

REiNS International Collaboration

Scott Plotkin, MD, PhD

Patient Representative Teleconference

November 20, 2017

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Where we want to be in 2025

Approved drugs for NF

- Drug A shrinks plexiform neurofibromas
- Drug B improves cognition in NF1 children
- Drug C improves hearing loss in NF2
- Drug D treats schwannomatosis pain

Endpoint questions

- How much shrinkage is significant? 20%? 50%
- What is cognition? IQ? Math skills? Attention?
- How measured? In a booth?
- How to measure pain? Is my pain same as yours?

Establishing and validating endpoints is critical for making progress!!

What is REiNS?

Response Evaluation in NF and Schwannomatosis

- The REiNS working group is an international effort to develop standardized response criteria for determining treatment response in patients with NF1, NF2, and schwannomatosis
- Collaboration across institutions, medical specialties; includes experts in NF and other areas (including patient representation)
- The criteria are a work in progress and will continue to be modified as we gain experience in trials for NF
- We hope these criteria will be incorporated into future clinical trials and will improve our ability to determine and compare treatment efficacy

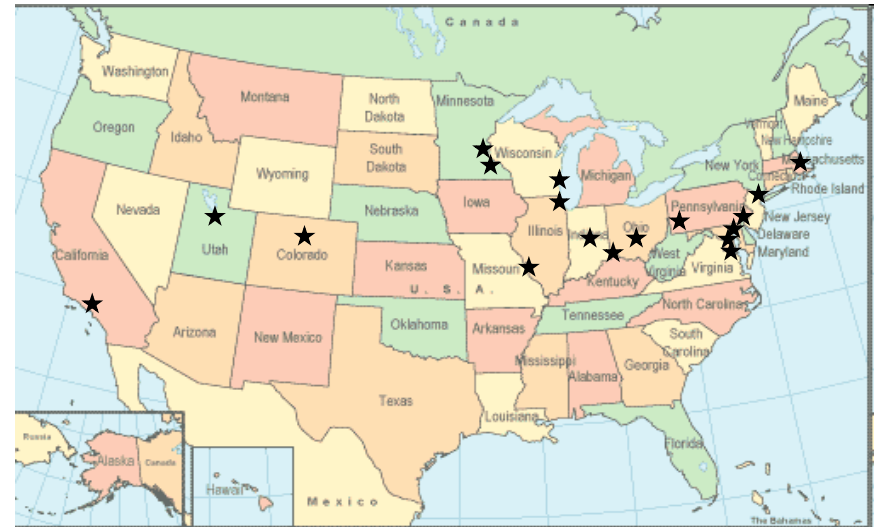
Why does the NF community need REiNS?

- Previous trials have use a variety of endpoints
- Multiple clinical trials are under way or in the planning stages
- The lack of consistency in endpoints makes it difficult to compare interventions
- Proactive discussion of endpoints with stakeholders will help facilitate approval of, and therefore access to, drugs for these rare conditions

Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS)

- Imaging response (Widemann, Dombi)
- Functional outcomes (Plotkin)
- Patient reported outcomes (Wolters)
- Whole body MRI (Ahlawat)
- Visual outcomes (Fisher)
- Biomarkers (Hanemann/Bettegowda)
- Neurocognitive outcomes (Janusz)
- Cutaneous neurofibromas (Cannon/Pichard)
- Patient representation

The REiNS working groups are open to all participants



- 7 working groups
- >60 active members

REiNS Collaboration

How REiNS Works

Endpoint development

- Meet semi-annually in June (CTF meeting) and December (Bethesda)
- Working groups set agenda and review literature on endpoints under discussion
- Working groups make recommendations to overall REiNS Collaboration
- Accepted endpoints are submitted for publication

Collaborations/Support

- Children's Tumor Foundation and other foundations
- Food and Drug Administration
- Cancer Therapy Evaluation Program
- NIH

REiNS publications 2013

Neurology® Step-Scan

Volume 81 Number 21 November 19, 2013 Supplement 1

Neurology®

Volume 81, Number 21, Supplement 1, November 19, 2013
Neurology.org



Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS)

Guest Editors: Scott R. Plotkin, MD, and Brigitte C. Widemann, MD

Supplement to *Neurology*®

1. Achieving consensus for clinical trials: The REiNS International Collaboration
2. Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials
3. Functional outcome measures for NF1-associated optic pathway glioma clinical trials
4. Hearing and facial function outcomes for neurofibromatosis-2 clinical trials
5. Recommendations for imaging tumor response in neurofibromatosis clinical trials
6. Conclusions and future directions for the REiNS International Collaboration

REiNS Collaboration



REiNS supplement 2016

1. Consensus for NF Clinical Trials: Recommendations of the REiNS Collaboration
2. Outcomes of Pain and Physical Functioning in NF Clinical Trials
3. Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1
4. Neurocognitive Outcomes in Neurofibromatosis Clinical Trials: Recommendations for the Domain of Attention
5. Current Whole-Body MRI Applications in the Neurofibromatoses: NF1, NF2 and Schwannomatosis
6. Current status and recommendations for biomarkers and biobanking in neurofibromatosis

PRO working group



Dr. Pamela
Wolters

- The REiNS PRO group goals:
 - to identify and recommend a pool of PRO measures appropriate for use as endpoints in NF clinical trials.
- The PRO group is assessing measures in the core domains of general QOL, disease-specific QOL, pain, and physical functioning using a systematic review and rating method we developed.
- Currently working on
 - final two core domains of general and disease-specific quality of life.
 - outcome measures to assess hearing and communication as well as young child pain

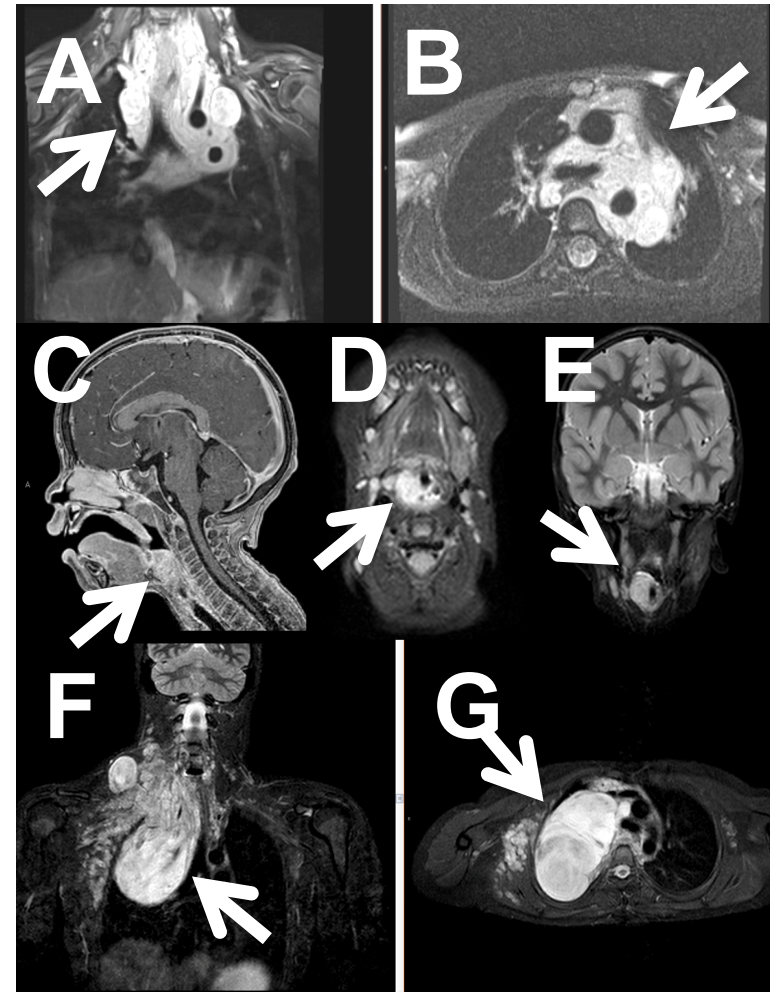


Functional working group



Dr. Scott Plotkin

- The goal of the functional group is to identify standardized functional measures appropriate for use as endpoints in NF clinical trials.
- Our group reviews measures for types of physical functioning that can be affected by NF
- Previous subjects include hearing, facial function, pulmonary function (breathing), walking and sleep
- Ongoing studies on measuring strength and swallowing function

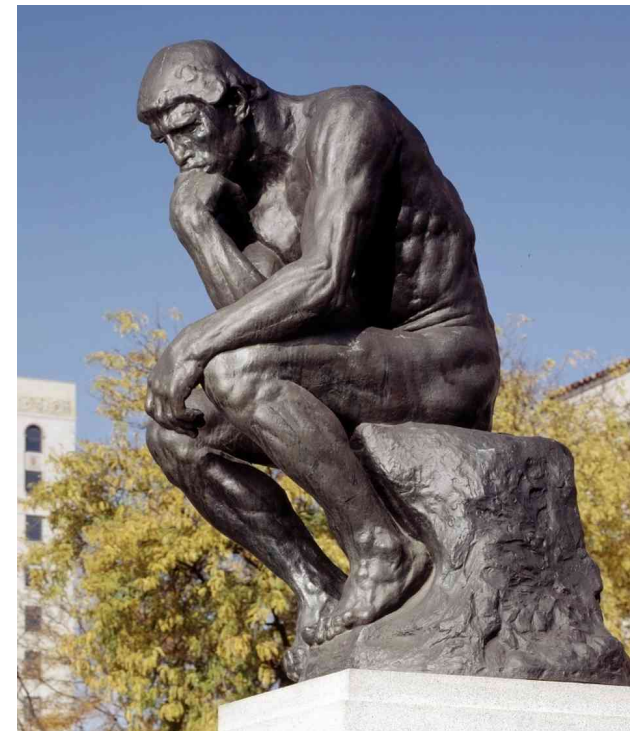


Neurocognitive group



Dr. Jennifer
Janusz

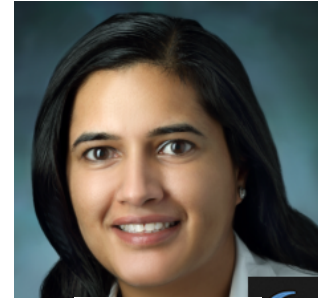
- The goal of the neurocognitive group is:
 - to identify standardized and specific cognitive assessment tools for use as endpoints in NF clinical trials
- To date, 9 clinical trials targeting cognitive outcomes in NF1
 - Each with a different battery of cognitive tests despite targeting the same primary constructs of attention, working memory, visual memory, intelligence, and emotional/behavioral functioning
- Group prioritized attention as the first domain of focus
- Currently working on reviewing measures related to social skills, including social communication, social cognition, and social motivation





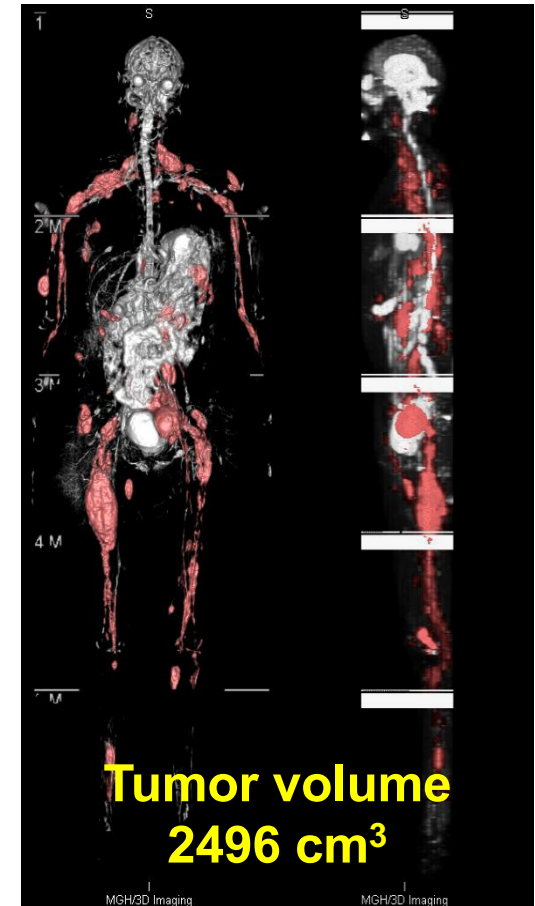
Dr. Jaishri
Blakeley

Whole body MRI group



Dr. Shivani
Ahlawat

- The goal of WBMRI group:
 - to generate consensus recommendations and identify priority areas for future research regarding WB-MRI as an NF clinical trials endpoint
- Current research areas include:
 - Evaluate the test-retest variability and interobserver performance of WB-MRI in NF
 - Investigate functional MRI vs. ^{18}F -FDG PET/CT for tumor characterization and assessment of treatment response
 - Investigate the added value of contrast enhanced imaging to WB-MRI protocol for tumor characterization and assessment of treatment response



Biomarkers group

- The goal of the biomarkers group is:
 - to assess biomarkers collected from blood, urine, and tissue samples for their utility in NF clinical trials
 - Report consensus recommendations for standard operation procedures (SOP) to collect biomarkers
 - Recommend minimal clinical dataset to accompany samples derived from patients with NF1, NF2 and SWN in decentralized biobanks



Dr. Oliver
Hanemann

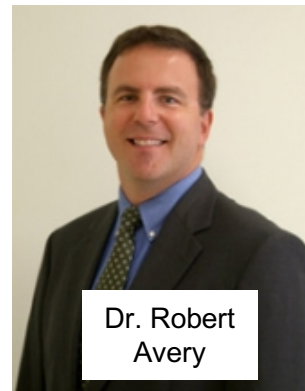


Dr. Chetan
Bettegowda

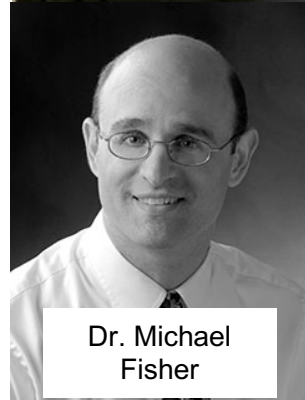


Visual outcomes group

- The goal of the biomarkers group is:
 - define the best outcome measures for use in clinical trials of NF1 associated optic pathway gliomas (OPG).
- Current projects include assessment of:
 - psychophysical components of vision
 - other ophthalmologic elements affected by OPG,
 - potential biomarkers of visual function
 - quality of life measures



Dr. Robert Avery



Dr. Michael Fisher



Tumor imaging group

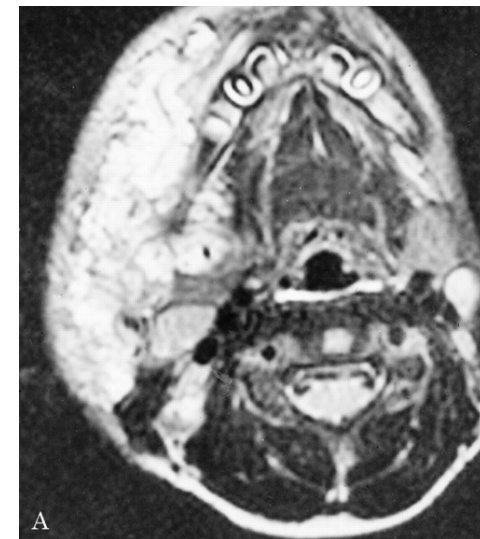
- The goal of the biomarkers group is:
 - To develop standardized consensus recommendations for imaging response evaluation in clinical trials for benign NF tumors
- Current projects include validation of:
 - Different volumetric analysis techniques for measurement of plexiform neurofibromas



Dr. Brigitte Widemann



Dr. Eva Dombi



Patient Representation Initiative for REiNS

Initial results

Process

- Online application developed by Pam Wolters, Scott Plotkin, Traceann Rose
- Online application available on 9/16/2017
- Application deadline 10/16/2017
- Includes personal statement and letter of recommendation

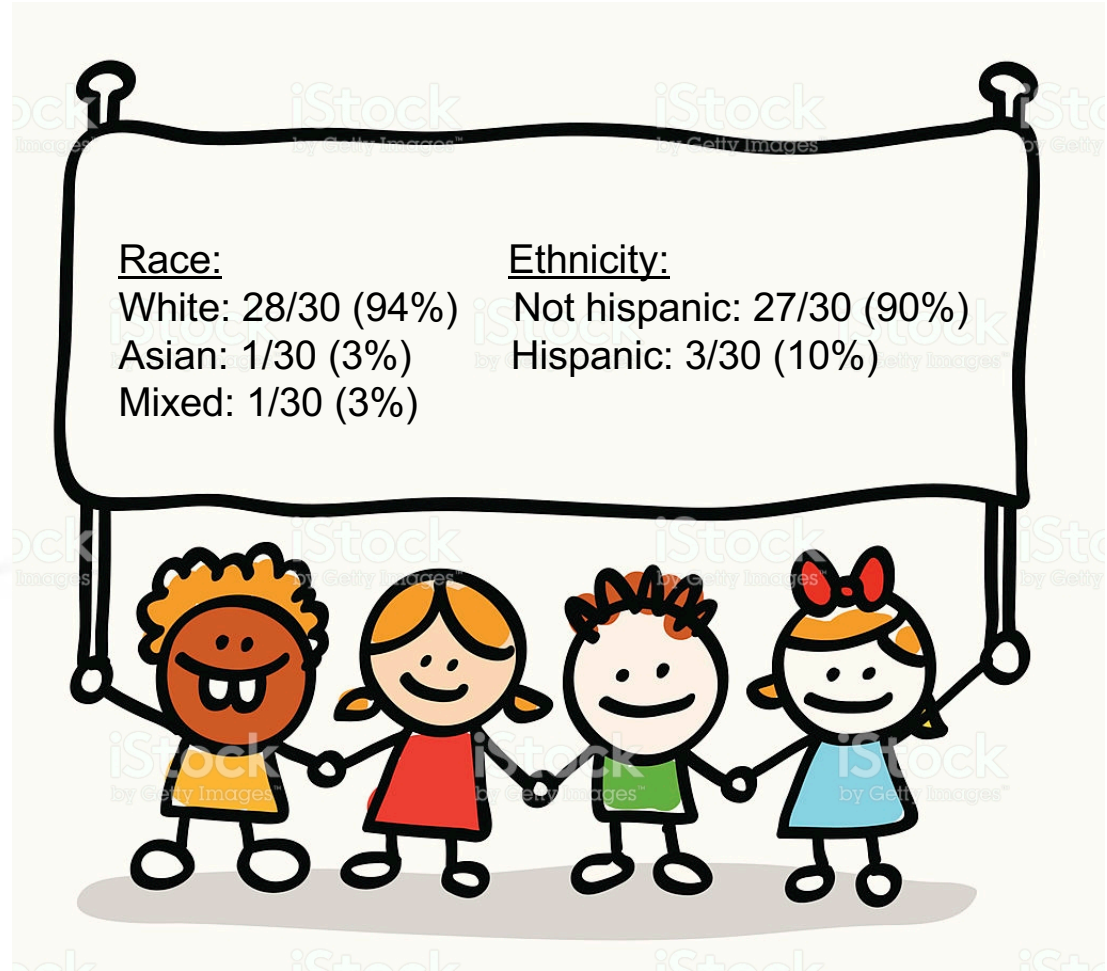
Response

- 54 online applications completed
- 30/54 (56%) applications completed including personal statement and letter of recommendation
- NF representation
 - NF1: 17/30 (57%)
 - NF2: 11/30 (37%)
 - SWN: 2/30 (7%)

Patient representative demographics



Patient: 17/30 (57%)
Parent: 12/30 (40%)
Spouse: 1/30 (3%)

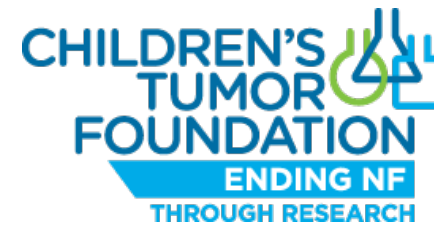
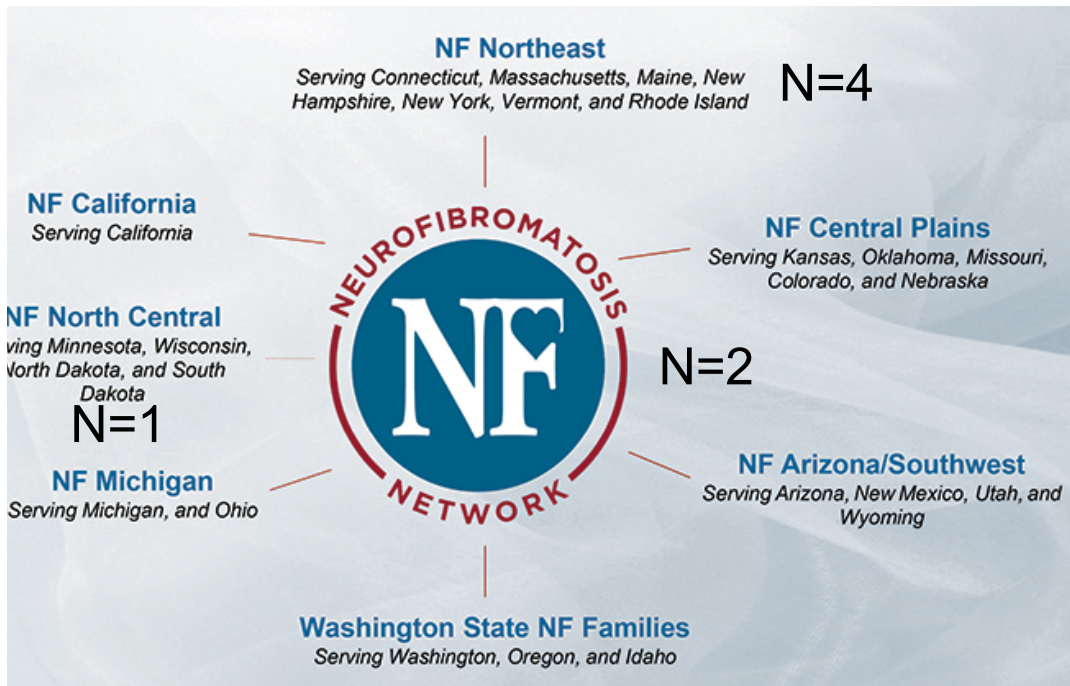


Highly educated cohort



Graduate school: 16/30 (53%)
College: 11/30 (37%)
High School: 3/10 (10%)

Employee or volunteer of organization



N=4



N=3



NF Kinder N=1

Neurofibromatose durch Forschung besiegen



N=1



N=1



New Futures Leaders: 1

No affiliation: 11

REiNS Collaboration

Results

- How did you hear about opportunity?
 - Email invitation: 13
 - NF Foundation: 9
 - CTF: 4
 - Health professional: 4

Applicant interests

Top choice

- 1) Patient reported outcomes (30%)
- 2) Disease biomarkers (20%)
- 3) Tumor imaging (13%)
- 4) Functional outcomes (10%)
- 5) Whole body MRI (7%)
 - Neurocognitive outcomes (7%)
 - Visual outcomes (7%)
- 8) Cutaneous neurofibromas (3%)

Top 3 choice

- 1) Patient reported outcomes (63%)
- 2) Disease biomarkers (40%)
 - Tumor imaging (40%)
- 4) Functional outcomes (37%)
- 5) Cutaneous neurofibroma (33%)
- 6) Whole body MRI (30%)
- 7) Neurocognitive outcomes (20%)
- 8) Visual outcomes (13%)

Working group allocations

- Based on patient representative preference
 - Patient reported outcomes: 3
 - Functional outcomes: 4
 - Tumor imaging: 3
 - Whole body MRI: 4
 - Visual outcomes: 2
 - Neurocognitive outcomes: 3
 - Disease biomarkers: 5
 - Cutaneous neurofibromas: 3

Training

- November
 - Distribute REiNS supplements for background
 - Teleconference(s)
 - Introduction to REiNS: mission and organization
 - Background on patient representation
 - Review goals for December meeting
- December
 - Learn from FDA training
 - Feedback from first meeting
 - PRs to help generate training focus

Training

- January-April
 - Establish patient representation working group with ALL PRs
 - Leadership: 2 PRs and some REiNS leaders
 - Goals:
 - Develop training
 - Define goals of PRs for REiNS
 - Develop financial model

Comments

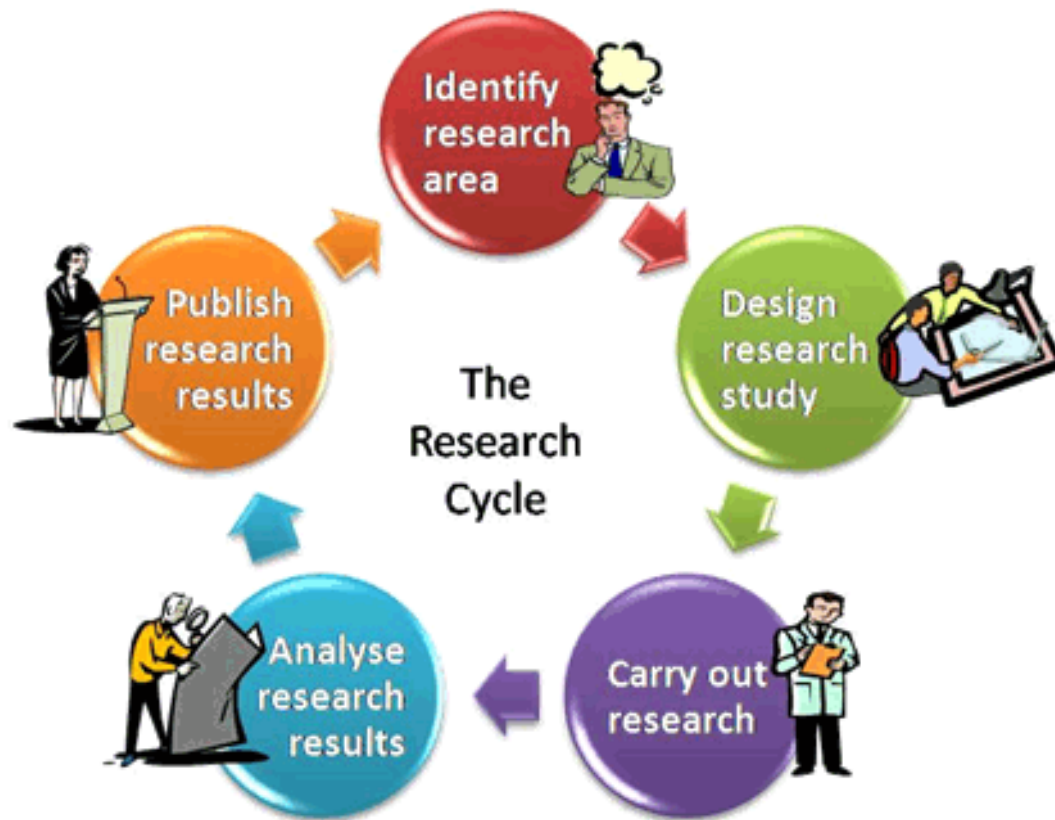
- Anticipate that some members of current class will drop out during first year
- Role/training of PR to develop over first year
- Need more diversity
- Paper to be developed for next REinS supplement

Expanding Patient Centered Research: Patient Research Partners

Patient representative working group

- Composed of all 30 patient representatives with some investigators
- To meet monthly by teleconference starting in December
- Goals to be decided by group

Patients add value throughout the research process



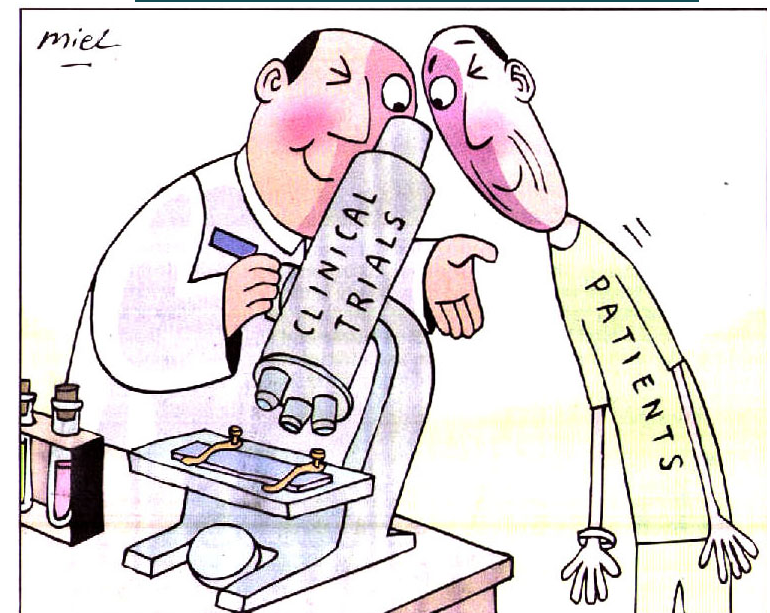
Planning the Study

- Identify important research questions and prioritize them
- Help plan methods that encourage participation and minimize burden to subjects
- Give input on what outcome measures are meaningful
- Review recruitment flyers and informed consent papers

Patients add value throughout the research process

Conducting the Study

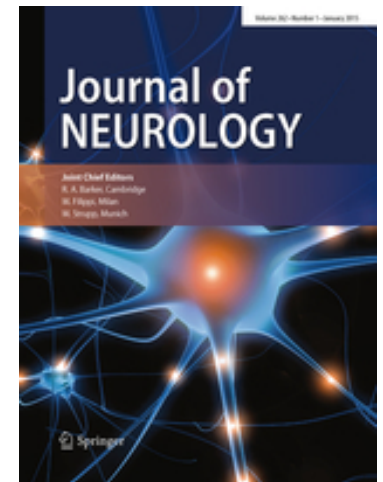
- Assist with recruitment and outreach
- Conduct interviews or administer surveys
- Answer questions from subjects
- Serve as representative on study advisory committee or safety boards



Patients add value throughout the research process

Sharing study results

- Identify best ways to inform patients and family member
- Help present findings at scientific conferences and lay events
- Co-author scientific manuscripts



Potential issues to discuss

- Duration of terms
- Content of training (with help from investigators)
- How to accommodate individual hard of hearing or deafened
- Financial model
- Best way to utilize talents of patient representatives

REiNS 2017 Winter Meeting

Comments