1. Overarching Goals

Insights in the pathogenesis of neurofibromatosis offer the promise of targeted therapies to improve the quality of life of affected individuals. Conducting clinical trials, however, presents many challenges, including recruitment of a sufficient number of qualified individuals and obtaining necessary regulatory and ethics committee approvals to conduct studies. The NF Consortium was established in 2006 to help overcome these obstacles by assembling a group of patient recruitment sites and providing an Operations Center to insure that clinical trials are conducted efficiently and in compliance with all regulatory requirements. Over the past four years, three clinical trials have been activated, one of which has completed its accrual, one is mid-way through its accrual, and one has recently begun accrual. The Consortium has added three *ad hoc* sites in support of one of the ongoing trials and has negotiated a relationship with the SARC group to conduct a fourth trial on malignant peripheral nerve sheath tumors. In addition, several other trials are in preparation, including one focusing on NF2.

The overarching goal of the NF Consortium remains *to develop and implement biologically-based clinical trials for children and adults with all forms of neurofibromatosis*. In this request for continued funding we plan several enhancements and additions, including:

- Electronic data reporting for all clinical trials and Consortium activities
- Expansion of the Consortium to include four additional sites, aiming to improve geographic balance and expertise in NF2 and schwannomatosis
- Launching of four new clinical trials in the first two years of funding

2. Consortium Structure

The NF Consortium consists of an Operations Center at University of Alabama at Birmingham and multiple patient recruitment sites.

Operations Center – University of Alabama at Birmingham

Dr. Bruce Korf serves as principal investigator for the NF Consortium. Dr. Korf has a career-long interest in the clinical management, natural history, and genetics of neurofibromatosis. He is responsible for overall coordination of Consortium activities, management of the budget, generation of progress reports, and organization of all protocol submissions and IRB and other regulatory documents. The Operations Center manages Consortium clinical trials under the supervision of Dr. Gary Cutter. Dr. Cutter is head of the Section on Research Methods and Clinical Trials in the UAB School of Public Health. His group operates coordinating centers for 16 clinical studies, ranging from small studies with fewer than 50 participants to large registries with over 30,000 participants; they support single site and multicenter studies with as few as 3 to 4 sites to hundreds of sites, nationally and internationally. Dr. Cutter will supervise a data manager who will internally monitor quality assurance; ensure timely cutoffs so that monitoring reports are produced efficiently and identified in time and sequence; oversee the generation of clinical report forms and data reporting required by regulatory agencies; and assist in reporting for the Data Safety Monitoring Boards for all Consortium protocols. All clinical report forms and study data will maintained in an electronic system managed by StudyTrax, a company that provides software for management of clinical trials that is compliant with HIPAA and FDA regulations.

Consortium Steering Committee

The Consortium is governed by a steering committee. The elected chair is Dr. Roger Packer of Children's National Medical Center, where he directs the Daniel and Jennifer Gilbert Neurofibromatosis Institute. Dr. Packer is a renowned expert in pediatric neuro-oncology with more than 25 years of experience in clinical trials and a longstanding interest and expertise in neurofibromatosis. The steering committee includes subcommittees on clinical manifestations of NF, including neurofibromas, gliomas, neurocognitive dysfunction, malignant tumors, skeletal dysplasia, NF2, and schwannomatosis, as well as biology, radiology, and pharmacology. There are also membership, site evaluation, quality assurance, publications, intellectual property, and by-laws committees. The steering committee maintains a liaison to the Children's Tumor Foundation Preclinical Consortium to monitor progress in identification of new drugs for future trials.

Patient Recruitment Sites

The initial nine sites were selected through a competitive process managed by the DOD in 2005. Four sites have been added by vote of the steering committee and two sites have expanded to include more NF2 expertise. A site monitoring committee tracks metrics of site performance. It is expected that the lowest performing sites will be re-balloted at the end of the first year of the renewal of the Consortium (*i.e.*, December 2012). The 13 sites are: University of Alabama at Birmingham, Children's National Medical Center/Johns Hopkins Hospital, National Cancer Institute, Children's Hospital, Boston/Massachusetts General Hospital, Children's Hospital of Philadelphia/Hospital of University of Pennsylvania, University of Chicago, Washington University, University of Utah, Cincinnati Children's Hospital, NYU Medical Center, Children's Hospital of Westmead, Children's Hospital of Los Angeles/House Ear Institute, and University of Indiana.

Cores and Shared Resources

Cores and shared resources have been identified on an as-needed basis for specific clinical trials. These have included a pharmacokinetics core at Univ. Cincinnati for the STOPN trial, volumetric MRI core at NCI for STOPN, and a tissue procurement core at University of Alabama at Birmingham for the skeletal dysplasia trial.

3. Research Plan

The Consortium is focused on development of critically needed, biologically-based, statistically sound, and appropriately powered clinical trials for children and adults with all forms of neurofibromatosis. Multidisciplinary working groups are developing protocols for patients with NF1 (neurofibromas, neurocognitive deficits, low-grade gliomas, malignant peripheral nerve sheath tumors, and bone disease), NF2 (vestibular schwannomas), and schwannomatosis (pain and tumor progression). These are summarized in Table 1. Two protocols have been selected to launch in the first year of the funding period and two more in the second year.

Year One

***A Phase 2 Trial of Imatinab Mesylate in NF1 for Patients with Airway or Pelvic/Paraspinal Plexiform Neurofibromas and Associated Respiratory or Urologic Dysfunction*:** The first Consortium trial for plexiform neurofibroma (PN)(1) was a Phase 2 study of the mTor inhibitor

sirolimus for NF1 patients with inoperable PNs. While this recently completed study is being analyzed, the initial plexiform neurofibroma study proposed for the next funding period is a phase 2 trial of imatinib mesylate (Gleevec®) in patients with symptomatic airway or pelvic PNs. This study builds on the results of a preclinical model(2) and preliminary evidence of efficacy from a completed DOD-sponsored trial. A focused phase 2 clinical trial is required to better define and quantify the response in patients with airway or urologic dysfunction.

***A Phase 2 Study of Bevacizumab for Treatment of Symptomatic Vestibular Schwannomas in Children and Adults with NF2*:** Bilateral vestibular schwannomas (VS) are the hallmarks of NF2, and as these tumors enlarge they can cause deafness and brainstem compression. Sporadic and NF2 related VS express vascular endothelial growth factor. Bevacizumab is a humanized IgG1 monoclonal antibody that binds all biologic active isoforms of human VEGF with high affinity. The initial experience in treatment of ten NF2 patients with VS was promising, with 6 having a greater than 20% reduction in tumor volume and 4 having demonstrable clinical improvement(3). For this reason, the NF consortium, in the next funding period, plans to open a Phase 2 trial to determine the activity of bevacizumab for the treatment of symptomatic VS in adults and children with NF2. Clinical response will be assessed by audiology and neuroimaging. This trial has also already received industry support and will open contingent on approval of funding for the Consortium.

Year Two

Neurocognitive Dysfunction: Neurocognitive dysfunction is the most common cause of long-term morbidity for individuals with NF1(4). The NF Consortium successfully launched a phase 2 trial of Lovastatin *vs.* placebo for children with NF1 and learning difficulties; enrollment is expected to be completed by early 2012. If Lovastatin is found to be efficacious, a follow-up phase 2 trial comparing the efficacy of Lovastatin to that of traditional stimulants(5) (with or without concomitant Lovastatin) on primary outcome measures, such as working memory, attention, reaction time, and inhibitory control, will be developed. At the same time, the use of nonpharmacological interventions, such as cognitive training for cognitive rehabilitation(6), will be explored. One form of cognitive intervention, the COGMED RM, is a computer-training program that has been designed for improving attention and working memory skills(7). There is evidence that children who participate in other COGMED trials have long-term gains in cognitive domains, and a pilot study is already underway in children with NF1.

Skeletal Dysplasia: Tibial pseudoarthrosis (TP) is one of the most serious and difficult to manage osseous complications of NF1. Despite progress in surgical techniques, TP often results in multiple surgeries, re-fractures, and, in some cases, amputation. Pre-clinical studies have shown that bone disease in NF1 is associated with both abnormal differentiation and function of osteoblasts and increased number and size of osteoclasts, leading to abnormalities in bone remodeling and reabsorption. For this reason, a combination trial of an anabolic agent to increase bone formation (bone morphogenetic protein-2)(8) and an antiresorptive agent (pamidronate) at the time of surgery is proposed(9). Healing will be assessed with the RUST radiographic scale of tibial bone healing. Time to healing will also be recorded. In addition to

consortium sites, other sites across the world will be utilized to accrue an adequate number of patients to complete this study.

Additional Protocols

Consortium committees are exploring several additional protocols that will be further developed as funding is available.

Low-Grade Gliomas: Low-grade gliomas (LGG) occur in up to 20% of children with NF1 and can cause significant morbidity(10). The most common location is in the visual pathway, but gliomas may also arise in the brainstem and supratentorial sites. Approximately 40% of patients develop progressive disease in spite of carboplatin/vincristine therapy. The biologic basis of glioma growth in patients with NF1 is increasingly understood, and mTor activation in NF1-deficient cells has shown to be dependent upon RAS and PI3 kinase activation(11). In Spring 2011, the Neurofibromatosis Consortium opened a study evaluating RAD001, an mTor inhibitor, for patients with LGGs failing initial treatment with a carboplatin-containing regimen. When this study is complete, other biologically-based studies will be undertaken, which are likely to include dual biologic inhibition, such as the use of a PI3 kinase inhibitor in addition to the mTor inhibitor (if mTor inhibition is found to be efficacious), the introduction of other biologic agents such as inhibitors of the RAS/Map kinase signaling pathway (BRAF or MEK inhibitor), and/or the addition of antiangiogenesis drugs. Preliminary studies with the use of bevacizumab has suggested that antiangiogenesis drugs are effective in some patients with recurrent NF1 LGGs(12), and an oral antiangiogenetic drug is presently under evaluation in a Phase 1 study through the Pediatric Brain Tumor Consortium. This drug is also a candidate, singly or in combination, for study in patients with NF1-associated LGGs.

Malignant Peripheral Nerve Sheath Tumor: Malignant peripheral nerve sheath tumors (MPNST) account for 10% of all soft tissue sarcomas. One-half of these cancers arise in patients with NF1, and the lifetime risk for MPNST in NF1 is 8-13%(13; 14). Outcome and chemotherapy response appear to be worse for individuals with NF1-associated MPNST(14; 15); complete surgical removal is the only current curative treatment(16). Targeted inhibition of signaling pathways upstream and downstream of the RAS/NF1 pathway (*e.g.,* Raf, P13K, mTOR) may selectively inhibit the growth and progression of NF1-related MPNST. The mTOR inhibitor sirolimus halts progression of MPNSTs in preclinical NF1 MPNST models(11; 17; 18). Angiogenesis contributes to the progression of MPNST. These findings provide the rationale for the combination of agents blocking mTOR and angiogenesis. The MPNST committee has developed a phase II trial of the mTOR inhibitor RAD001 in combination with the angiogenesis inhibitor bevacizumab for patients with sporadic or NF1-associated refractory MPNST. The trial will be coordinated and sponsored by the sarcoma cooperative group SARC, and can begin enrollment in 2012.

Plexiform Neurofibroma: Depending on the outcome of the Sirolimus trial and the proposed imatinib mesylate trial, the neurofibroma committee is considering additional protocols for plexiform neurofibromas. At present, the most likely prospect is a phase II study of mitogen-activated protein (MEK1) inhibitor(19), AZD6244, in children and adults with inoperable

plexiform neurofibromas. Upon determination of the recommended phase II dose (anticipated in July 2012 from two ongoing studies), a consortium-wide trial is planned to determine the activity of the drug in children and adults with inoperable PNs.

Schwannomatosis: Schwannomatosis is a syndrome of multiple tumors of the peripheral nervous system that commonly result in severe pain. The most common molecular finding in these tumors is a dual mutation in INI1/SMARCB1 and NF2 mutations(20). This may result in over-expression of some of the tropomyosin receptor kinase (Trk) family of receptors. The Trk family is essential for normal nervous system development, has been recognized as a mediator of injury in the peripheral nervous system and recently has been implicated in tumorgenesis in other central and peripheral nervous system tumors including neuroblastoma and astrocytoma (21). In addition, Trk is upstream of important pathways for schwannoma growth including Ras/Ref/MEK. Lestaurtinib is an oral tyrosine kinase inhibitor that targets both Trk and FLT(22) and may have efficacy against painful schwannomas in schwannomatosis. We will investigate the tolerability of lestaurtinib at doses required to accomplish peripheral blood monocyte inhibition of Trk and FLT in adult patients with confirmed schwannomatosis and pain $\geq$4 on the Brief Pain Inventory in a phase 1 study. As a secondary objective we will assess changes in the Brief Pain Inventory score and volumetric changes in schwannomas with whole body MRI after one month of treatment.

Disorder	Target	Intervention	Stage	Sites	IND	Comments
NF1	PN	Imatinib mesylate	Protocol written	All	Exemption	Follows on pilot trial; drug supplied by Novartis
NF2	Vestibular schwannoma	Bevacizumab	Protocol Written	All	UAB application pending	
NF1	Bone	BMP + pamidronate	Protocol written	All	IND/IDE	
NF1	Neurocognitive	Cogmed training	LOI	All	n/a	Either the cogmed or the lovastatin/methylphenidate trial will be the next neurocognitive trial
NF1	Neurocognitive	Lovastatin + methylphenidate	Concept	All	TBD	
NF1	PN	MEK Inhibitor	LOI	All	CTEP	Phase II trial to be written upon completion of ongoing phase I trial
NF1	PN	Sirolimus/AKT inhibitor	Concept	All	TBD	
NF1	MPNST	TBD	Concept	All	TBD	
NF1	Low grade	TBD	Concept	All	TBD	

	glioma					
Schwannomatosis	Schwannoma	lestaurtinib	Concept	All	TBD	

Table 1. Status of proposed clinical trials for all forms of neurofibromatosis. Those highlighted in red will launch in the first year of the Consortium; those highlighted in green will launch by the end of the second year.

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