AWARD NUMBER: W81XWH-19-1-0177
NF180027

TITLE: Using Administrative Health Data to Identify Patients with NF1 in Ontario, Canada, and to Assess Prevalence, Mortality, and Health Care Utilization Patterns

PRINCIPAL INVESTIGATOR: Carolina Barnett-Tapia

CONTRACTING ORGANIZATION: University Health Network

REPORT DATE: July 2021

TYPE OF REPORT: Annual Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
July 2021	Annual	June 15 2020 - June 14 2021

4. TITLE AND SUBTITLE

Using Administrative Health Data to Identify Patients with NF1 in Ontario, Canada, and to Assess Prevalence, Mortality, and Health Care Utilization

5a. CONTRACT NUMBER
W81XWH-19-1-0177

5b. GRANT NUMBER
NF180027

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Barnett-Tapia, Carolina

E-Mail: c.barnetttapia@utoronto.ca

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University Health Network
200 Elizabeth St, Toronto, ON
M5G 2C4

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
We are using electronic medical records and administrative database to study health care use of people living with NF1 in Ontario, Canada. Using electronic medical record database (EMRPC, previously called EMRALD), we estimated a minimum prevalence of NF1 between 1:2532 to 1:3851.

A previously developed billing algorithm has poor performance and won't allow proper assessment of health utilization patterns. Therefore, we have moved forward with a mitigation strategy, whereby we have created a registry of people with confirmed NF1 followed at tertiary centers This registry will be liked to administrative database, and matched to healthy controls to compare mortally and use of health care.

We are also studying mortality and healthcare use in patients identified through electronic medical records, using EMRPC and UTOPIAN databases

15. SUBJECT TERMS
NF1, prevalence, billing codes, EMR

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	19	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

INTRODUCTION:

The objective of this study is to develop an algorithm to identify people with NF1 living in the province of Ontario, Canada (population ~ 14 million), through administrative health databases. This algorithm will be used to study incidence, prevalence, NF1-related mortality and health care utilization patterns of patients with NF1. The specific aims for this project are outlined below.

Specific Aim 1: To develop and validate an algorithm to identify patients with NF1 in the province of Ontario.

Specific Aim 2: To estimate the incidence, prevalence and mortality of patients with NF1 in Ontario, Canada. We hypothesize that we can obtain reliable estimates of incidence and prevalence of NF1 in the province which we expect to be within previously published ranges. We also plan to calculate mortality ratios stratified by age and hypothesize that individuals with NF1 have higher mortality ratios compared to the general population.

Specific Aim 3: To study the health-utilization patterns of NF1 patients which includes the number of primary care, specialist and emergency visits, outpatient surgeries, hospital admissions, mental health care and pain treatments Compared to a matched cohort of healthy controls, we hypothesize that patients with NF1 will have, on average, significantly more visits at all levels of health care.

For the report period, our statement of work was focused in completing Aim 1.

1. KEYWORDS:

NF1, neurofibromatosis 1, electronic medical record, EMR, administrative health databases, algorithm, prevalence, health utilization.

2. ACCOMPLISHMENTS:

What were the major goals of the project?

Mayor goals/tasks for reporting period (as stated in SOW)

1. **Specific Aim 1, Major task 4:** Manuscript preparation and publication: 80% completed. Final draft being revised by authors for submission
2. **Specific Aim 2, Major task 1 :** Create dataset and obtain data: Completed 75%. Regulatory approvals ay UHN obtained October 2020; at the Hospital for Sick Children in May 2021. The, datasets compiled in each center. Pending data transfer to ICES and creating matched cohort.
3. **Specific Aim 2, Major task 2:** Analyze data for incidence, prevalence, mortality: 50% completed. Prevalence estimated from EMRALD data, will update in UTOPIAN. Mortality rations to be assessed form EMRALD and registry data

What was accomplished under these goals?

Based on our SOW, the second year of the grant was focused on using the billing algorithm to identify people with NF1 living in Ontario, Canada to study incidence, prevalence and mortality. As stated in our annual report for the first year, the billing algorithm had poor performance, therefore we are using our mitigation strategies to accomplished Aims 2 and 3. In our proposal we had 2 mitigation strategies and we are using both: using electronic medical records data to assess health utilization, and also creating a registry of individuals with NF1 from tertiary care and linking it to the administrative databases at ICES.

We were able to estimate prevalence form the electronic medical records database, and we estimated a minimum prevalence between 1 in 2,800 and 1 in 3,800; within published rates. A new electronic medical record database is now available (UTOPIAN), with coverage of ~600,000 individuals; this is also which is also linked to ICES. We will validate our EMR algorithm in this database and we will also obtain an estimate of prevalence of confirmed NF1 cases within this database. UTOPIAN database is managed through the University of Toronto and we have obtained REB approval to use this deidentified data as part of our mitigation strategy.

During the past year, we have been developing a registry of individuals with NF1 treated at the main 2 academic centres with specialised NF1 care in Ontario: the University Health Network and the Hospital for Sick Children. We will link this registry to ICES databases, to study mortality rates and compare them to matched controls (Aim 2). We will use the same cohort to study health utilization patterns (Aim 3). So, while we have been delayed due to COVID-19 restrictions, our cohort will allow us to study Aims 2 and 3.

We have obtained regulatory approvals at the University Health Network and The Hospital for Sick Children to transfer the health card numbers of people with confirmed NF1 treated at these centres over the years. We have identified ~800 individuals at UHN and ~ 1000 at Sick children. We expect some overlap (i.e. patients who graduated from pediatric care and are now followed at UHN) and these duplicated records will be deleted at ICES, since patients have a unique healthcare number. We expect to have ~1,500 unique records of people with NF1 to link to admin databases.

We are also obtaining regulatory approval from ICES to study mortality and Health utilization patterns form the original EMR algorithm database. Our goal is to compare the health utilization patterns between the different data sources, so that our findings are more generalizable. For example, people identified from electronic medical records database are not all followed at the tertiary centres, so may reflect a different spectrum of disease (i.e. people eat academic centres having more severe disease)

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

We presented a poster at the Children Tumor Foundation (CTF) meeting in 2021.

What do you plan to do during the next reporting period to accomplish the goals?

i. We will compare study mortality and health utilization patterns within the EMRALD cohort, comparing NF1 individuals to matched controls.

ii. We will compare mortality and health utilization patterns between the registry patients and the general population.

iii. We will compare billing code patterns between the NF1 patients identified through UTOPIAN and the patients form EMRALD

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

i. We have obtained approvals to develop a large registry of fully linked outcomes for people with confirmed NF1.

ii. We have secured access to a new EMR database to validate our EMR algorithm, which will add generalizability

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

We have already validated a simple EMR search that may be used in any healthcare setting that uses electronic medical records, to identify individuals with NF1. We will do external validation, which can lead to further administrative data studies in NF1, and can help studies in other health care systems.

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

As described above, our SOW has not changed, but we had to change our approach by using registry data and EMR data.

Actual or anticipated problems or delays and actions or plans to resolve them

As expected, we had many delays over the past year, as ICES has prioritized COVID-related projects. However, we have almost completed all administrative approvals and we will be able to create the matched cohort within the next months. Once this is completed, extraction of administrative data for analyses is relative fast and we will be able to obtain outcome data for Aims 2 and 3.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

Significant changes in use or care of human subjects

We have obtained approvals to link registry data for tertiary care to ICES data. All the analyses are the same, and all data are deidentified.

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Carolina Barnett Tapia, Elisa Candido, Branson Chen, Patricia Parkin, Priscila Pequeno, Karen Tu. Development of algorithms to identify individuals with Neurofibromatosis Type 1 within administrative data and electronic medical records. CTF Meeting, June 2021

-

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

EMR search strategy to identify NF1 cases. We will disseminate this through a publication.

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Carolina Barnett-Tapia*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-5546-0221
Nearest person month worked:	3.6
Contribution to Project:	*Dr. Barnett-Tapia has coordinated this project. She performed final chart review to classify records as definitive or possible NF1. She reviewed all billing codes from cases to develop the algorithms*
Funding Support:	

Name:	*Elisa Candido*
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	*Ms. Candido coordinated the ICES personnel, directed the algorithm development, and helped draft mitigation strategies for Aims 2 and 3*
Funding Support:	NA

Name:	Karen Tu
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	ORCID ID: 0000-0003-0883-4934
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Tu provided expertise in developing search strategy within EMRALD and developing billing algorithms. She has provided access to UTOPIAN for external validation of EMR algorithm*
Funding Support:	

Name:	*Patricia Parkin*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.0
Contribution to Project:	*Dr. Parkin has provided clinical expertise to determine billing codes to use in algorithms; she also has helped with registry of patients followed at the Hospital for Sick Children since the 1990s.*
Funding Support:	

Name:	*Branson Chen*
Project Role:	Health Information Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Mr. Chen conducted the search within EMRALD, analyzed abstractor reliability, and developed EMR algorithm*
Funding Support:	

Name:	*Priscila Pequeno*
Project Role:	Senior Research Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Ms. Pequeno developed and tested all the billing algorithms*
Funding Support:	

Name:	Meg Mendoza
Project Role:	Research Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	*Mr.* Mendoza prepared UHN REB application for linkage to ICES data and coordinated with HSC

Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

1. **Organization Name:** Institute for Clinical Evaluative Science (ICES)
2. **Location of Organization:** *Toronto, Canada*
3. **Partner's contribution to the projec**t: Collaboration

The ICES hosts all health administrative data for the province of Ontario, and we contracted their services for this study.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *NA*

QUAD CHARTS: *NA*

9. APPENDICES:

1) CTF Abstract
2) CTF Poster
3) UHN REB approval for linkage
4) Sick Kids REB approval for linkage
5) UTOPIAN approval

Development of algorithms to identify individuals with Neurofibromatosis type 1 within administrative data and electronic medical records

Authors: Carolina Barnett[1], Elisa Candido[2], Branson Chen[2], Priscilla Pequeno[2], Patricia Parkin[3], Karen Tu[4].

1. Elisabeth Raab Neurofibromatosis Clinic, University Health Network
2. Institute for Clinical Evaluative science
3. Hospital for Sick Children
4. Department of Family Medicine, University of Toronto

Funding: US Department of Defense

Background: There is limited population-based data in Neurofibromatosis 1 (NF1). Accurate case detection in administrative and medical records can fill this gap.

Objectives: To develop and validate algorithms using health administrative data and electronic medical records (EMR) to identify individuals with NF1 in Ontario, Canada.

Methods: We identified individuals with NF1 using the Electronic Medical Records Primary Care Database. We conducted an electronic free-text search of 15 commonly-used terms related to NF1 (e.g. neurofibroma, NF1). Records were reviewed by two trained abstractors. An investigator with clinical NF1 expertise reviewed all records initially classified as confirmed and probable, and performed final NF1 case allocation. Patients were classified as confirmed NF1 if there was a diagnosis recorded in the chart, meeting NIH criteria. Records were classified as probable if 1) NF1 was recorded in the history, but no clinical information to support the diagnosis; 2) patients had one criterion for diagnosis (e.g. child of confirmed case) but no clinical data to confirm or rule out the diagnosis. Records with no NF1 terms were assumed to not have NF1.

To identify confirmed NF1 cases, we tested different combinations of outpatient and inpatient diagnostic billing codes. We also tested a free text search algorithm in the cumulative patient profile (CPP) of the EMR to identify confirmed NF1 cases within the EMR.

Results: Of 273,440 eligible records, 2,058 had one or more NF1 terms. Records with ”NF”, “café-au-lait”, or “Sheath tumour” as the only NF1 term, were not NF1. Using these terms in combination with another NF1 term resulted in 837 records: 37 with probable and 71 with confirmed NF1. The population prevalence ranged from 1 in 3851 (including confirmed NF1) to 1 in 2532 (including probable and confirmed NF1). The diagnostic properties of the EMR algorithm were: sensitivity 85% (CI:74-92%), specificity 100% (CI:100-100%), positive predictive value (PPV) 80% (CI:69-88%), negative predictive value 100% (CI:100-100%), and false positive rate 20% (CI:11-33%). Of false positives, 53% were probable NF1. The billing code algorithms had poor performance, with overall low PPV (highest was 71%).

Conclusions: A free-search algorithm within the EMR has high sensitivity, specificity and predictive values. Algorithms based on billing codes had poor performance, likely due to lack of NF-specific codes in the Ontario Health Insurance Plan for outpatient visits. While NF1 ICD-9 and 10 codes are used for admissions, only ~30% of confirmed NF1 cases had an admission with an NF1 code.

Development of algorithms to identify individuals with Neurofibromatosis Type 1 within administrative data and electronic medical records.

UNIVERSITY OF TORONTO

Carolina Barnett, Elisa Candido, Branson Chen, Priscilla Pequeno, Patricia Parkin, Karen Tu.

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

Objectives

Objectives

- To develop algorithms to identify individuals with NF1 in Ontario, Canada through administrative data and electronical medical records.
- Study the incidence, prevalence and mortality of patients with NF1.
- Study the healthcare utilization patterns of patients with NF1.

IDENTIFICATION OF TRUE NF1 CASES

Ontario Health Insurance Plan (OHIP)

95% of Ontarians covered by OHIP

Institute for Clinical Evaluative Sciences (ICES)

IC/ES

Houses OHIP data

Identification of true NF1 cases

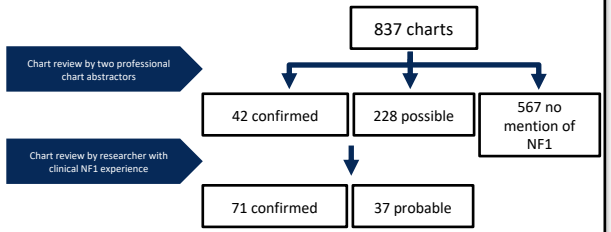
Electronic Medical Record Primary Care Database (EMRPC)
273,440 eligible patient records
(Age 43.9±23years, 55.8% Female)

→ *Free-text search for NF1 related terms

→ 837 patient charts fully abstracted

*NF1 terms : NF, NF1, neurofibromatosis, neurofibroma, café-au-lait, Lisch, plexiform, axillary freckling, inguinal freckling, peripheral nerve sheet tumor, malignant peripheral nerve sheath tumor, MPNST and optic glioma.

CHART REVIEW AND CASE CONFIRMATION



In 273,440 patient records, the minimum prevalence of NF1 ranged from **1:3851** (confirmed NF1) to **1:2532** (probable and confirmed NF1)

DEVELOPMENT OF BILLING ALGORITHMS

Billing code algorithms

- Uses OHIP, ICD-9 and ICD-10 billing codes commonly used by NF1 healthcare providers (ex. 216:Dermatofibroma, Q85.0:Neurofibromatosis)
- Includes billing codes found in definitive NF1 cases during chart abstraction.
- Tested **200** billing code algorithms

Table 1. Sample of billing code algorithm performances

Algorithm	Sensitivity	Specificity	PPV	NPV
ICD9/10 or NACRS or SDS	31%(CI:20-42%)	100%(CI:100-100%)	69% (CI:53-85%)	100%(CI:100-100%)
OHIP in 3yrs	70%(CI:60-81%)	83%(CI:83-83%)	0.1% (CI:0.1-0.1%)	100%(CI:100-100%)
ICD9/10 or NACRS or SDS or 2 OHIP in 1yr	75%(CI:65-85%)	85%(CI:85-85%)	0.1% (CI:0.1-0.2%)	100%(CI:100-100%)
ICD9/10 or 2 OHIP	77%(CI:68-87%)	81%(CI:81-81%)	0.1% (CI:0.1-0.1%)	100%(CI:100-100%)
ICD9/10 or 3 OHIP	69%(CI:58-80%)	87%(CI:87-87%)	0.1% (CI:0.1-0.2%)	100%(CI:100-100%)

National Ambulatory Care Reporting System (NACRS), Same Day Surgery (SDS)

DEVELOPMENT OF EMR ALGORITHMS

EMR algorithm

- Free-text search of EMR
- Searched for "NF1" in cumulative patient profile (CPP)

Table 2. EMR algorithm performance

Algorithm	Sensitivity	Specificity	PPV	NPV
EMR free-text search	85%(CI:74-92%)	100%(CI:100-100%)	80% (CI:69-88%)	100%(CI:100-100%)

COMMON BILLING CODES FOR TRUE NF1 CASES

Table 3. Most common billing codes for true NF1 cases

Billing Code	Billing Code Description	Frequency
304	Drug dependence, drug addiction	1216
787	Anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	605
709	Other disorders of skin and subcutaneous tissue	438
781	Leg cramps, leg pain, muscle pain, joint pain, arthralgia, joint swelling, masses	372
300	Anxiety neurosis, hysteria, neurasthenia, obsessive compulsive neurosis, reactive depression	347
216	Skin (e.g., pigmented naevus, dermatofibroma)	308
192	Cranial nerves, spinal cord, other parts of nervous system	278
349	Other diseases of central nervous system (e.g., brain abscess, narcolepsy, motor neuron disease, syringomyelia)	266
379	Other disorders of the eye	227
739	Other diseases of musculoskeletal system and connective tissue	190
758	Chromosomal anomalies (e.g., Down's syndrome, other autosomal anomalies, Klinefelter's syndrome,Turner's syndrome, other anomalies of sex chromosomes)	141
225	Brain, spinal cord, peripheral nerves	102
191	Brain	98

CONCLUSIONS

1. In review of 273,440 patient charts in EMRPC, we estimate a prevalence of NF1 in Ontario to be 1:3851
2. Developed a high performing EMR algorithm
3. Billing code algorithm performed poorly, possibly due to lack of NF-specific billing codes in OHIP.
4. Drug dependence/addiction was the most common billing code reported in definitive NF1 charts.

Acknowledgments

1. Elisabeth Raab Neurofibromatosis Clinic
2. ICES

Funding

US Department of Defense

CDMRP

University Health Network
Research Ethics Board
10th Floor, Room 1056
700 University Ave.
Toronto, Ontario, M5G 1Z5
Phone: (416) 581-7849

NOTIFICATION OF REB INITIAL APPROVAL

Date: October 28, 2020

To: Carolina Barnett-Tapia
Toronto General Hospital, Eaton Building, 200 Elizabeth St., 5th Floor, 5EC - Room 334, Toronto, Ontario, Canada, M5G 2C4

Re: 20-5072
Using Administrative Health data to Identify Patients with NF1 in Ontario, Canada and to assess prevalence, Mortality, and Health care Utilization Patterns

REB Review Type:	Delegated
REB Initial Approval Date:	October 28, 2020
REB Expiry Date:	October 28, 2021

Documents Approved:

Document Name	Version Date	Version ID
Protocol	October 27, 2020	version 3

The University Health Network Research Ethics Board approves the above mentioned study as it has been found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004.

Best wishes on the successful completion of your project.

Sincerely,
Morris Sherman
Co-Chair, University Health Network Research Ethics Board
Approved and Digitally signed by Morris Sherman on October 28, 2020 at 10:21 AM

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.
Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

Research Ethics Board (REB)
Study Approval Letter

2021-05-20

Dr. Patricia Parkin
Paediatric Medicine

REB number: 1000075571
Study Title: Neurofibromatosis Registry: A prospective study of children with neurofibromatosis.

Date of Approval: 2021-05-20
Expiry Date: 2022-05-20

Thank you for the application submitted on **2021-04-21.** The above referenced study was reviewed through a delegated process (not by Full Board review). Any concerns arising from this review have been documented and resolved.

The REB voted to approve this study, and your participation as Principal Investigator, as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004.

The Hospital for Sick Children Research Ethics Board hereby issues approval for the above named study. This approval is effective from **2021-05-20** to **2022-05-20.** Continuation beyond that date will require further review of REB approval.

The following documents have been reviewed and are approved:

1. Protocol – May 7, 2021 [1. Neurofibromatosis Registry Protocol (2021 05 07) - Clean.docx (1.0)]
2. Assent – April 28, 2021 [9. Neurofibromatosis Registry Assent Form (2021 04 28)_REB_Clean.docx (1.0)]
3. Participant Consent – April 28, 2021 [Neurofibromatosis Registry - Participant ICF (2021 04 28) Clean.docx (1.0)]
4. Parent Consent – April 28, 2021 [Neurofibromatosis Registry - Parent ICF (2021 04 28) Clean.docx (1.0)]
5. Participant Information Email – April 28, 2021 [3. Neurofibromatosis Registry Information Email Template (2021-04-28)_REB_Clean.docx (1.0)]
6. Parent Information Email – April 28, 2021 [3. Neurofibromatosis Registry Parent Information Email Template (2021-04-28) -NEW.docx (1.0)]
7. Participant Information Letter – April 28, 2021 [2. Neurofibromatosis Registry Information Letter (2021-04-28)_Clean.docx (1.0)]
8. Parent Information Letter – April 28, 2021 [2. Neurofibromatosis Registry Parent Information Letter (2021-04-28) - NEW.docx (1.0)]
9. Brochure – November 10, 2020 [6. NF1 Registry Brochure (2020 11 10)b.pdf (1.0)]
10. Certificate of Participation – June 7, 2021 [7. Neurofibromatosis Registry Certificate of Participation (2020 10 29) - New.docx (1.0)]
11. Parent Verbal Recruitment Telephone Script – April 28, 2021 [5. Neurofibromatosis Registry Verbal Recruitment Telephone Script Parent (2021-04-28) - NEW .docx (1.0)]
12. Participant Verbal Recruitment Telephone Script – April 28, 2021 [5. Neurofibromatosis Registry Verbal Recruitment Telephone Script (2021-04-28)_REB_Clean.docx (1.0)]

The following documents have been reviewed and are acknowledged:

1. Master Code Breaking File – April 28, 2021 [Master Linking Log_9482.xlsx (1.0)]

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB.

Arbelle Manicat-Emo

Arbelle Manicat-Emo REB Vice-Chair
555 University Avenue, Toronto, ON M5G 1X8
Tel: (416) 813-8279 Fax: (416) 813-6515

June 2, 2021

Carolina Barnett-Tapia, MD, PhD
Assistant Professor of Medicine (Neurology), University of Toronto
Prosserman Centre for Neuromuscular Diseases
Toronto General Hospital / UHN
200 Elizabeth Street, 5EC-322
Toronto, Ontario M5G 2C4
c.barnetttapia@utoronto.ca

Re: Validation of an EMR algorithm to identify individuals with Neurofibromatosis type 1 | UoT_2021_05_26_CBT

Dear Carolina,

This letter confirms approval by University of Toronto Practice-Based Research Network (UTOPIAN) of your project entitled: *Validation of an EMR algorithm to identify individuals with Neurofibromatosis type*.

UTOPIAN is a University of Toronto initiative comprised of a network of over 1700 family physicians affiliated with the Department of Family and Community Medicine throughout the Greater Toronto Area and beyond, looking after the health of a million patients. Since being fully established in 2013, UTOPIAN has participated in clinical research projects on topics ranging from social determinants of health to the study of chronic conditions (hypertension, diabetes) to large scale Electronic Medical Record databases for research and quality improvement. Patients have been integral to many projects, including large, multi-provincial randomized controlled trial on safer prescribing for elders taking at least ten different medications, improving the collection of social determinants of health and advance care planning in primary care. Patients are also members of UTOPIAN's Scientific Advisory Committee, which reviews clinical research projects.

UTOPIAN is pleased to be involved in this proposed research project. Your team Your team involves a diverse and experienced group of investigators. The research team includes expertise and experience in UTOPIAN EMR data with Dr Karen Tu, UTOPIAN Associate Director, Data.

UTOPIAN will support this project by generating the dataset for this project and providing access to relevant data and analytical software in our Secure Analytic Virtual Environment. UTOPIAN also provides analytical and methodological expertise relevant to EMR data. The precise details of support will be included in a Research & Data Access Agreement, which will be completed once the data set creation plan is approved.

UTOPIAN's initial financial estimate for this support is estimated at a total of $5,400.00. The details of this support are included in the attached *Estimate for Services* letter.

The UTOPIAN Research Project Manager will connect you to the data team to begin the data set creation plan.

Please contact the UTOPIAN Research Projects Manager (DFCM.UTOPIAN@utoronto.ca) if you have any questions or concerns.

We look forward to working with you.

Sincerely,

Dr. Michelle Greiver MD, MSc, CCFP, FCFP
Gordon F. Cheesbrough Chair in Family and Community Medicine, North York General Hospital
Director | University of Toronto Practice-Based Research Network (UTOPIAN)
Associate Professor, Department of Family and Community Medicine, University of Toronto
Lead - Digital Health for Research and Care, Diabetes Action Canada
Adjunct Scientist, Institute for Clinical Evaluative Sciences