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Award Number: DAMD17-01-1-0710

TITLE: Neurofibromatosis Type 2 (NF2) Natural History Consortium

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REPORT DATE: January 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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20050630 096

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE January 2005		3. REPORT TYPE AND DATES COVERED Annual (1 Jan 2004 - 31 Dec 2004)
4. TITLE AND SUBTITLE Neurofibromatosis Type 2 (NF2) Natural History Consortium			5. FUNDING NUMBERS DAMD17-01-1-0710	
6. AUTHOR(S) William H. Slattery, III, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) House Ear Institute Los Angeles, California 90057 E-Mail: wslattery@hei.org			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) Neurofibromatosis 2 (NF2) is an autosomal disorder characterized by the development of multiple tumors within the brain and spinal canal. The purpose of the study is to define the growth rates and clinical course of tumors associated with NF2-affected individuals. An international consortium of clinical centers and expertise in NF2 will be developed, further expanding the infrastructure developed in the "Natural History of Vestibular Schwannomas in NF2" US Army grant. We will standardize the volumetric analysis of intracranial and spinal tumors, assess the patients' audiological, neurological, and ophthalmological functioning, and analyze molecular and clinical features of the disease over the course of 4 years. Ninety-six subjects are enrolled in the study. Of the 96 subjects enrolled 12 have withdrawn. Of the 86 subjects who have completed and have had the scans sent to WorldCare for analyzing for Year 1 84 (97%) cranial exams and 83 (97%) spinal exams have been sent. Of the 57 subjects who have completed the Year 2 exams, 49 (86%) cranial exams and 46 (81%) spinal exams have been sent. Of the 27 subjects who have completed the Year 3 exams, 20 (74%) cranial exams and 17 (63%) spinal exams have been sent. Of the 86 subjects who have completed the Year 1 exams, 79 (92%) audiology exams, 83 (97%) neurology exam, 84 (98%) ophthalmology exams, 81 (94%) SF-36 questionnaire and 82 (95%) Physical Functioning Interview have been received. Of the 57 subjects who have completed the Year 2 exams, 48 (84%) audiology exams, 52 (91%) neurology exam, 42 (74%) ophthalmology exams, 50 (88%) SF-36 questionnaire and 48 (84%) Physical Functioning Interview have been received. Of the 27 subjects who have completed the Year 3 exams, 13 (48%) audiology exams, 23 (85%) neurology exam, 13 (48%) ophthalmology exams, 23 (85%) SF-36 questionnaire and 23 (85%) Physical Functioning Interview have been received.				
14. SUBJECT TERMS No subject terms provided.				15. NUMBER OF PAGES 11
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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Introduction

Neurofibromatosis 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All subjects develop bilateral vestibular schwannomas that lead to deafness and death if untreated. Subjects also tend to develop multiple meningiomas and spinal tumors, which result in significant motor and sensory deficits if left untreated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to these tumors, and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of the natural history of these tumors, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study is to define the growth rates and clinical course of tumors associated with NF2. We seek to accomplish this goal through the following steps:

1. Develop an international consortium of clinical centers with expertise in NF2, further expanding the infrastructure developed in the Natural History of Vestibular Schwannomas in NF2 US Army grant. All subjects will be evaluated at local centers with full neurological, ophthalmological, radiographical, and audiometric evaluations and the data will be sent to a centralized center for analysis.
2. Develop standardized volumetric analysis of intracranial and spinal tumors. Currently, we have standardized the volumetric analysis of tumors on the hearing and balance nerves. We will attempt to standardize the measurement of the other tumors associated with NF2.
3. Form an infrastructure for use in future clinical trials. All NF2 subjects identified at clinical centers will be categorized as potential subjects for future clinical trials.
4. Examination of molecular and clinical features which may predict tumor behavior.

This study will lead to a better understanding of the natural history and clinical course of tumors associated with NF2. The knowledge will allow better recommendations regarding current treatment options. An understanding of the natural history is also fundamental to the determination of efficacy of future medical or surgical therapies. Finally, the framework of clinical centers, data management, and scientific expertise established during this project will form the core for future studies investigating other aspects of the natural history of NF2 and for therapeutic treatment trials in NF2.

Body**STATEMENT OF WORK**
NF2 Natural History Consortium**Task 1.** *Standardize Clinical Data Collection for NF2 Subjects***a. Finalize proposed case record forms. (month 1): Completed**

All case record forms were created, finalized, and sent to all participating investigational sites. A Manual of Procedures, with the case record forms, has been sent to all investigational sites. The Manual of Procedures details the exact protocol to be followed to obtain the specified measurements in tumor size, hearing, eye evaluation, and quality of life and physical functioning.

b. Creation of Comprehensive Care database and tracking system (months 1-3): Completed

A coordinated system for collecting and transmitting study data was established.

As detailed in the Manual of Procedures, House Ear Institute (HEI) serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators send all original data to HEI. A Central Tracking System was established at HEI to track each subject and assure the consistent inflow of data from each site.

Files for each subject have been created and kept in a locked cabinet. A computerized database has been created to house the study data. As forms are sent to HEI, the data are entered into the database.

c. Assist in translation of quality of life questionnaire and Comprehensive Care case record forms into Japanese and German (1-4): Completed

At the outset of the study, Japan was included as one of the investigational sites of the NF2 Natural History Consortium. However, since that time, Japan has withdrawn from participation and a new investigational site has been added in France. Questionnaires and case record forms were sent to both the France and Germany investigational sites.

d. Modify previous NF2 Natural History Consortium methods for data transfer to comply with extra requirements required for Comprehensive Care database (months 1-3): Completed.

Study methods have been created to ensure transmittal of data to HEI. Clinical Coordinators from each study site are in charge of contacting subjects, setting up appointments or receiving scheduling information from subjects, assisting with insurance authorizations, communicating facility name and contact information to the Project Manager at HEI and to Meera Gupta, WorldCare. The Clinical Coordinator also attends the subject's exams, ensures completeness of the exams, and fills out the MRI Examination Outcome form and Data Transmission CRFs.

The MRI Facility performs the cranial and spinal MRI exams according to protocol, fills out the MRI Data Acquisition CRFs and gives them to the Clinical Coordinator, and invoices the investigational site for the stipend for completing the CRF.

WorldCare received notification of subject information, exam date, and facility from the Clinical Coordinator. WorldCare ensures that test data are sent from the MRI facility to WorldCare and are acceptable.

Original, completed CRFs are sent to HEI. Queries regarding incomplete or inconsistent information on CRFs are answered by the Clinical Coordinator and WorldCare.

HEI tracks and monitors data flow, logs, dates and notes facilities, notes if data are received by WorldCare, follows up with the status of data.

Task 2. Standardize Volumetric Analysis of Intracranial Tumors and Spinal Tumors.

a. Development of standard operating procedure for digital analysis of MRIs (months 1-3): Completed

A Manual of Procedures is complete for the Investigators, Clinical Coordinators and WorldCare. The manual contains information for the data flow, acquisition protocol, and data transfer of images. WorldCare guidelines were merged with the HEI Manual of Procedures and were distributed to the Clinical Coordinators and Investigators at each investigational site.

b. Preparation of facilities at WorldCare, Inc. (month 1): Completed

A private suite for the NF2 Natural History Consortium has been prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data have been used for the collection and analysis of subject data. Also, the filing system, logbooks, and subject database are established to accept and track the workflow of subject data. An additional worksite has been set up next to the initial worksite to facilitate the radiologist reading the scans. The additional worksite has resulted in saving considerable time when transferring between images.

c. Perform test retest data of other cranial tumors and spinal tumors to determine amount of change required to be considered a statistically significant difference (months 1-3): In Progress

Test/retest data has been collected for other cranial tumors, specifically meningiomas. Acquisition of test/retest data is complete. Analysis of test/retest data for spinal tumors is in process.

d. Perform qualitative and quantitative analysis of MRIs (months 4-33): In Progress

The radiologist in charge of reading the MRIs indicates whether the MRI scans and corresponding data are acceptable to include in data analysis. Case record forms are checked to ensure accuracy of the data. Data cleaning is an ongoing process as data is received at HEI, entailing the checking of irregular data values, data editing, corrections and updating.

e. Collection of yearly MRI data (months 1-35): In Progress

Of the 86 subjects who have completed and have had the scans sent to WorldCare for analyzing for Year 1 84 (97%) cranial exams and 83 (97%) spinal exams have been received. Of the 57 subjects who have completed the Year 2 exams, 49 (86%) cranial exams and 46 (81%) spinal exams have been sent. Of the 27 subjects who have completed the Year 3 exams, 20 (74%) cranial exams and 17 (63%) spinal exams have been sent. WorldCare has analyzed, and sent HEI 60 (71%) Year 1 Cranial MRI CRFs, 33 (67%) of the Year 2 Cranial MRI CRFs, 11 (55%) of the Year 3 Cranial MRI CRFs. WorldCare has analyzed, and sent HEI 55 (66%) of the Year 1 Spinal MRI CRFs, 27 (59%) of the Year 2 Spinal MRI CRFs and 8 (47%) of the Year 3 Spinal MRI CRFs.

Task 3. Prepare International Consortium of Clinical NF2 Centers.**a. Modify previous NF2 natural history database for additional requirements of this study: Completed**

The NF2 Natural History Database has been modified to include data for visual tests, quality of life and physical functioning questionnaires as well as modifications to CRFs for subject medical history, MRI, audiology, neurological, and molecular biology exams.

b. Obtain local IRB approval (months 1-2): In Progress

Eight of the nine study sites have received local IRB approval. New York University is in the process of receiving local IRB approval.

c. Obtain Army IRB approval and single project assurance approval (months 2-18): In Progress

Of the nine sites that are participating in the study, all but one domestic site and one foreign site have received Army IRB approval and project assurance

SITE	APPROVAL
House Ear Institute	11/01/01
University of Texas	03/25/02
Massachusetts General Hospital	09/23/02
Royal Victorian Eye and Ear Hospital	10/10/02
Ohio State University	10/20/02
Universitätsklinikum Hamburg-Eppendorf	11/03/02
Hopital Beaujon	06/21/04

The two sites that are in the process of receiving approval are St. Mary's Hospital in England and New York University in New York.

d. Train centers on study protocol (spine, ophthalmology, quality of life, comprehensive care) (months 3-6): Completed

A meeting was held for all Clinical Coordinators and Co-Principal Investigators to review the study protocol. Study protocol and Manual of Procedures were distributed to each Co-Principal Investigator and Clinical Coordinator at each site. HEI maintains ongoing telephone discussions with the Clinical Coordinators to facilitate the study and the timely collection of data.

e. Train centers in data transfer to Data Management Center (months 3-6): Completed

All Clinical Centers have been given a Manual of Procedures informing them of the protocol for data transfer to the Data Management Center at HEI. Clinical Coordinators are responsible for sending all original, completed CRFs for audiology, neurological, and ophthalmology exams and medical history, SF-36 quality of life and physical functioning interview to the Project Manager at HEI. Original, completed MRI CRFs are sent to HEI by WorldCare.

Task 4. Subject Recruitment and Data Collection (month 3-30)**a. Enroll previous Natural History of Vestibular Schwannoma in NF2 subjects in current study: Completed**

Some subjects elected not to enroll in the new study and some subjects were dropped by the local centers as they were non-compliant with the first study. The following subjects have been enrolled

Subject Collection Center	Location	Subjects Enrolled From Previous Study	New Subjects Enrolled	Total Subjects Enrolled
House Ear Institute	Los Angeles, CA	21	27	48
Massachusetts General Hospital	Boston, MA	9	4	13
St. Mary's Hospital	Manchester, UK	NA	NA	NA
Universitätsklinikum Hamburg-Eppendorf	Hamburg, Germany	11	0	11
New York University	New York, NY	NA	NA	NA
Royal Victorian Eye and Ear Hospital	Melbourne, Australia	4	1	5
Ohio State University Hospital	Columbus, OH	1	0	1
Hopital Beaujon	Paris, France	0	16	16
University of Texas, Houston	Houston, TX	0	2	2
Total Subjects Enrolled		46	50	96

NA – Sites that have not yet received IRB approval.

b. Individual centers identify potential subjects to replace subjects who dropped out: Completed.

Clinical Coordinators at each investigational site screened their subject population and identified potential subjects for the NF2 Natural History Consortium study. Enrollment closed December 31, 2004.

c. New subjects will complete baseline audiometric, MRI, neurological, ophthalmologic exams, SF-36 and physical functioning questionnaires and provide blood and tumor samples: In Progress

Clinical Coordinators are responsible for ensuring subjects yearly exams. Although a subject may have completed an exam, it is not considered complete until the original copy is received at HEI and entered into the database. Of the 86 subjects who have completed the Year 1 exams, 79 (92%) audiology exams, 83 (97%) neurology exam, 84 (98%) ophthalmology exams, 81 (94%) SF-36 questionnaire and 82 (95%) Physical Functioning Interview. Of the 57 subjects who have completed the Year 2 exams, 48 (84%) audiology exams, 52 (91%) neurology exam, 42 (74%) ophthalmology exams, 50 (88%) SF-36 questionnaire and 48 (84%) Physical Functioning Interview. Of the 27 subjects who have completed the Year 3 exams, 13 (48%) audiology exams, 23 (85%) neurology exam, 13 (48%) ophthalmology exams, 23 (85%) SF-36 questionnaire and 23 (85%) Physical Functioning Interview.

A review of the Cranial and Spinal CRFs can be found under Task 2 E. Forty-one (89%) of the 46 subjects enrolled from the previous study have provided blood and tumor samples and analysis has been completed. Blood and tumor samples from 21 (43%) new subjects have been collected. Of these 21 samples, 16 have been analyzed and 5 are in the process of being analyzed.

d. All enrolled subjects will be seen for yearly examinations: In Progress

HEI is in contact with the Clinical Coordinator from each site, providing information on upcoming follow-up exams to be scheduled.

*Task 5. Interim Analysis (months 12-18)***a. Interim statistical analysis and data obtained from initial audiometric, MRI studies, and clinical evaluations will be performed: In Progress**

Preliminary data analysis has begun. Currently, we are in the process of cleaning the data. Each subject is reviewed individually to clearly identify the start point and endpoint of any analysis. Each tumor (either spinal, vestibular schwannoma (VS) or meningioma) is the unit of analysis with the start point being the date of each Year 1 exam and the endpoint being either the date of the first VS treatment or date of last follow-up if no treatment was performed.

*Task 6. Final Analysis and Report Writing (months 30-36)***a. Final analysis of data will be performed: Pending**

Final analysis of the data will be performed when all CRFs have been received and all data have been entered into the database.

b. Final report and initial manuscripts will be prepared: Pending

After all data has been entered into the database and all CRFs logged into our tracking system, a final report will be prepared, detailing the completion of all goals established at the outset of the study. Manuscripts on data obtained from the study will cover MRI exam methodology, vestibular schwannoma growth, growth of other NF2 tumors, audiological changes over time, neurological changes over time, quality of life in NF2 subjects and visual characteristics of subjects.

Key Research Accomplishments

- ❖ Development of an international consortium of clinical centers with expertise in NF2.
- ❖ Establishment of standardized study protocol for multi-institutional, multi-national natural history study.
- ❖ Development of NF2 specific database which includes clinical, radiographical, audiometrical, ophthalmologic, quality of life, and molecular biology/genetic information.
- ❖ Development of standard operating procedure for digital analysis of MRIs utilizing information from a variety of MRI machines from different manufacturers.

Reportable Outcomes

CONFERENCES

- ✓ Steering Committee Meeting, June 4, 2002:
Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators
- ✓ Steering Committee Meeting, June 1, 2003
Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators
- ✓ Steering Committee Meeting, June 4, 2004:
Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators

PRESENTATIONS

- ✓ American Academy of Otolaryngology Head & Neck Surgery Meeting, September 22-25, 2002
Volumetric Analysis of Vestibular Schwannomas in NF2.
- ✓ The Auditory Brainstem Implant and Neurofibromatosis Type 2. AAO-NHSF Annual Meeting & OTO EXPO, New York, NY. September 22, 2004 (course)
- ✓ ABR Change Over Time in Neurofibromatosis Type 2. AAO-NHSF Annual Meeting & OTO EXPO, New York, NY. September 22, 2004

PUBLICATIONS

- ✓ Hearing Changes After Diagnosis in Neurofibromatosis Type 2. Otol Neurotol. 2004 Mar; 25(2): 150-4.
- ✓ Magnetic resonance Imaging Scanner Reliability for Measuring Changes in Vestibular Schwannoma Size. Otol Neurotol. 2003 Jul; 24(4):666-70; discussion 670-1.
- ✓ Vestibular Schwannoma Growth Rates in Neurofibromatosis Type 2 Natural History Consortium Subjects. Otol Neurotol. 2004 Sept; 25(5):811-7.

Conclusions

The infrastructure necessary for this project to be successful has been assembled. A consortium of nine international sites with clinical expertise in NF2 has been established. All sites have received copies of standardized protocols for all data to be collected and a centralized database to store all information has been created. Subject enrollment had been difficult due to the delay in achieving Army approval of the informed consent forms for each institution. Much effort was given to ensuring that the MRI facilities used by study participants were compatible with WorldCare's systems.

References

None

Appendices

None