Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1

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ABSTRACT

Objective: Plexiform neurofibromas (PNs) are complex, benign nerve sheath tumors that occur in approximately 25%–50% of individuals with neurofibromatosis type 1 (NF1). PNs that cause airway compromise or pulmonary dysfunction are uncommon but clinically important. Because improvement in sleep quality or airway function represents direct clinical benefit, measures of sleep and pulmonary function may be more meaningful than tumor size as endpoints in therapeutic clinical trials targeting airway PN.

Methods: The Response Evaluation in Neurofibromatosis and Schwannomatosis functional outcomes group reviewed currently available endpoints for sleep and pulmonary outcomes and developed consensus recommendations for response evaluation in NF clinical trials.

Results: For patients with airway PNs, polysomnography, impulse oscillometry, and spirometry should be performed to identify abnormal function that will be targeted by the agent under clinical investigation. The functional group endorsed the use of the apnea hypopnea index (AHI) as the primary sleep endpoint, and pulmonary resistance at 10 Hz (R_{10}) or forced expiratory volume in 1 or 0.75 seconds (FEV_1 or $FEV_{0.75}$) as primary pulmonary endpoints. The group defined minimum changes in AHI, R_{10}, and FEV_1 or $FEV_{0.75}$ for response criteria. Secondary sleep outcomes include desaturation and hypercapnia during sleep and arousal index. Secondary pulmonary outcomes include pulmonary resistance and reactance measurements at 5, 10, and 20 Hz; forced vital capacity; peak expiratory flow; and forced expiratory flows.

Conclusions: These recommended sleep and pulmonary evaluations are intended to provide researchers with a standardized set of clinically meaningful endpoints for response evaluation in trials of NF1-related airway PNs. *Neurology*® 2016;87 (Suppl 1):S13–S20

GLOSSARY

AASM = American Academy of Sleep Medicine; **AHI** = apnea hypopnea index; **CPAP** = continuous positive airway pressure; **$FEV_{0.75}$** = forced expiratory volume in 0.75 seconds; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **NF1** = neurofibromatosis type 1; **OSA** = obstructive sleep apnea; **PEF** = peak expiratory flow; **PN** = plexiform neurofibroma; **PSG** = polysomnography; **REiNS** = Response Evaluation in Neurofibromatosis and Schwannomatosis.

Plexiform neurofibromas (PNs) are complex, benign nerve sheath tumors that occur in approximately 25%–50% of individuals with neurofibromatosis type 1 (NF1). The frequency and type of PN-associated morbidities are influenced by tumor location and volume (figure).[1–7] A total of 15%–38% of all PNs occur in the head/neck region and 6%–25% occur in the thorax/mediastinum. Airway PNs are a subset of PNs that arise in close proximity to the airway. Symptomatic PNs that cause airway compromise or pulmonary dysfunction are uncommon (reported in 5%–7% of children with PNs) but clinically important. If left untreated, these lesions can be fatal. Surgical resection is often not feasible, and tracheostomy is required in some patients.[3,5]

Obstructive sleep apnea (OSA) is caused by repeated collapse of the airway during sleep resulting in partial obstruction (hypopnea) or total obstruction (apnea). In the general pediatric

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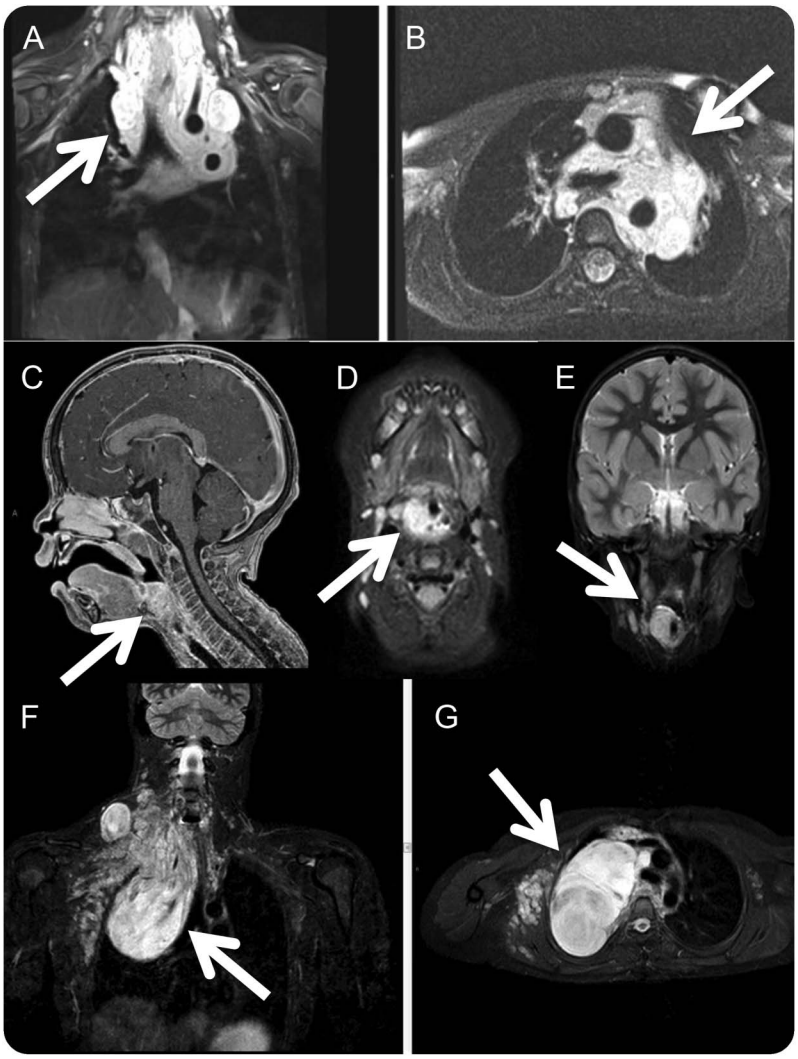
Figure MRI examples of plexiform neurofibromas (PNs) affecting the airway



Coronal (A) and axial (B) MRI of a large neck/mediastinal PN in a child. Functional improvement would be a more clinically meaningful endpoint compared to imaging response (defined as a ≥20% decrease in the entire PN volume) as even a small volume change could result in clinical benefit. Sagittal (C), axial (D), and coronal (E) MRI of an extrathoracic pharyngeal PN in a child who presented with snoring. Oscillometry should serve best to monitor changes in pulmonary function. Coronal (F) and axial (G) MRI of a predominantly intrathoracic chest PN in a child. Spirometry should serve best to monitor changes in pulmonary function.

population, risk factors include adenotonsillar hypertrophy, obesity, airway encroachment, abnormal respiratory control, and dysfunctional upper airway muscles. Symptoms include snoring, pauses in breathing, and excessive sleepiness. However, there is only a modest correlation between OSA symptoms and objectively measured polysomnographic parameters of OSA severity.[8,9] Overnight polysomnography (PSG) is the study of choice for patients with suspected OSA.[10,11] The most widely used measure of PSG is the apnea hypopnea index (AHI), the number of apneas plus hypopneas/h of sleep. The American Academy of Sleep Medicine (AASM) provides 2 definitions of hypopneas for adults: the definition requiring 3% desaturation or arousal should be used; this definition is consistent with the pediatric definition.[12] In children, a normal AHI is <1.5. In adults, a normal AHI is <5; the degree of OSA can be classified as mild (AHI 5–14), moderate (AHI 15–30), or severe (AHI >30). Treatment of OSA is directed at maintaining patency of the upper airway. Adenotonsillectomy is the standard treatment for childhood OSA,[11] and continuous positive airway pressure (CPAP) is the standard treatment if surgery is not an option.

Pulmonary function tests are used to evaluate patients with airway and lung disease. Impulse oscillometry measures airway mechanics by applying pressure oscillations that propagate throughout the airway as the patient tidal breathes in a stable pattern. It is used to measure pulmonary resistance (pressure required to propagate flow through the respiratory system) and reactance (pressure required to overcome elastic and inertive properties of the respiratory system).[13] Spirometry measures the amount (volume) or speed (flow) of air that can be inhaled and exhaled. Forced vital capacity (FVC) is the maximal volume of air exhaled from full inspiration.

Previously, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) group published recommendations for hearing and facial function outcomes.[14] In this report, the group proposes consensus recommendations for sleep and pulmonary outcomes in clinical trials that target airway PNs. In recent years, shrinkage of PNs has been observed after treatment with PEG-intron, imatinib, and selumetinib.[15–17] Because clinical benefit may occur with minimal volume changes, sleep and pulmonary outcomes may be more sensitive than radiographic changes at detecting a meaningful response to treatment. Our objectives were to define reproducible and clinically meaningful measures of sleep and pulmonary function, which can be used as primary endpoints in clinical trials targeting airway PNs.

METHODS The REiNS functional outcomes group has approximately 20 active participants including professionals from various disciplines involved in NF care. The group engaged

experts in sleep and pulmonary medicine (C.L.M., S.D.D., J.A.) to help draft these recommendations, which represent expert consensus based on review of the literature.

RESULTS For patients with airway PNs, overnight PSG, impulse oscillometry, and spirometry should be performed during screening to identify abnormal function. Based on performance on these studies, investigators should select a primary measure that will serve as the functional endpoint of interest for each patient. Once a measure has been selected as the primary functional endpoint, it should be tested consistently during a clinical trial with reference to baseline.

Recommended PSG outcomes. For clinical trial outcomes, the group considered the following measures as primary or secondary endpoints: AHI, oxygen saturation, end tidal CO_2, and arousal index (table 1). The group recommended use of AHI as primary outcome because it (1) is a clinically meaningful measure of upper airway function; (2) is widely available at most centers; (3) is the most commonly used endpoint in both pediatric and adult sleep studies, including the effects of adenotonsillectomy, upper airway stimulation, and bariatric surgery for OSA[18–20]; and (4) has been validated in relation to neurocognitive and cardiovascular outcomes of OSA.[21,22] To date, no studies using AHI for patients with NF1 with airway PNs have been published.

Feasibility. PSG is widely available in most developed countries and a full-night study should be performed in a sleep laboratory.[23,24] The detailed parameters, settings, filters, technical specifications, and event scoring should be done in accordance with the guidelines in the *AASM Manual for the Scoring of Sleep and Associated Events*.[12] Note that the criteria for scoring of obstructive apnea in children differ from those in adults.

Patient characteristics. PSG has been validated in adults and in children, with standardized norms available for children. Physical examination should be performed to document obesity and signs of upper airway narrowing such as tonsillar hypertrophy, retrognathia, macroglossia, enlarged uvula, abnormal hard palate, and nasal abnormalities. Potential participants should be evaluated by a qualified practitioner prior to enrollment to determine whether adenotonsillectomy may result in sufficient improvement in airway function. Patients who meet the criteria for baseline AHI noted below may be considered eligible for trials; patients with an AHI <5 would be ineligible based on the criteria defined for improvement. Patients with tracheostomy are not eligible for trials with primary sleep outcomes but may be appropriate for trials with primary imaging outcomes.

Currently, the group does not endorse the use of home sleep studies in clinical trials. This recommendation is based on the paucity of validation studies for children, the limited number of EEG channels in home studies, and the lack of reliable CO_2 monitoring (which is important for identifying individuals with hypoventilation). This recommendation should be reconsidered as additional data on home sleep studies in young children become available.

Sleep efficiency (total sleep time as a percentage of total recording time), the amount of REM sleep as a percentage of total sleep time, and body position should be measured to assess the adequacy of PSG. If a patient sleeps very poorly in the laboratory setting and has decreased total sleep time or REM sleep time, the AHI may appear artificially low. Body position

Table 1 Proposed outcome measures for sleep and pulmonary studies

Endpoint	Definition
Sleep studies	
Apnea hypopnea index	Number of apneic and hypopneic events per hour of sleep
Oxygen saturation (SpO_2)	Mean or nadir in SpO_2 or as a percentage of total sleep time with SpO_2 <90%
End tidal CO_2	Mean, peak, or % total sleep time with CO_2 >50 Torr
Arousal index	Number of arousals/h scored by change in EEG
Oscillometry	
R_5, R_{10}, R_{20}, X_{rs}	Airway resistance at 5 Hz (R_5), 10 Hz (R_{10}), and 20 Hz (R_{20}), and where the reactance measurement crosses zero (resonant frequency, X_{rs})
X_5, X_{10}, X_{20}	Airway reactance at 5 Hz (X_5), 10 Hz (X_{10}), and 20 Hz (X_{20})
Spirometry	
$FEV_{0.75}/FEV_1$	Volume of air exhaled from full inspiration either at 0.75 second ($FEV_{0.75}$) in preschoolers or in 1 second (FEV_1) in all others
Forced vital capacity	Maximum amount of air exhaled from the lungs after a maximum inhalation
Peak expiratory flow	Maximum speed of expiration
Forced expiratory flows	Speed of air exhaled at specific time points or during the mid-portion of the maneuver

Table 2 Proposed response criteria for sleep studies

Baseline AHI	Events per 8 hours of sleep	Response (AHI)	Progression (AHI)	Stable (AHI)
≤5	Not eligible for trials due to ceiling effect (see text)			
6	48	≤1	≥11	2-10
7	56	≤2	≥12	3-11
8	64	≤3	≥13	4-12
9	72	≤4	≥14	5-13
10	80	≤5	≥15	6-14
11	88	≤6	≥16	7-15
12	96	≤7	≥17	8-16
13	104	≤8	≥18	9-17
14	112	≤9	≥19	10-18
15	120	≤10	≥20	11-19
16	128	≤11	≥21	12-20
17	136	≤12	≥22	13-21
18	144	≤13	≥23	14-22
19	152	≤14	≥24	15-23
20	160	≤15	≥25	16-24
21	168	≤15	≥27	16-26
22	176	≤15	≥29	16-28
23	184	≤15	≥31	16-30
24	192	≤15	≥33	16-32
25	200	≤15	≥35	16-34
26	208	≤16	≥36	17-35
27	216	≤17	≥37	18-36
28	224	≤18	≥38	19-37
29	232	≤19	≥39	20-38
30	240	≤20	≥40	21-39
31	248	≤21	≥41	22-40
32	256	≤22	≥42	23-41
33	264	≤23	≥43	24-42
34	272	≤24	≥44	25-43
35	280	≤25	≥45	26-44
36	288	≤26	≥46	27-45
37	296	≤27	≥47	28-46
38	304	≤28	≥48	29-47
39	312	≤29	≥49	30-48
40	320	≤30	≥50	31-49
41	328	≤31	≥51	32-50
42	336	≤32	≥52	33-51
43	344	≤33	≥53	34-52
44	352	≤34	≥54	35-53
45	360	≤35	≥55	36-54
46	368	≤36	≥56	37-55
47	376	≤37	≥57	38-56
48	384	≤38	≥58	39-57
49	392	≤39	≥59	40-58
≥50	Not eligible for trials due to floor effect (see text)			

Note that values for individual patients should be calculated according to the baseline apnea hypopnea index (AHI) at study initiation.

may affect the severity of OSA. While this is generally less of an issue in children than adults,[25] it may be important in patients with airway tumors. Serial studies with large differences in the percentage of time in different body positions should be interpreted with caution. Protocols should provide explicit guidance for assessing adequacy of sleep studies in clinical trials. In general, a PSG is considered adequate if there are at least 6 hours of total sleep time (as measured by EEG, not total recording time) and at least an hour of REM sleep (as most sleep-disordered breathing occurs during REM sleep).

Response criteria. AHI response criteria are defined in reference to the baseline AHI at study initiation. Studies of night-to-night variation in AHI suggest that individuals with higher AHI at baseline demonstrate more variability than individuals with lower AHI.[26,27] Thus, the group recommended a larger absolute change in AHI for patients with higher baseline AHI in order to minimize the rate of false-positive or false-negative responses.[26,27] Additional studies on night-to-night variation in AHI for patients with NF1 with airway PN are needed to refine these response criteria. Until these studies are complete, the functional group recommends using criteria based on expert opinion (table 2).

Functional improvement is defined as an absolute decrease in AHI by ≥5 events/h (for patients with baseline AHI ≤20) or an absolute decrease in AHI by ≥10 events/h (for patients with baseline AHI ≥25). Functional decline is defined as an absolute increase in AHI by ≥5 events/h (for patients with baseline AHI ≤20) or an absolute increase in AHI by ≥10 events/h (for patients with baseline AHI ≥25). See table 2 for recommendations when the baseline AHI is 21–24. Stable function is defined as all other responses. Table 2 outlines the amount of change in AHI that represents response or progression based on baseline AHI.

Special notes on AHI. AHI is a bounded variable: it is an average number of events during an overnight sleep study (typically 8 hours or more) and the

variable ranges from 0 (no events) to >100 events/h. The existence of upper and lower boundaries introduces a ceiling and floor effect for patients with values near the top and bottom of the range, respectively. As table 2 shows, patients with an AHI ≤5/hour are not eligible for response since these patients cannot improve enough to meet criteria for functional improvement. The functional group recommends that patients with an AHI ≥50/hour should not be enrolled in clinical trials at this time given the availability of alternative treatments for very severe OSA.

Patients treated with CPAP should undergo PSG off CPAP if they are clinically stable to do so, as judged by their medical team. PSG on the first night off CPAP may show milder OSA than on subsequent nights.[28–30] Because of this transient improvement, CPAP should be discontinued for 48 hours prior to PSG. During this time, patients should be monitored for clinical exacerbations. The research polysomnogram should be discontinued for any event that the research team considers unsafe, such as pathologic cardiac arrhythmia during sleep other than sinus arrhythmia.

To ensure the safety of patients during subsequent sleep studies, the group proposes that patients who meet the following parameters during a study should be declared as functional decline and CPAP should be reinstituted to meet safety needs: any condition for which the research team considers the patient medically unstable, such as treatment-emergent pathologic cardiac arrhythmia during sleep other than sinus arrhythmia not explained by electrolyte abnormalities.

Secondary outcomes for sleep studies. Alternative measures of sleep function are available from a standard PSG. These measures include the change in (1) oxygen saturation (SpO_2) measured as mean or nadir SpO_2, or as percentage of total sleep time with SpO_2 <90%; (2) end tidal CO_2 measured as mean or peak CO_2, or as percentage of total sleep time with CO_2 >50 Torr; and (3) arousal index, defined as the number of arousals per hour scored by EEG. While the group committee does not endorse changes in these variables as a primary outcome measure, we do recommend that all of these variables, and possibly other measures such as neurocognitive, imaging, patient-reported, or quality of life measures, be recorded as secondary outcomes to provide additional data about the effectiveness of the intervention.

Recommended outcome for pulmonary function. For patients in whom pulmonary function is the primary endpoint of interest, investigators should select either oscillometry or spirometry as the primary measure based on physiologic findings. In general, the functional group endorsed the use of oscillometry for pulmonary studies of extrathoracic/upper airway lesions and spirometry for pulmonary studies of intrathoracic/peripheral airway lesions. Oscillometry has been used as a primary or secondary endpoint in studies on adenoidectomy for exercise-induced bronchoconstriction, in a prospective trial of a multifaceted intervention to decrease asthma onset or severity, and in a study evaluating pulmonary exacerbation response in cystic fibrosis.[31–33] The following measures were considered as potential endpoints for impulse oscillometry: R_5, R_{10}, R_{20}, X_5, X_{10}, X_{20}, and changes in resistance at the resonant frequency (table 1). The group recommended resistance at 10 Hz (R_{10}) as the primary outcome measure for oscillometry. A pulmonary resistance measure (R) was preferred over a pulmonary reactance measure (X) since airway PNs are more likely to impact the resistance properties than the elastic and inertive properties of airways. Further, R_{10} was selected among the resistance measures since R_{10} is a better measure of central airways compared with R_5 and has been used in more trials as an outcome measure compared to R_{20}.

For spirometry, forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) (in preschool children), forced expiratory volume in 1 second (FEV_1) (in all others), FVC, and peak expiratory flow (PEF) were considered as potential endpoints (table 1). FEV_1 has been used as a primary endpoint or secondary endpoint in a number of clinical trials for asthma[34] and cystic fibrosis.[35] The group recommended $FEV_{0.75}$ for preschool children and FEV_1 for all others as primary outcome measure for spirometry. $FEV_{0.75}$ and FEV_1 were preferred since these measures reflect airway obstruction, have low variability on repeat testing, and are widely accepted as primary outcomes for studies of children with airway disease.

Feasibility. Impulse oscillometry is available at many large medical centers but is not standard at all medical centers. Children should be instructed to breathe normally during the test and to avoid crossing the legs as this position can contract the abdominal wall and lead to diminished resting end-expiratory pulmonary volumes. Further, the cheeks must be firmly supported by hands to compensate for cheek compliance. In general, a 30-second interval of testing is performed, and an average of 3–5 measurements is obtained for analysis. Spirometry is widely available for clinical trials. Studies should be attended by trained personnel in order to monitor for technical adequacy and patient compliance. For both spirometry and impulse oscillometry, equipment quality control and calibration are essential for accurate and valid testing. The detailed parameters and technical specifications should be performed as described in the *Standardization of Spirometry* published by the American Thoracic Society.[36] Additional guidelines for young children are also available.[37]

Patient characteristics. Impulse oscillometry is commonly employed in children since it requires only

passive cooperation of the patient (in contrast to spirometry, which requires active participation of the patient). Standardized normative values for adults and children down to 2 years of age have been published.[37,38] Spirometry is highly dependent on patient cooperation and effort and can only be used in children who are able to follow instructions reliably. In general, spirometry can be performed in children who are 6 years or older; however, cooperative preschoolers are able to produce acceptable results.[36,37] Normative values for $FEV_{0.75}$ and FEV_1 are available for individuals aged 3–90 years.[39–41]

Response criteria. Response criteria for R_{10} are defined in reference to the baseline R_{10} at study initiation. Functional improvement is defined as ≥20% decrease in R_{10}, functional decline is defined as ≥20% increase in R_{10}, and stable function is defined as all other responses. A threshold of 20% was chosen based on data showing the average coefficient of variation for resistance is ≤10% between tests.[37]

Response criteria for $FEV_{0.75}/FEV_1$ are defined in reference to the baseline $FEV_{0.75}/FEV_1$ at study initiation. Functional improvement is defined as ≥12% increase in $FEV_{0.75}$ (preschoolers) or in FEV_1 (all others). Functional decline is defined as ≥12% decrease in $FEV_{0.75}$ (preschoolers) or in FEV_1 (all others). Stable function is defined as all other responses. The working group adopted these thresholds based on the recommendation of the American Thoracic Society/European Respiratory Society Task Force.[42]

Special notes on R_{10} and FEV. In clinical practice, R_{10} is an unbounded variable. For clinical trials, the group recommended excluding patients with R_{10} ≤120% predicted for age in order to allow for sufficient improvement on clinical trial to meet response criteria. No recommendation was made for a maximum R_{10} value for trial participation given lack of published data on this topic. Similarly, FEV is an unbounded variable in clinical practice that can range from <10% to >100% of predicted for age, sex, and height. For clinical trials, the group recommended including patients with $FEV_{0.75\ or\ 1}$ ≥40% and ≤80% of predicted for age, sex, and height in order to allow for sufficient improvement or decline in a clinical trial to meet response criteria.

Secondary outcomes for pulmonary function. Alternative measures of pulmonary function are available from oscillometry and spirometry. For oscillometry, these measures may include change in resistance measurements at 5 or 20 Hz (R_5, R_{20}), change in reactance measurements at resonant frequency (frequency at which reactance = 0), and change in reactance at 5, 10, and 20 Hz. For spirometry, these measures may include changes in FVC, PEF, and forced expiratory flows. The committee recommends that all of these variables, and possibly other measures such as imaging, patient-reported, or quality of life measures, be recorded as secondary outcomes to provide additional data about the effectiveness of the intervention under study.

Additional recommendations. ***Double baseline evaluations.*** The group does not recommend the use of double baseline studies for all clinical trials at this time, due to the substantial resources and time required to obtain these evaluations, and the resulting burden to the patient. However, given the unknown variability of the outcome measures for patients with airway PN and the possibility of regression to the mean, the group recommends that the baseline variability of these measures be determined in a select group of patients to refine the proposed response criteria.

Frequency of reevaluation. No evidence-based guidelines are available to help determine the optimal interval between evaluations. The group recommends reevaluation of primary endpoints (AHI, R_{10}, or $FEV_{0.75}/FEV_1$) every 3–6 months during prolonged treatment, although the group recognizes that the timing of reevaluation may be influenced by the design of each particular study and the agent being tested. In general, evaluation of primary endpoints should be performed at the same interval as imaging studies to facilitate correlation of functional changes with imaging changes in symptomatic PNs.

Confirmatory measurement. Confirmation of functional response is desirable in nonrandomized trials where response is the primary endpoint and in PN trials where the focus is on reducing long-term morbidity rather than on extending survival. In addition, confirmation of response would increase the confidence that a measured response is the result of the intervention and not due to baseline variability. Confirmation of response may not be necessary for randomized trials or for trials where time to progression is the primary endpoint.

Duration of response and stable disease. The duration of functional response is calculated from the date when the primary endpoint first meets criteria for functional response compared with baseline until the first date that the primary endpoint no longer meets criteria for functional response (table 2). Stable function is calculated from the initiation of treatment until the time that primary endpoint meets criteria for functional decline. In order to declare stable function in any study, testing must document stable function for a minimum of time established by the study protocol (generally 6 months). Patients without subsequent evaluation after baseline evaluation should be considered nonevaluable. Importantly, estimates of duration of response and time to progression are influenced by the interval of evaluations. For this reason, protocols should specify the interval between evaluations.

Proportion free from functional decline. Patients with NF1 with growing PN involving the airway are at risk for worsening of OSA or pulmonary function. In this trial design, freedom from functional decline at specified time points might be an acceptable endpoint to provide evidence of drug activity. Because freedom from decline is liable to bias in uncontrolled phase 2 trials, this variable is best evaluated by a randomized trial.

Reporting best response. For phase 2 studies, response assessment should include all patients in the trial, including nonevaluable patients and those whose treatment deviates from the study protocol. Responses should be categorized as functional improvement, stable function, functional decline, or nonevaluable (e.g., due to death, toxicity, or lack of assessment). For phase 3 studies, functional response may be a primary or secondary endpoint. When functional response is the primary endpoint, the study must include only patients who are capable of functional improvement and all enrolled patients must be analyzed. When functional response is a secondary endpoint, the study may include patients regardless of sleep or pulmonary function. In this design, functional response may also be reported using a predefined subgroup analysis (with only the patients capable of response in the denominator). The study protocol should include the plan to report responses, including any subgroup analyses.

DISCUSSION

These recommendations are designed to supply investigators with a shared group of functional endpoints for clinical trials of airway PN in patients with NF1. It is hoped that the use of these endpoints will improve the ability to identify active agents and facilitate comparison across studies with different agents. The recommended outcomes have not been prospectively used in NF1 PN trials to date, and the REiNS International Collaboration expects to revisit these recommendations as data from trials of airway PN are published.

AUTHOR CONTRIBUTIONS

C.L. Marcus: design and conceptualization of the study, collection and interpretation of the data, revising the manuscript. S.D. Davis: conceptualization of the study, collection and interpretation of the data, revising the manuscript. K.A. Robertson: conceptualization of the study, revising the manuscript. S. Akshintala: interpretation of the data, revising the manuscript. J. Allen: interpretation of the data, revising the manuscript. M.J. Fisher: design and conceptualization of the study, interpretation of the data, revising the manuscript. J.O. Blakeley: conceptualization of the study, interpretation of the data, revising the manuscript. B.C. Widemann: conceptualization of the study, interpretation of the data, revising the manuscript. R.E. Ferner: conceptualization of the study, drafting and revising the manuscript. S.R. Plotkin: design and conceptualization of the study, collection and interpretation of the data, drafting and revising the manuscript.

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