

Achieving consensus for clinical trials

The REiNS International Collaboration

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ABSTRACT

The neurofibromatoses (NF)—including neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis—are related tumor-suppressor syndromes characterized by a predisposition to multiple tumor types and other disease manifestations, which often result in functional disability, reduced quality of life, pain, and, in some cases, malignancy. With increasing knowledge of the biology and pathogenesis of NF, clinical trials with targeted agents directed at NF tumors have become available. Most clinical trials for patients with NF have used designs and endpoints similar to oncology trials. However, differences in the disease manifestations and natural history of NF (compared to cancers) require the development of new designs and endpoints to perform meaningful NF clinical trials. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 at the Children's Tumor Foundation meeting to achieve consensus within the NF community about the design of future clinical trials, with a specific emphasis on endpoints. The REiNS Collaboration includes 7 working groups that focus on imaging of tumor response; functional, visual, patient-reported, and neurocognitive outcomes; whole-body MRI; and disease biomarkers. This supplement includes the first series of recommendations by the REiNS Collaboration. The hope is that these recommendations will be used by members of the group and by researchers outside of the REiNS International Collaboration to standardize the measurement of outcomes and thus improve clinical trials for patients with NF. Ultimately, we plan to engage industry partners and national regulatory agencies in this process to facilitate the approval of drugs for patients with NF. **Neurology® 2013;81 (Suppl 1):S1-S5**

GLOSSARY

FDA = US Food and Drug Administration; **NF** = neurofibromatosis; **REiNS** = Response Evaluation in Neurofibromatosis and Schwannomatosis.

The neurofibromatoses (NF)—including neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis—are a group of related tumor-suppressor syndromes characterized by a predisposition to multiple nerve sheath tumors. Neurofibromas are the hallmark tumor of NF1, whereas schwannomas are the hallmark of NF2 and schwannomatosis. Patients with NF are at risk for a range of other tumors, including optic gliomas, non-optic gliomas, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, pheochromocytomas, and gastrointestinal stromal tumors (NF1); ependymomas (NF2); and meningiomas (NF2 and schwannomatosis).^{1,2} In addition, patients with NF1, NF2, and schwannomatosis are at risk for nontumor manifestations affecting multiple organ systems. Learning disability, cognitive dysfunction, and bony abnormalities are more common in NF1 patients, cataracts and neuropathy in NF2 patients, and chronic pain in schwannomatosis patients.³ Together, these disease manifestations may result in functional disability and reduced quality of life for patients.

Standard treatment for most histologically benign NF tumors is limited to surgery. Over the past 2 decades, researchers have used cell cultures and mouse models to better understand the

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REiNS International Collaboration members are listed on the *Neurology*® Web site at www.neurology.org.

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biology, pathogenesis, and array of disease manifestations in NF1, NF2, and schwannomatosis. The increased availability of targeted antitumor agents in the early 2000s led directly to the design and execution of clinical trials for plexiform neurofibroma in NF1 patients.⁴⁻⁶ In 2007, the Department of Defense Neurofibromatosis Research Program established the Neurofibromatosis Clinical Trials Consortium with a mandate to accelerate the development of multicenter clinical trials for affected patients. Under the leadership of Drs. Roger Packer and Bruce Korf, the Consortium was refunded in 2012 and has established a goal of hosting 6 clinical trials in the next 5 years.

Most early NF trials adopted trial designs similar to those used in oncology trials. However, due to differences in the manifestations of NF and its natural history compared to solid cancers, standard trial designs and endpoints used in oncology have limited applicability to NF trials for histologically benign tumors. The NF community continues to struggle with the optimum design of clinical trials for this group of patients. Currently, there is a wide range of endpoints used for clinical trials in NF patients, with no published consensus among investigators. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 at the Children's Tumor Foundation meeting to achieve consensus within the NF community about future clinical trials and to accelerate the identification of agents that will benefit individuals with NF. This supplement summarizes the recommendations from the REiNS group to date.

ORGANIZATION OF THE REiNS INTERNATIONAL COLLABORATION The REiNS Collaboration is organized around 7 working groups that focus on the following topics: imaging of tumor response, functional outcomes, visual outcomes, patient-reported outcomes, neurocognitive outcomes, whole-body MRI, and disease biomarkers. Leaders of the 7 working groups were identified based on their expertise at the initial meeting in 2011. The 7 group leaders comprise the leadership team of the overall REiNS Collaboration. Membership in each working group is open to any interested party, and representatives from patient advocacy groups and funding agencies have

been invited to participate in the effort. Each REiNS group establishes a meeting schedule; the majority of meetings are held by teleconference. In-person meetings of the entire group are held at least twice per year to coordinate efforts among the working groups and to achieve consensus for recommendations. The leadership team held a preliminary meeting with the US Food and Drug Administration (FDA) to discuss endpoints for NF trials. At this meeting, the FDA encouraged the REiNS Collaboration to use validated functional and patient-reported outcomes for trials intended for drug approval.

SUMMARY OF PUBLISHED CLINICAL TRIALS FOR NEUROFIBROMATOSIS Clinical trials for NF patients published to date are shown in the table. In these 15 studies, there has been a range of designs and primary and secondary endpoints. The majority of phase II studies were designed with imaging response as the primary endpoint. In these studies, change in 1- or 2-dimensional measurements or volume was used as the primary outcome measure and a variety of secondary endpoints was reported. Of note, few of these studies included endpoints evaluating functional outcomes (e.g., hearing or vision), patient-reported outcomes (e.g., pain), or neurocognitive outcomes. Thus, the majority of these trials used endpoints adapted from oncology trials to establish drug activity against NF-related tumors.

WHY CURRENT ENDPOINTS ARE NOT APPROPRIATE FOR NF TRIALS A diagnosis of NF1 or NF2 is associated with decreased survival compared with nonaffected controls.⁷ However, overall survival for patients with histologically benign tumors is extended, and use of overall survival as an endpoint for clinical trials in NF is not appropriate. Many NF tumors are complex and grow substantially more slowly than solid cancers, which limits the utility of standard response criteria used in solid tumor trials.^{8,9} In addition, there has been increasing concern by the NIH and the FDA about the use of imaging response (a decrease in tumor size) as a surrogate marker for clinical improvement. This concern stems from the finding that decreases in tumor size may not lead to clinical improvement for patients. For this reason, there has been increased support for the use of clinical and functional outcomes and extensive discussion about the most appropriate endpoints for NF patients since this group is burdened with significant morbidity.

FUTURE GOALS/PLANS This supplement presents the initial progress of several of the working groups and includes the first series of consensus recommendations for NF clinical trial endpoints by the REiNS International Collaboration. The goal of the group's efforts is to recommend outcome measures and methodologies

Table Published clinical trials for neurofibromatosis patients in the literature

Year	Drug	Tumor type/ manifestation	Phase	Age	Primary endpoint	Secondary endpoints	Reference
1993	Ketotifen	Cutaneous neurofibroma	II	Not stated	Itching and pain severity score		10
2002	13-cis-retinoic acid (CRA) or interferon α -2a	Plexiform neurofibroma	II	Children and adults	Imaging response (bidimensional)	Time to progression	11
2003	Thalidomide	Plexiform neurofibroma	I	>5 years	Maximum tolerated dose	Imaging response (bidimensional)	4
2006	Tipifarnib	Plexiform neurofibroma	I	2-18 years	Maximum tolerated dose	Toxicity, pharmacokinetics, pharmacodynamics, imaging response (bidimensional), patient-reported outcome (QOL)	12,13
2006	Pirfenidone	Plexiform neurofibroma	II	>15 years	$\geq 15\%$ decrease in tumor volume	Toxicity, patient-reported outcome (QOL)	6
2007	Pirfenidone	Plexiform neurofibroma	I	3-21 years	Pharmacokinetically comparable dose	$\geq 20\%$ change in tumor volume, patient-reported outcome (QOL)	14
2008	Simvastatin	Learning disability		8-16 years	Cognitive outcomes (attention, memory, executive function), mean apparent diffusion coefficient	Cognitive outcomes (attention, memory, executive function)	15
2008	Carboplatin & vincristine	Low-grade glioma	III	<10 years	Event-free survival	Imaging response (bidimensional), toxicity, patient-reported outcome (QOL)	16
2010	Sirolimus	Plexiform neurofibroma	II	≥ 3 years	Response and time to progression (volumetric)	Patient-reported outcomes (QOL, pain)	17
2011	Simvastatin	Learning disability	I	10-17 years	Maximum tolerated dose	Cognitive outcomes (attention, executive function, memory); visual-spatial, motor, and social-emotional functions	18
2012	Peginterferon alfa-2b	Plexiform neurofibromas	I	1.3-21 years	Toxicity	Tumor size (volumetric)	19
2012	Lapatinib	Vestibular schwannoma	II	>3 years	$\geq 15\%$ decrease in tumor volume	Significant improvement in word recognition score (hearing)	20
2012	Imatinib	Plexiform neurofibroma	II	3-65 years	$\geq 20\%$ decrease in tumor volume	Toxicity	21
2012	Photodynamic therapy (talaporfin sodium)	Plexiform neurofibroma	I	≥ 3 and ≤ 21 years	Maximum tolerated dose	Tumor size, patient-reported outcome (QOL)	22
2013	Sorafenib	Plexiform neurofibroma	I	3-18 years	Maximum tolerated dose	Patient-reported outcome (QOL)	5

Abbreviation: QOL = quality of life.

that will be used by REiNS members and by other researchers to standardize endpoints for NF clinical trials. Ultimately, we plan to engage industry partners and national regulatory agencies in this process to facilitate the approval of drugs for patients with NF. We expect that these recommendations will be modified with time as more data on NF-specific endpoints become available. Until that time, these guidelines may help researchers design clinical trials for patients with NF and improve the comparability of results between trials.

AUTHOR CONTRIBUTIONS

SR Plotkin: drafting the manuscript, study concept, interpretation of data. JO Blakeley: revising the manuscript for content, study concept, interpretation of data. E Dombi: revising the manuscript for content, study concept, interpretation of data. MJ Fisher: revising the manuscript for content, study concept, interpretation of data. CO Hanemann: revising the manuscript for content, study concept, interpretation of data. KS Walsh: revising the manuscript for content, study concept, interpretation of data. PL Wolters: revising the manuscript for content, study concept, interpretation of data. BC Widemann: drafting the manuscript, study concept, interpretation of data.

ACKNOWLEDGMENT

The authors would like to acknowledge the support of the Children's Tumor Foundation for the REiNS International Collaboration and for this supplement.

STUDY FUNDING

Supported by the Children's Tumor Foundation.

DISCLOSURE

S. Plotkin has been reimbursed by the American Academy of Neurology and the Children's Tumor Foundation for travel for educational activities. He has received research support from the Department of Defense (W81XWH-091-0182, NF050202, W81XWH-12-1-0155, PI), the Children's Tumor Foundation (PI), and Johns Hopkins Medical Institutes (site PI). J. Blakely received travel support from the Children's Tumor Foundation, the American Academy of Neurology, and the American Society of Clinical Oncology. She receives research support from GlaxoSmithKline, Sanofi-Aventis, Eli Lilly, the Cancer Therapy Evaluation Program, and the Children's Tumor Foundation. E. Dombi reports no disclosures. M. Fisher received reimbursement from the Children's Tumor Foundation to attend their annual Neurofibromatosis Conference, is funded by the Department of Defense (W81XWH-12-1-0155, W81XWH-05-1-0615), Thrasher Research Fund, the Children's Tumor Foundation, and Sarcoma Alliance for Research through Collaboration, and received research support from the Pediatric Low Grade Astrocytoma Foundation, Bayer, Children's Discovery Institute, NIH (NR009651-01), and the Department of Defense (W81XWH-08-1-0051). C. Hanemann received a travel grant from Baxter International and receives grant support from Novartis, The Brain Tumor Charity, CR-UK, and Action Medical Research. K. Walsh reports no disclosures. P. Wolters received research support from the Childhood Brain Tumor Foundation and holds stock options in Bristol-Meyers-Squibb, General Electric, and Zimmer Holdings, Inc. B. Widemann is a member of the scientific advisory board of the Neurofibromatosis Therapeutic Acceleration Program. She is a member of the editorial board of *The Oncologist* and an associate editor of *Frontiers in Pediatric Oncology*. Go to Neurology.org for full disclosures.

Received May 9, 2013. Accepted in final form August 13, 2013.

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Neurology 2013;81;S1-S5

DOI 10.1212/01.wnl.0000435743.49414.b6

This information is current as of November 18, 2013

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