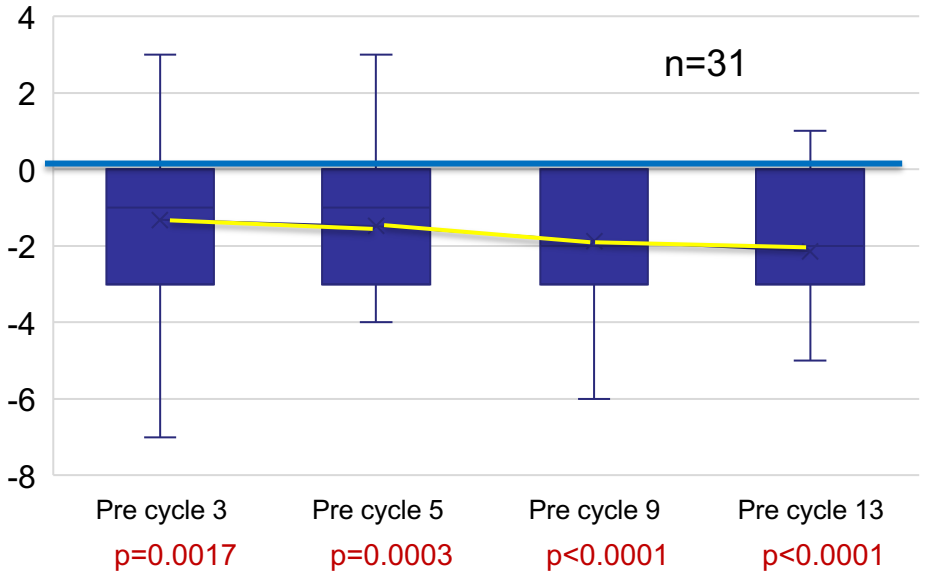


NRS-11 Self-report of Tumor Pain Intensity

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 ≥2 points

Slide courtesy of Dr. Pamela Wolters

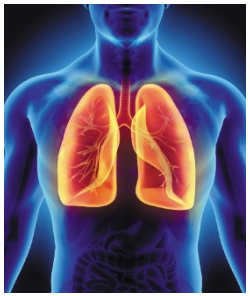
Implementation of REiNS Criteria: Lessons Learned

Functional Measures

	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_1 (absolute)	
Sleep Study: Apnea-Hypopnea Index	



Airway Results

Airway Morbidity (n = 16)	Baseline Median (range)	After 12 Cycles Median (range)	Median Ratio of PreC13: Baseline (range)
FEV_1 (liters) (n=11)	1.32 (0.64–3.84)	1.36 (0.72–4.08)	**1.15** (0.98–1.97)**
FEV1 % Predicted (n = 11)	84 (35–110)	92 (41–131)	1.021 (0.88–1.75)
Impulse Oscillometry (cmH_2O)			
R_5 (n = 10)	7.01 (2.96–15.5)	6.08 (2.51–10.76)	**0.78* (0.61–1.17)**
R_{20} (n =10)	3.76 (2.54–5.81)	3.56 (2.54–5.17)	0.95 (0.76–1.62)
Impulse Oscillometry % Predicted			
R_5 (n = 10)	124 (80–317)	110 (73–194)	**0.83* (0.61–-1.17)**
R_{20} (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

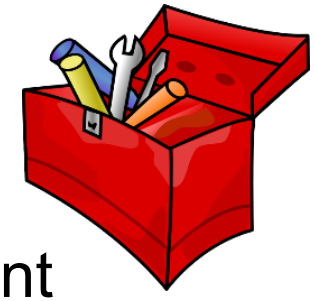
- REiNS Clinically Meaningful Thresholds:
  - FEV_1:
    - 7/11 patients had >12% improvement in FEV_1
    - 3/11 patients had >12% improvement FEV_1% pred
  - Impulse Oscillometry
    - 5/10 patients had > 20% improvement in R5 absolute and R5 % pred

Next Steps…

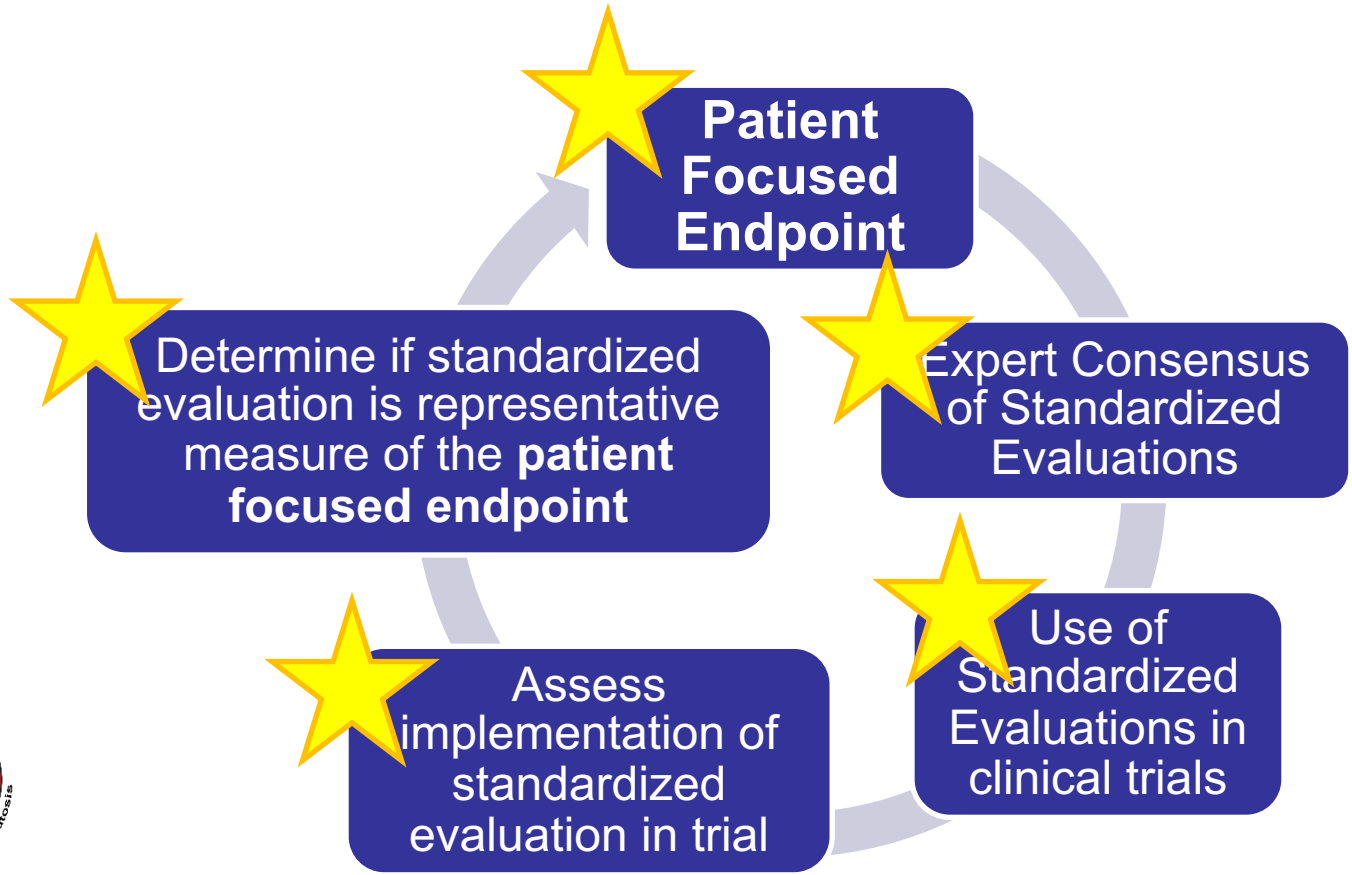
- Reassessing Current Recommendations
- Expand the current toolbox!
- Recommended Tools Needed For:
  - Disfigurement
    - PN related, cNF related, orbital PN
  - Skeletal endpoints
  - Motor Function
  - Speech/swallow endpoints
  - Bowel/Bladder dysfunction

Work ongoing in REiNS and elsewhere!

Key Conclusions



- REiNS criteria were ESSENTIAL to FDA submission and approval of selumetinib
- Able to demonstrate clinically meaningful improvement
- Learned important lessons about practical implementation of the measures for future trials



Any Questions?