



NF Clinic Network (NFCN) Application Form*

Clinic Name:

Children's National Medical Center Neurofibromatosis Clinic

Affiliated Hospital:

Children's National Medical Center

Affiliated University or Institution:

The George Washington University

Clinic Address:

Children's National Medical Center
Department of Genetics and Neurology
111 Michigan Avenue, NW
Washington, DC 20010

Clinic Director:

Cynthia Tift, MD, PhD
Kenneth Rosenbaum, MD
Maria Acosta, MD
Roger Packer, MD

Clinic Coordinator Name:

Deborah Copenheaver, MS, CGC

**Note: Some non-public information has been removed from this application form.*



The Neurofibromatosis Clinic Network (NFCN)

FORM PART A: Affiliate Clinic Application

1. ABOUT YOUR NF CLINIC

a. Is your NF Clinic:

Freestanding

Hospital based

In an academic center

Other (please describe): _____

b. Describe overall your NF Clinic, when it meets and how it functions.

The Neurofibromatosis Clinic at the Children's National Medical Center is one of the longest standing continuously-operating neurofibromatosis clinics in the United States. The clinic initially opened in 1982 under the direction of **Dr. Kenneth Rosenbaum**, who continues to be a co-director of the clinic. It was enlarged when **Dr. Cynthia Tifft**, presently chairman of Genetics at the Children's National Medical Center, joined Dr. Rosenbaum as co-director in the early 1990's. Because of the large size of the program and the multi-disciplinary needs of children with neurofibromatosis, **Dr. Roger Packer** joined the clinic in 1992. Most recently, **Dr. Maria Acosta** was recruited to the clinic as a child neurologist in 2004. **Drs. Tifft, Rosenbaum, and Acosta co-direct the clinic with Dr. Packer.** The clinic meets the first, third and fourth Tuesdays of each month in the Genetics outpatient area. The clinic is coordinated by **Deborah Copenheaver**, a genetics counselor with extensive experience in neurofibromatosis type 1. All patients in the clinic are seen by one of the geneticists - either Dr. Rosenbaum or Dr. Tifft, and Dr. Acosta. Dr. Packer is available to the clinic, on a weekly basis, for patients with intracranial tumors or progressive plexiform neurofibromas.

Because of the size of the program, an increasing number of referrals, and the opening of multiple clinical studies for children with NF1, a second clinic, coordinated by Dr. Acosta and Dr. Packer, meets every Tuesday afternoon. This clinic focuses on children with neurofibromatosis type 1 with neurologic complications. It also acts as the primary clinic responsible for care for those patients on neurofibromatosis clinical trials, including those for plexiform neurofibromas, optic nerve gliomas, and neurocognitive disabilities. The clinic coordinator, Deborah Copenheaver, is also available to the neurofibromatosis afternoon clinic.

There is ongoing, concurrent ophthalmologic support for the Neurofibromatosis Clinic, as **Dr. Kelly Hutcheson**, from the Division of Pediatric Ophthalmology, is available to evaluate patients on the day of their NF clinic visit. Further supporting the effort is a nurse practitioner, **Laurie Williams, PNP**, who supports the activities of the physicians at each clinic (.6 FTE effort in neurofibromatosis). **Dr. Gilbert Vezina**, Chief of Neuroradiology at CNMC, directs a weekly genetics and a weekly neuro-oncology radiology review which evaluates all studies on NF patients seen in the clinic. Thus, the overall structure of the NF Clinic allows for multidisciplinary care by experienced physicians from multiple subspecialties including, genetics, neurology, ophthalmology, and neuroradiology.

In addition to the Neurofibromatosis Type 1 clinic, a multidisciplinary Neurofibromatosis Type 2 clinic is to open at Children's National Medical Center in October of 2007. This clinic, which meets on the 2nd Tuesday morning of every month, is directed by **Dr. Amanda Yaun**, a pediatric neurosurgeon with expertise in pediatric neurosurgery and the use of the gamma knife. It is co-directed by Dr. Kenneth Rosenbaum, the senior geneticist at Children's National Medical Center, who co-directs the Neurofibromatosis Type 1 Clinic, and **Dr. David Schessel**, a professor of

otolaryngology at both the Children's National Medical Center and the George Washington University. In addition, an adult neurosurgeon at Georgetown University, **Dr. Walter Jean**, specializing in skull base neurosurgical procedures, is part of the NF2 program. Supporting the NF2 program is Deborah Copenheaver and Dr. Kelly Hutcheson, who are also actively involved in the NF 1 clinic.

In total, the NF1 program has eight clinics per month dedicated to patients (both children and adults) with both neurofibromatosis type 1 and type 2. On any given week, the clinics evaluate between 8 and 16 patients and are well supported administratively and clinically with a major focus on clinical research (which will be described later in the application).

2a. Clinic Director

As outlined, the NF1 program at Children's is multidisciplinary and the co-directors have significant experience in NF1. **Dr. Rosenbaum**, who began the clinic in 1982, was part of the initial consensus conference determining the diagnostic criteria for NF1. For the past quarter century, he has evaluated neurofibromatosis patients from across the region and nationally. Through his efforts, some of the earliest work in the delineation of the cognitive phenotype of NF1 was performed. It was his vision that made the program multi-disciplinary, involving not only genetics but neurology, ophthalmology, and neuropsychology. This work has been continued and expanded by **Dr. Tifft**, who is Chairman of Genetics at Children's National Medical Center.

Dr. Packer has a long track record in clinical care and research in NF1. Prior to coming to Washington, DC in 1989, Dr. Packer was the neurologist to the NF Clinic at the Children's Hospital of Philadelphia. Dr. Packer has led multiple clinical trials for children with NF1 and visual pathway gliomas and plexiform neurofibromas. He was previously on the Advisory Board of the Children's Tumor Foundation and is on the Advisory Board of Neurofibromatosis Inc. He was recently elected Group Chair of the Department of Defense newly funded Neurofibromatosis Clinical Trial Consortium. Dr. Packer has been the principal investigator of the pirfenidone study for patients with progressive plexiform neurofibromas and a collaborator on multiple other studies. **Dr. Maria Acosta** has taken a national and international leadership role in investigations of the neurocognitive aspects of neurofibromatosis type 1. She has extensive expertise in learning disabilities and in ADHD research and intervention. She is working with Dr. Kathryn North, of the University of Sydney, on studies, funded by the Department of Defense, defining the cognitive profile of children with neurofibromatosis type 1 and how this profile changes over time. Dr. Acosta is Chair of the first United States study evaluating the toxicity and efficacy of lovastatin, a drug that among other effects, targets the ras system in children with neurocognitive deficits and NF1. She is working on studies evaluating the effect of stimulant medication on learning patterns in children utilizing functional MRI and is applying functional MRI, in collaboration with other researchers at the Children's National Medical Center, to the problem of cognitive dysfunction in children with NF1. In cooperation with the Neuropsychology department

and the Developmental Pediatrics department, an extensive evaluation and plan for intervention is provided for each patient. Direct communications, with recommendations, are made with both the parents and the school in each case.

2. CLINIC DIRECTOR and STAFF EXPERTISE

a. CLINIC DIRECTOR: Please describe:

i. Your experience to date with NF care

The Neurofibromatosis Program and Clinic at the Children's National Medical Center has a long-standing experience with clinical care. The Clinic has been in continuous operation since 1982 and is a multidisciplinary program. It takes care of both adults and children with neurofibromatosis and actively follows over 750 patients with NF1 and NF2. Approximately 20% of the patients are adults. The Clinic, as outlined, is multidisciplinary. All the physicians who have been involved with the clinic are experienced in neurofibromatosis type 1. As outlined previously, Dr. Rosenbaum has been directing the clinic since 1982 and Dr. Tifft has expanded this effort. Dr. Packer has been involved in neurofibromatosis clinical care and research since the mid-1980's (beginning at Children's Hospital of Philadelphia) and since 1990 at the Children's National Medical Center.

In 2003, the Clinic was awarded a Center of Excellence Award by the National Neurofibromatosis Foundation.

ii. Your past and current association with NF clinical trials

The members of the NF1 Clinic at the Children's National Medical Center have been leaders in developing clinical trials for children with neurofibromatosis. The clinical trials have been performed for multiple different medical conditions. The Children's National Medical Center, under the direction of Dr. Packer, was a collaborator in the study funded by the Department of Defense, entitled, "Natural History of Plexiform Neurofibromas" and was one of the most active institutions in this consortium, entering 33 children and adults. The CNMC Neurofibromatosis Program participated in, and is still participating in, multiple therapeutic trials for children and adults with NF1 and plexiform neurofibromatosis. It entered multiple patients on a trial evaluating either cis-retinoic acid or alpha interferon (10 patients) which was completed and also entered patients on a trial utilizing thalidomide for adults and children with progressive plexiform neurofibromas. It is participating in an ongoing PEG-intron study.

In 2001, Children's National Medical Center was awarded a grant by the Department of Defense to develop and coordinate a prospective nationwide (11 institutions) translational study of the use of Pirfenidone, a novel antifibrotic agent that interferes with

multiple growth factors (R. Packer, PI), in children with progressive plexiform neurofibromas. Gene array profiling performed at CNMC demonstrated the over-expression of multiple growth factors in plexiform neurofibromas and this was used as a component of the scientific rationale for this translational study. The Phase 1 component of this study has been completed and the Phase 2 study is nearly completed. The Children's National Medical Center, through Dr. Packer and Dr. Acosta, has also been involved in the development of, and are participating in, a plexiform neurofibroma study, led by the National Cancer Institute, evaluating another biologic agent - an oral farnesyl transferase inhibitor - (FTI). The pifrenidone study was designed to utilize the same eligibility and evaluation criteria as the FTI study, and results from the FTI study are being used as a component of the evaluation of the efficacy of the nationwide pifrenidone study.

Another study through the Department of Defense Clinical Trials Consortium is soon to be opened utilizing an mTOR inhibitor, rapamycin, for children with plexiform neurofibromas.

Children's National Medical Center has also been a leader in the evaluation and clinical management of children with NF1 and gliomas. In the late 1980's and early 1990's, Dr. Packer developed a treatment approach utilizing carboplatin and vincristine for children less than ten years who have progressive visual pathway gliomas. This innovative approach demonstrated significant efficacy for children with NF1 and was incorporated in one of two treatment arms of a national study through the Children's Oncology Group for children with progressive visual pathway gliomas. Dr. Packer remains the neurologist assigned to this trial. Dr. Packer has also been actively involved in evaluating other agents for progressive gliomas in children with NF1 and has recently submitted to Children's National Medical Center's IRB a study evaluating the combination of Tarceva, an anti-epidermal growth factor receptor drug, and rapamycin, an mTOR inhibitor, in children with progressive visual pathway or other low-grade gliomas who have failed conventional therapy. The clinical program at Children's National Medical Center for gliomas in children with neurofibromatosis type 1 is supported by research being performed by Dr. Tobey MacDonald's laboratory at Children's National Medical Center evaluating the signal transduction pathways active in gliomas in patients with NF1

In addition to these two areas, the Children's National Medical Center has been a leader in developing therapeutic trials for patients with neurofibromatosis type 1 and neurocognitive difficulties. The Children's National Medical Center recently completed a trial utilizing functional MRI in patients with NF1 and attention deficit disorder to characterize the functional anatomy of components of executive function and the impact of stimulant medication (Ritalin) on fMRI to assess the frontal lobe underactivation. Mouse studies have suggested that the ras pathway is integral in the neurocognitive difficulties that occur in NF1 and

that treatment with an oral farnesyl transferase inhibitor can, in part, reverse some of these abnormalities. Based on this information, the Children's National Medical Center completed a Phase 1 trial utilizing Lovastatin, a drug which interferes with the ras pathway, for children with NF1 and cognitive difficulties, to determine the potential use of this drug for these patients. This trial has shown no significant toxicity and preliminary results have demonstrated an improvement in neurocognitive function in some of the children on the phase 1 trial. Based on this information, a phase 2 trial has been developed and is soon to be submitted, through the Department of Defense NF1 Clinical Trials Consortium.

The strength of the clinical program in Neurofibromatosis Type 1 at the Children's National Medical Center led to its inclusion as one of the eight institutions chosen to be part of the new **Department of Defense-funded Clinical Trials Consortium in Neurofibromatosis**. **Dr. Packer was elected group chair for this consortium**, based on his past experience in developing clinical trials for patients with neurofibromatosis type 1 and his similar experience in developing trials for children with brain tumors. **Dr. Maria Acosta** was chosen to lead the initial neurocognitive study for the consortium. **Dr. Gerry Gioia**, Chief of Neuropsychology at Children's National Medical Center, is co-director of the Clinical Trials Consortium's Neurocognitive Committee. **Dr. Gilbert Vezina**, who has worked closely with Dr. Packer and colleagues at Children's National Medical Center on the development of these clinical trials, is the head of the Neuroradiology committee of the consortium.

3. Your past and current association with other clinical trials e.g. oncology trials

One of the major strengths of the Neurofibromatosis Program at the Children's National Medical Center has been its experience in coordinating other clinical trials for children with neurologic conditions, especially brain tumors. Dr. Packer, who is one of the co-directors of the clinic, has wide experience in developing clinical trials and has led multiple clinical trials on a regional, national, and international level in various aspects of neuro-oncology, including medulloblastoma, optic nerve gliomas, brainstem gliomas, and other rarer forms of childhood cancer. Children's National Medical Center, under the direction of Dr. Packer, has been selected as one of the institutions to participate in the NIH peer reviewed chosen Pediatric Brain Tumor Consortium and within that consortium Dr. Packer acts not only as the institutional principal investigator at Children's National Medical Center, but also the chair of the Embryonal Tumor Committee. Within the international Children's Oncology Group (COG), Dr. Packer has had multiple leadership roles in the development of clinical trials including being past director of its Brain Tumor Strategy Group, past director of its Neurology and Neuroscience committees, and present director of its Medulloblastoma Committee. Dr. Packer has led multiple COG clinical trials including a recent trial for children with non-disseminated medulloblastoma, which entered over 400 patients nationally.

The neurocognitive aspects of NF1 patients have become an important aspect in the Children's National Medical Center's clinical research. Dr. Acosta is the PI at the Children's National Medical Center of a currently ongoing Phase 1 study for evaluation of Lovastatin as a treatment for neurocognitive deficits in 10-17 y/o children with NF1. This is the first study in the United States for evaluation of this potential intervention to improve learning in this population. In addition, it will provide fundamental information to move towards a Phase 2 study for evaluation of this intervention in a bigger number of patients.

In addition, other cognitive studies are currently on-going at the Children's National Medical Center. These include a multi-site study for "Early Detection of Cognitive Deficits in Patients with NF1". This study, designed and developed in cooperation with Dr. Kathryn North of Australia, is recruiting two populations of patients with NF1. The first group is made up of NF1 patients younger than 40 months for a series of developmental evaluations between 5 - 40 months of life. A second group, only recruited at Children's National Medical Center, is enrolling patients who had developmental evaluation between ages of 3 months to 6 years of age, and are currently older than 6 years of age. In addition, correlations with MRI findings are being done in these patients.

Additional studies include a pilot study for evaluation of brain function using MRI techniques to learn about patterns of brain activation in children with NF1 and ADHD compared with ADHD children. A more comprehensive study, which has been submitted for funding consideration, has been designed to assess brain functioning in patients with NF1 using fMRI techniques.

In addition, evaluation of quality of life, resilience, and other behavioral components in patients with NF1 is currently ongoing. This evaluation is being done primarily with NF1 Camp participants during the summer and will begin to include patients from our clinic during the fall of 2007. These studies have been coordinated by Dr. Acosta along with social worker, Sandra Cushner-Weinstein, and genetic counselor, Debbie Copenheaver.

a. CLINIC DIRECTOR: Please provide information on:

i. Present and past funding you have received for NF research. Include funding source, date received, amount and project description.

A. 1993 to 1997 Packer RJ (PI, CNMC)

A randomized Phase 2 trial of cis-retinoic acid, alpha interferon for the treatment of patients with progressive enlargement of plexiform neurofibromas and neurofibromatosis type 1 (NF1)

Funded by: United States Army through the Children's Hospital of Philadelphia.

Project Description:

This was a prospective phase 2 trial evaluating either cis-retinoic acid or alpha interferon for children with progressive plexiform neurofibromas

Funding Amount

The drugs were delivered free of charge, although no other costs were covered.

- B. 1999 to 2004 Packer RJ (PI, CNMC)**
Natural history of plexiform neurofibromas in NF1

Funded by: Department of Defense

Project Description

The Children's National Medical Center was one of multiple institutions that participated in this study. The study evaluated the growth rate of plexiform neurofibromas

Funding Amount

Funding was per patient and study: CNMC entered 33 patients on the study and received per capita payment (approximately \$3,000) per patient.

- C. 2002 to 2006 Packer RJ (PI, CNMC)**
Phase I/Phase 2 Study of Pirfenidone in NF1 and Plexiform Neurofibromas

Funded by: Department of Defense/Department of Army

This is a Phase 1/Phase 2 study of Pirfenidone, a novel antifibrotic and anti-growth factor agent in children with progressive neurofibromas.

Amount of Funding: \$2.4 Million

- D. 2002 to 2004 (Packer RJ - PI CNMC)**
Phase 1 study of Pirfenidone in NF1 and plexiform neurofibromas

Funded by: FDA Orphan Drug Program

Project Description

This was a supplementary grant to support patients care costs and ancillary clinical costs for the phase 1 study of Pirfenidone.

Amount of Funding: \$500,000

- E. 2004 to 2007 (Packer RJ - PI CNMC)
Phase 2 study of Pirfenidone in NF1 and plexiform neurofibromas

Funded by: FDA Orphan Drug Program

Project Description

This was a supplementary grant to support patients care costs and ancillary clinical costs for the phase 2 study of Pirfenidone.

Amount of Funding: \$700,000

- F. 2005 to 2006 (Packer RJ - PI CNMC)
Neurofibromatosis Planning Grant

Funded by: Department of Defense

Project Description:

This was a planning grant to develop a clinical trials consortium for children and adults with NF

Amount of Funding: \$30,000

- G. 2006 to 2011 (Packer RJ - PI CNMC)
Neurofibromatosis Clinical Trials Consortium

Funded by: Department of Defense

Project Description:

This is a national clinical trials consortium for children and adults with NF

Amount of Funding: Pending final deliberations. Total \$8,000,000 to \$10,000,000.

- H. 2006 to 2008 (Acosta MT - PI CNMC)
Phase 1 study of Lovastatin for Neurocognitive Dysfunction in Children with Neurofibromatosis Type 1

Funded by: RAC CNMC

Project Description:

Safety evaluation in a Phase 1 design of Lovastatin as a potential pharmacologic intervention for neurocognitive deficits in patients with NF1 age 10-17 y/o

Amount of Funding: \$29,785

I. 2004 to 2008 (Acosta MT - PI CNMC)

Early Identification of Cognitive Deficits in Children with NF1

Funded by: Department of Defense

Project Description:

Longitudinal evaluation of developmental patterns in children (5 months - 40 months) with Neurofibromatosis and correlation with MRI findings. A second phase includes evaluation of cognitive profiles in children and young adults with NF1 (6 years to 40 years)

Amount of Funding: \$500,000

ii. Your NF-related clinical and scientific publications.

Include Journal, Citation and Title.

Acosta MT, Seldin-Sommer L, Marcus D, Tiffit C, Rosenbaum K, Shapiro M, Silva A, Gioia G, Packer R: Lovastatin as a pharmacological treatment for learning disabilities in patients with NF1: Safety data from Phase 1 study (abs). Accepted for presentation at Children's Tumor Foundation Conference at Park City Utah, June 7-10, 2007.

Acosta MT, Seldin-Sommer L, Gioia G, Marcus D, Shapiro M, McCarter R, Molina P, Arcos-Burgos M, Silva A, Tiffit C, Rosenbaum K, Packer R: Pharmacological intervention with Lovastatin for learning disabilities in patients with NF1: Preliminary data in neuropsychological result in a phase I study (abs). Accepted for presentation at Children's Tumor Foundation Conference at Park City Utah, June 7-10, 2007.

Acosta MT: Neurobiology of learning disabilities: Neurofibromatosis type 1 as a model for research. Rev Neurol 2007; 44(supp 2) S3-8.

Acosta MT, Gioia G, Silva A: Neurofibromatosis type I: Neurocognitive new insights into neurocognitive issues. Curr Neurol Neurosci Rev 2006;6:136-143.

McLean SD, Stern HJ, Rosenbaum KN, Tiffit CJ, Saal HM. The natural history of café-au-lait spots in young children with neurofibromatosis 1. Amer. J. Human Genetics 1993; 53:474.

Cohen MS, Nies B, Tiftt CJ. Neurofibromatosis type 1 and pregnancy. *Amer. J. Human Genetics* 1994; 35:36.

Samango-Sprouse CA, Cohen MS, Mott SH, Custer DA, Vaught DR, Stern HJ, Tiftt CJ, Rosenbaum KN. The effect of familial vs. sporadic inheritance of the neurodevelopmental profile of young children with neurofibromatosis type 1. *Amer. J. Human Genetics* 1994; 35:21.

Vezina LG, Samango-Sprouse CA, Cohen MS, Fitz CR, Mott SH, Brasseux CO, Tiftt CJ, Stern HJ, Rosenbaum KN. Cranial magnetic resonance imaging (MRI) findings and their relationship to age and sexual maturation in neurofibromatosis type 1. *Amer. J. Human Genetics* 35:536.

Cohen BM, Kaplan AM, Packer RJ: Management of intracranial neoplasms in children with neurofibromatosis type 1 and 2. *Pediatric Neurosurgery* 16: 66-72,1991.

Packer RJ, Lange B, Ater J, et al: Carboplatin and vincristine for progressive low-grade gliomas of childhood. *Journal of Clinical Oncology* 11: 850-857, 1993.

Packer RJ, Ater J, Allen J, et al: Treatment utilizing carboplatin and vincristine for children with newly-diagnosed progressive low-grade gliomas. *J of Neurosurgery* 56: 747-754, 1997.

Listernick R, Louis DN, Packer RJ, and Gutmann DH: Optic pathway gliomas in children with neurofibromatosis 1: Consensus statement from the NF1 Optic Pathway Glioma Task Force. *Neurology* 41:143-149, 1997.

Schmandt SM, Packer RJ, Vezina G, and Jane J: Spontaneous regressions of a chiasmatic glioma in a child with neurofibromatosis. *Pediatric Neurosurgery* 32:132-136, 2000.

Lui G, Schmandt SM and Packer RJ: Visual Loss in Childhood. *Survey of Ophthalmology* 46:35-41, 2001.

Packer RJ: Chemotherapy: Low-grade gliomas of the hypothalamus and thalamus. *Ped Neurosurg* 32:259-263, 2000.

Gupta A, Cohen BH, Ruggieri P, Packer RJ and Phillips P: Phase I study of thalidomide for the treatment of plexiform neurofibroma in neurofibromatosis 1. *Neurology* 60:130-132, 2003.

Ruggieri M and Packer RJ: Why do benign astrocytomas become malignant in NF1. *Neurology* 56:827-829, 2001.

Packer RJ, Gutmann DH, Rubenstein A, Viskochil D, Zimmerman RA, Vezina G, Small J and Korf B. Plexiform neurofibromas in NF1: Towards biologic-based therapy. *Neurology*, 58:1461-1470, 2002.

Rosser T and Packer RJ. Intracranial neoplasms in children with neurofibromatosis type 1. *Journal of Child Neurology* 17:630-637, 2002.

Packer RJ and Rosser T. Therapy for plexiform neurofibromas in children with NF1: An overview. *Journal of Child Neurology* 17:638-641, 2002.

Rosser T and Packer RJ. Neurofibromas in children with NF1. *Journal of Child Neurology*, 17: 585-591, 2002.

Dombi E, Solomon J, Gillespe AJ, Fox E, Balis FM, Petronas N, Korf B, Babovic-Vuksanovic D, Packer RJ, Belasco J, et al: NF1 plexiform neurofibroma growth rate by volumetric MRI: Relationship to age and body weight, *Neurology* 68:643-647, 2007.

Babovic-Vuksanovic D, Packer RJ, et al: Phase I trial of pirfenidone in children with neurofibromatosis type 1 and plexiform neurofibromas. *J Ped Neurol* 36:293-300, 2007.

c. Who are the key staff in your NF clinic facility?

Name	Degree/Qualifications;	Title	Role in Clinic.
Cynthia J. Tifft, MD, PhD;	Genetics/Metabolism;	Geneticist/Co-Director	
Kenneth Rosenbaum, MD;	Genetics;	Geneticist/Co-Director	
Maria Acosta, MD;	Neurology;	Neurologist/Co-Clinic Director	
Roger J. Packer, MD;	Neurology/Neuro-Oncology;	Neurologist/Co-Clinic Director	
Kelly Hutchinson, MD;	Ophthalmology;	Ophthalmologist	
Laurie Williams, PNP;	Nurse Practitioner;	Nurse Practitioner	
Gilbert Vezina, MD;	Neuroradiology;	Neuroradiologist	
Deborah Copenheaver, MS;	Genetic Counselor;	Clinic Coordinator	

d. Who within this core staff currently coordinates NF patient services? Describe this individual's NF clinic related duties.

The multidisciplinary clinic is coordinated by Deborah Copenheaver, the genetics counselor to the NF program at the Children's National Medical Center. The neurology ancillary clinic which meets four times monthly is coordinated by Laurie Williams, nurse practitioner to the clinic.

- e. Describe any areas of NF care in which your clinic has particular expertise (e.g. optic glioma, vestibular schwannoma, bone manifestations, learning disabilities etc.) and the clinic staff that provide this care.

The NF program at the Children’s National Medical Center has developed particular expertise for children with plexiform neurofibromas, other types of compromising neurofibromas, optic nerve gliomas, visual pathway gliomas, other low-grade gliomas, and the neurocognitive aspects of neurofibromatosis. There is also special expertise in the management of schwannomas and gliomas in patients with neurofibromatosis type 2. The large multidisciplinary staff supports these activities.

4. PATIENT SCHEDULING and REFERRALS

- a. Provide the details of the ‘typical’ timeframe in which patients receive a response to a request for scheduling, are actually scheduled for an appointment, how patients are prioritized, etc.

For the multidisciplinary clinic, new patients are typically seen within four weeks of first contact. The Clinic Coordinator, Deborah Copenheaver, in concert with the clinicians involved in the program, is responsible for triage of patients. In addition, because of the special interest of the clinic in neurologic aspects of disease and clinical trials, new patients with neurologic issues or significant problems due to neurofibromas, are seen within one week of a referral by Dr. Acosta or Dr. Packer. The patients with neuro-oncologic issues are immediately triaged to Dr. Packer and are given immediate emergency appointments in one of Dr. Packer’s emergency slots (within 3 days of referral).

- b. Provide details of those specialists to whom (either within or outside our own clinic facility) your clinic refers NF patients for the following specialty care. **These should individuals familiar and experienced with consensus guidelines for care of individuals with NF** (Please provide information for PEDIATRIC CARE referrals in the first table and ADULT CARE in the second table).

PEDIATRIC CARE

SPECIALTY	DOCTOR	CLINIC ADDRESS	PHONE	EMAIL (if available)
Genetics	Kenneth Rosenbaum, MD/ Cynthia Tifft, MD,PhD	Children’s Nat’l. Medical Ctr Dept of Genetics & Metabolism 111 Michigan Avenue, NW Washington, DC	202-884-2187	
Neurology	Maria Acosta, MD Roger Packer, MD	Children’s Nat’l. Medical Ctr Dept of Neurology	202-884-5513/ 202-884-2120	

		111 Michigan Avenue, NW Washington, DC		
Orthopaedics	Laurel Blakemore, MD	Children's Nat'l. Medical Ctr Dept of Orthopaedics 111 Michigan Avenue, NW Washington, DC	202-884-2112	
Developmental Pediatrics/ Learning disabilities	Marla Shapiro, PhD Gerry Gioia, PhD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-5513	
Ophthalmology	Kelly Hutchenson, MD	Children's Nat'l. Medical Ctr Dept of Ophthalmology 111 Michigan Avenue, NW Washington, DC	202-884-3017	
Neurosurgery	Robert Keating, MD Derek Bruce, MD John Myseros, MD Amanda Yaun, MD	Children's Nat'l. Medical Ctr Dept of Neurosurgery 111 Michigan Avenue, NW Washington, DC	202-884-3020	
Plastic surgery	Michael Boyajian, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-2157	
Neurooncology	Roger Packer, MD Tobey MacDonald, MD	Children's Nat'l. Medical Ctr Dept of Neurology/ Hematology 111 Michigan Avenue, NW Washington, DC	202-884-2120/ 202-884-2800	
Medical Oncology/Radia tion Oncology	Tobey MacDonald, MD Brian Rood, MD Deborah Citrin, MD (NIH)	Children's Nat'l. Medical Ctr Dept of Hematol/Oncology 111 Michigan Avenue, NW Washington, DC	202-884-2800	
Endocrinology	Susan Nunez, MD	Children's Nat'l. Medical Ctr Dept of Endocrinology 111 Michigan Avenue, NW Washington, DC	202-884-2121	
Audiology/ENT	Sheela Stuart, PhD David Schessel, MD	Children's Nat'l. Medical Ctr Dept of Speech-Language Pathology/ENT 111 Michigan Avenue, NW Washington, DC	202-884-5600/ 202-884-2159	
Radiology/ Neuroradiology	Gilbert Vezina, MD	Children's Nat'l. Medical Ctr Dept of Neuroradiology 111 Michigan Avenue, NW Washington, DC	202-884-3651	
General Surgery/Surgic al Oncology	Anthony Sandler, MD	Children's Nat'l. Medical Ctr Dept of Pediatric Surgery 111 Michigan Avenue, NW Washington, DC	202-884-2151	
Dermatology	Rosalyn Epps, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-3026	

Cardiovascular Disease	Richard Jonas, MD	Children's Nat'l. Medical Ctr Dept of Cardiology 111 Michigan Avenue, NW Washington, DC	202-884-2811	
Oral and Maxillofacial Surgery	George Obeid, DDS	Children's Nat'l. Medical Ctr Dept of Dentistry 111 Michigan Avenue, NW Washington, DC	202-884-2160	
Behavioral Issues	Gerry Gioia, MD Sandra Cushner-Weinstein	Children's Nat'l. Medical Ctr Dept of Ped. Neuropsychology/Neurology 111 Michigan Avenue, NW Washington, DC	301-738-8936/ 202-884-5142	

ADULT CARE

SPECIALTY	DOCTOR	CLINIC ADDRESS	PHONE	EMAIL (if available)
Genetics	Kenneth Rosenbaum, MD	Children's Nat'l. Medical Ctr Dept of Genetics 111 Michigan Avenue, NW Washington, DC	202-884-2187	
Neurology	Maria Acosta, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-5513	
Orthopaedics	Laurel Blakemore, MD	Children's Nat'l. Medical Ctr Dept of Orthopaedics 111 Michigan Avenue, NW Washington, DC	202-884-2112	
Developmental pediatrics/ learning disabilities	Maria Acosta, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-5513	
Ophthalmology	Kelly Hutcheson, MD	Children's Nat'l. Medical Ctr Dept of Ophthalmology 111 Michigan Avenue, NW Washington, DC	202-884-3017	
Neurosurgery	Robert Keating, MD Amanda Yaun, MD	Children's Nat'l. Medical Ctr Dept of Neurosurgery 111 Michigan Avenue, NW Washington, DC	202-884-3020	
Plastic surgery	Ananth Murthy, MD	Children's Nat'l. Medical Ctr Dept of Plastic Surgery 111 Michigan Avenue, NW Washington, DC	202-884-4947	
Neurooncology	Roger Packer, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-2120	
Medical Oncology/Radiation Oncology	Tobey MacDonald, MD Roger Packer, MD	Children's Nat'l. Medical Ctr Dept of Hematol/Oncology 111 Michigan Avenue, NW Washington, DC	202-884-2800	

Endocrinology	Susan Nunez, MD	Children's Nat'l. Medical Ctr Dept of Endocrinology 111 Michigan Avenue, NW Washington, DC	202-884-2121	
Audiology/ENT	Sheela Stuart, PhD David Schessel, MD	Children's Nat'l. Medical Ctr Dept of Speech-Language Pathology/ENT 111 Michigan Avenue, NW Washington, DC	202-884-5600/ 202-884-2159	
Radiology/ Neuroradiology	Gilbert Vezina, MD	Children's Nat'l. Medical Ctr Dept of Neuroradiology 111 Michigan Avenue, NW Washington, DC	202-884-3651	
General Surgery/Surgical Oncology	Anthony Sandler	Children's Nat'l. Medical Ctr Dept of Surgery 111 Michigan Avenue, NW Washington, DC	202-884-2151	
Dermatology	Rosalind Epps, MD	Children's Nat'l. Medical Ctr Dept of Dermatology 111 Michigan Avenue, NW Washington, DC	202-884-3026	
Cardiovascular Disease	Richard Jonas, MD	Children's Nat'l. Medical Ctr Dept of Cardiology 111 Michigan Avenue, NW Washington, DC	202-884-2811	
Oral and Maxillofacial Surgery	George Obeid, DDS -	Children's Nat'l. Medical Ctr Dept of Dentistry 111 Michigan Avenue, NW Washington, DC	202-884-2160	
Behavioral Issues	Maria Acosta, MD	Children's Nat'l. Medical Ctr Dept of Neurology 111 Michigan Avenue, NW Washington, DC	202-884-5513	

5. NUMBER OF NF PATIENTS YOUR CLINIC SEES

- a. How many NF PATIENTS did you see in the past 12 months?
- b. How many of these were **NEW** patients to your clinic?

Insert numbers below

	NF1	NF2	SCHWANNOMATOSIS	OTHER
NUMBER OF PATIENTS SEEN IN PAST 12 MONTHS - 600 ??	580	20	?	
NUMBER OF <u>NEW</u> PATIENTS SEEN IN PAST 12 MONTHS - 120 ??	115	5	?	
TOTAL	705	25	?	

c. Overall what proportion of patients seen in the past year were (give finite numbers if these are available, or estimate percentage):

Under 18 ___ 18+ ____ (give numbers - if data available)

OR estimate

Under 18 80% 18+ 20%

6. TRANSITIONING PEDIATRIC TO ADULT NF CARE

How does your clinic facilitate continuity of care for patients transiting from pediatric to adult care?

The transition from pediatric to adult care is handled predominantly by the neurology department, as neurologists are boarded both in adult and pediatric neurology. In addition, Dr. David Schessel, an ENT surgeon who cares for both children at the Children's National Medical Center and adults at The George Washington University, is actively involved in the clinics. In addition, there is a formal proposal being reviewed by the "Adult Continuum Committee" of Children's National Medical Center to allow adults (those over 21 years of age) with specific NF1-related conditions to be hospitalized at CNMC.

Explain how continuity of care is accomplished. Describe those partnering clinics with which you coordinate services, and explain any limitations:

As outlined previously, the Children's National Medical Center has made a commitment to develop a care continuum from childhood to the adult years. The Children's National Medical Center and the Neurofibromatosis Program have also partnered with Georgetown University, through their chairman, Dr. Edward Heaton; one of their adult neurosurgeons, Dr. Jean; and, through a joint rehabilitation program with the National Rehabilitation Hospital. Dr. Sally Evans, head of Physical Medicine and Rehabilitation at the Children's National

Medical Center, who is also Director of the inpatient and outpatient pediatric rehabilitation program at the National Rehabilitation Hospital, will provide continuity of rehabilitative care.

7. INTERNAL CONFERENCES

Provide details on internal conferences in your institution which are related to NF patient care in your clinic (e.g. NF Clinic case management conference, etc.)

The Neurofibromatosis has two conferences which meet on a weekly basis to review neurofibromatosis patients. The first is a long-standing conference, coordinated by Drs. Tiff and Rosenbaum, in collaboration with Dr. Gilbert Vezina, head of Neuroradiology, to review all NF1 cases with neuroradiographic features.

The second is a weekly Neuroradiology and Neurology conference, coordinated by Dr. Packer, to review all children with neural tumors, including plexiform neurofibromas and intracranial tumors. In this conference, all patients are reviewed with Drs. Packer, Vezina, and MacDonald.

In addition, Dr. Acosta coordinates a monthly research meeting of the Neurofibromatosis Program to review the clinical research activities of the program.

8. CLINICAL TRIALS

Our clinic is willing and able to provide our NF patients with information on, and to facilitate their participation in, clinical trials for which NF patients are eligible (check box)

: Yes No

If 'no', briefly describe why.

Do you currently refer patients to clinical trials?

:Yes No

If 'yes', provide details of current clinical trial protocols in which you currently or have had patients involved in the past 5 years.

There are multiple clinical trial protocols underway at Children's National Medical Center, as outlined previously, and described previously. In the past 5 years, these include:

1. Phase 1 Study of Pirfenidone for children with neurofibromatosis and progressive plexiform neurofibromas.
2. Phase 2 Study of Pirfenidone for children with neurofibromatosis and progressive plexiform neurofibromas.
3. Phase 1 Study of Interferon (peg Intron) for children with neurofibromatosis and progressive plexiform neurofibromas.
4. Phase 2 Study of Interferon (peg Intron) for children with neurofibromatosis and progressive plexiform neurofibromas.
5. Phase 1 Study of Lovastatin for children with neurofibromatosis and neurocognitive disabilities.
6. Phase 2 Study of the utility of fMRI in the assessment of children with plexiform neurofibromas and attention deficit disorder treated with stimulant medication.
7. Longitudinal neurocognitive study
8. Neurobiology of executive function in adolescents and young adults with NF1.
9. Phase 1 study for evaluation of Lovastatin for treatment of neurocognitive deficits in children with NF1.

9. PATIENT REGISTRY

Do you currently have an NF specific patient database/registry?

Yes No

If 'yes', please describe.

We have a comprehensive data base compiling the demographic and clinical aspects of all children and adults with neurofibromatosis seen at the institution. The database, which is IRB approved, is actively following over 750 children and adults with NF1.

Clinical parameters which are being followed include the neurocognitive status of patients, their degree of developmental disability, the presence of neurofibromas, the presence of vascular anomalies, the presence of brain tumors and their status, and any other significant medical conditions that children have. This is a dynamic database which is constantly being updated.

Would you be willing to transfer this data to a centralized CTF NF Database?

: Yes ? No

If 'no', explain your limitations.

This would have to be done only after seeing the design of this CTF NF database and ensuring patient confidentiality.

9. PUBLICATIONS and RESEARCH (IF APPLICABLE)

a. Please list any relevant NF publications from your clinic in the past 5 years. Include Journal, Citation and Title.

Ruggieri M and Packer RJ: Why do benign astrocytomas become malignant in NF1. *Neurology* 56:827-829, 2001.

Packer RJ, Gutmann DH, Rubenstein A, Viskochil D, Zimmerman RA, Vezina G, Small J and Korf B. Plexiform neurofibromas in NF1: Towards biologic-based therapy. *Neurology*, 58:1461-1470, 2002.

Rosser T and Packer RJ. Intracranial neoplasms in children with neurofibromatosis type 1. *Journal of Child Neurology* 17:630-637, 2002.

Packer RJ and Rosser T. Therapy for plexiform neurofibromas in children with NF1: An overview. *Journal of Child Neurology* 17:638-641, 2002.

Rosser T and Packer RJ. Neurofibromas in children with NF1. *Journal of Child Neurology*, 17: 585-591, 2002.

Dombi E, Solomon J, Gillespe AJ, Fox E, Balis FM, Petronas N, Korf B, Babovic-Vuksanovic D, Packer RJ, Belasco J, et al: NF1 plexiform neurofibroma growth rate by volumetric MRI: Relationship to age and body weight, *Neurology* 68:643-647, 2007.

Babovic-Vuksanovic D, Packer RJ, et al: Phase I trial of pirfenidone in children with neurofibromatosis type 1 and plexiform neurofibromas. *J Ped Neurol* 36:293-300, 2007.

Abstracts

Rosser T, Dubowsky E, Vezina G, Cooney K, Packer RJ and Tiftt C. Hippocampal abnormalities in a population of children with neurofibromatosis type 1. *Ann Neurol* 52(S1): 137, 2002.

Rosser T, Cooney K, Packer R, Tiftt C and Rosenbaum K. spectrum of cerebrovascular disease in a population of children with neurofibromatosis type 1. *Ann Neurol* 54:S139, 2003.

Acosta MT, Packer RJ, Williams L, Rosser T, Vezina G, Tiffet C and Rosenbaum K: Children with neurofibromatosis type 1 (NF1) non-visual pathway brain tumors. *Annals of Neurol* 58(S82-83), 2005.

Ater J, Mazewski C, Roberts W, Sposto R, Zhou T, Frey D, Jakacki R, Kadota R, Lazarus K, Packer RJ, et al: Phase e randomized study of two chemotherapy regimens for treatment of progressive low-grade gliomas in young children: Preliminary report from the Children's Oncology Group protocol A9952. *Neuro-Oncol* 9:204, 2007.

b. Please provide information on NF-related research ongoing in your clinic or performed by personnel affiliated with your clinic.

As outlined previously, there are multiple areas of NF research ongoing at the Children's national Medical Center. There are active clinical trials for children with plexiform neurofibromas, optic nerve glioma, and interventions for the neurocognitive aspects of neurofibromatosis type 1. The Children's National Medical Center has been chosen as being one of the institutions participating in the new Department of Defense funded NF funded Clinical Trials Consortium, which will ensure that continuation of this clinical activity. There are clinical studies also ongoing evaluating the utility of new imaging techniques, such as functional MRI, and evaluating the efficacy of agents being used for patients with neurofibromatosis type 1 and cognitive disabilities.

In collaboration with Dr. Kathryn North at the University of Sydney, there are ongoing studies defining the cognitive phenotype of children with neurofibromatosis and also a longitudinal study determining how this phenotype changes over time.

Through the laboratory of Dr. Tobey MacDonald, there are ongoing research studies defining the molecular makeup of plexiform neurofibromas, visual pathway gliomas, and work to define innovative molecular targets.

10. PATIENT SUPPORT

Do you have an NF patient support group that meets in association with your NF Clinic?

If 'yes' provide details.

If 'no', are you interested in starting such a group?

What resources would help you to do this?

The Children's National Medical Center has a social worker, Sandra Cushner-Weinstein, who is assigned to the Neurofibromatosis Clinic, working with Deborah Copenheaver, the genetics counselor who is also assigned to the program, to provide patient support.

A parents group is currently being formed to start actively working in the fall. Dr. Acosta and our social worker, Sandra Cushner-Weinstein, are coordinating activities to provide communication and support to families and

parents. Several parents are currently an active part of this process. The goal is to provide support, information and intervention options in different areas.

In addition, the Children's National Medical Center has, for the last five years, coordinated a highly successful camp for children with neurofibromatosis type 1. This camp, which is overnight camp that meets for one week out of the year, draws children from all around the region, and all around the United States. It is one of the few camps of its type in the world. It is coordinated by Sandra Cushner Weinstein. Deborah Copenheaver, NF clinic coordinator. Throughout the year clinic patients from 8-16 years of age are provided information and encouraged to attend camp. Scholarships are available for families who cannot afford the cost of camp. Every year, 40 to 60 campers participate in the program and younger patients and their families are encouraged to participate in a "come and see" day at camp. NF children ages 16-18 serve as "counselors in training", and young adult NF patients serve as camp counselors. There has been research ongoing at this camp to determine how the camp impacts the quality of life for both the campers and the counselors. Each year campers meet in small gender and age-specific groups with participating physicians to discuss NF and their own personal experiences of living with the disorder.

11. OTHER INFORMATION

Please provide any additional information that is pertinent to your request to join the CTF NF Clinic Network.

None

II NF1 related clinical and scientific publications (from CV)

See Section 3a-ii, 22 publications.

Key staff in the NF Clinic Facility

See Section 3c and Section 4b.