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TITLE: Prevalence, Nature and Biopsychosocial Correlates of Sleep Disorders Among Children with Neurofibromatosis Type 1

PRINCIPAL INVESTIGATOR: Dr Natalie Pride

CONTRACTING ORGANIZATION: Sydney Children's Hospital Network
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This research will characterize the nature and extent of sleep disturbance and sleep disorders in children with Neurofibromatosis type 1 using subjective and objective measures of sleep. The research aims to also identify predictors of sleep disturbance in NF1 and how sleep disturbance can impact neurodevelopmental outcomes in this condition. Currently, there are no major findings or results to report.

15. SUBJECT TERMS

Neurofibromatosis type 1; sleep; neurocognitive; cognition; melatonin

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1. Introduction

Adequate sleep in childhood is essential for health, physical and intellectual growth and normal development. The prevalence of sleep disturbance in children with NF1, based on parent questionnaires, has been estimated to be as high as 50%. The impact of this has been augmented by preliminary data by PI Pride that indicates sleep disturbance may be impacting on the cognitive, adaptive and academic functioning of children with NF1. This research study will characterize the nature and extent of sleep disturbance in children with NF1 using both subjective and objective measures of sleep. This work will provide novel insight into the frequency of sleep disturbances and sleep disorders and identity the biopsychosocial and contextual factors contributing to poor sleep in NF1. It will also examine the relationship between sleep disturbance and neurodevelopmental outcomes in children with NF1.

2. Keywords

Neurofibromatosis 1; Sleep; Cognition; Melatonin; Sleep Disorders; Circadian Rhythms.

3. Accomplishments

3.1 What were the major goals of this project?

- To determine whether sleep disturbance and sleep duration differs in children with NF1 compared to typically developing (TD) children based on subjective and objective assessment of sleep.
- To estimate the prevalence of sleep disturbance in children with NF1 and compare to TD children.
- To compare circadian rhythm functioning and melatonin concentrations in children with NF1 to TD children through the use of actigraphic activity, sleep/wake cycle assessment and collection of urinary excretion of the melatonin metabolite 6-sulfatoxymelatonin (aMT.6S).
- To examine the influence of biopsychosocial and contextual factors on sleep disturbance in children with NF1.
- To examine the relationship between sleep duration, sleep disturbance and neurodevelopmental outcomes including executive functions, memory and learning, academic functioning, intelligence, fatigue and QoL.

Major milestones to achieve the above goals

Major Milestones (SOW)	SOW timeline	Completion
Local Ethics (IRB) and HRPO approval and setup of project	Month 5	100%
Recruitment of NF1 participants (n=130) and control participants (n=65)	Month 30	0%
Collection of Data	Month 30	0%
Data analysis and Interpretation	Month 34	0%
Dissemination of study findings	Month 36+	0%

3.2 What was accomplished under these goals/milestones?

1) Major activities during this reporting period

a) Creation of research protocol

b) Local ethics (IRB) approval of research project for both sites

c) HRPO approval achieved

d) Monthly meetings with co-investigators to ensure consistency in project setup procedure

e) Purchasing of materials, study setup, creation of operating guidelines.

f) Creation of study database

2) Specific Objectives for this reporting period

a) Local IRB and HRPO approval

b) Research Project Setup

b). Commencement of Recruitment

3.3 What opportunities for training and professional development has been provided?

Nothing to report.

3.4 How were the results disseminated to communities of interest?

Nothing to Report

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

Milestones for the next reporting period are to commence recruitment on the 1st July 2020 and complete a large proportion (over 70%) of data collection including collection of cognitive, behavioural, and sleep data as well as collection of urine samples of children with NF1 and typically developing children. This is planned to occur over the next 12 months. All investigators will participate in monthly telephone calls to discuss work in progress.

4. Impact

4.1 What was the impact of development of the principal discipline of the project

Nothing to report

4.2 What was the impact on other disciplines

Nothing to report

4.3 What was the impact on technology transfer

Nothing to report

4.4 What was the impact on society beyond science and technology

Nothing to report

5. Changes/Problems

5.1 Changes in approach and reasons for change

Nothing to report

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

Recruitment of participants did not commence during this reporting period for the following reasons:-

1. Delay in achieving HRPO approval. Protocol and associated documents were submitted to HRPO August 2019. Approval was received April 2020.

2. Recruitment was further delayed by the COVID-19 pandemic. A halt on new recruitment was put in place 13 April 2020. This halt in recruitment ended (1st July 2020) and recruitment is due to start 1st July 2020. To overcome the lack of recruitment during this period due to COVID-19 the SCHN clinical trial coordinator will double their time commitment during a 3 month period in Year 2 to increase recruitment of participants in order to reach recruitment targets.

5.3 Changes that has a significant impact on expenditures

Due to the halt in new recruitment over a period of approximately 3 months due to COVID 19, expenditures related to recruitment were not requested during this reporting period. We expect to increase our recruitment in Year 2 to overcome the shortfall in recruitment during Year 1. Furthermore the costs associated with the salary for the SCHN clinical trial coordinator for a 3 month period was not requested in this period as recruitment was on hold.

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

Nothing to report

6. Products

Nothing to report

7. Participants & Other Collaborating Organizations

What individuals have worked on the project

Name:	Natalie Pride
Project Role:	PI
Nearest person month worked:	4.8
Contribution to project:	-Development or protocol and the sleep medical and psychological history interview in collaboration with Prof Banks. Submission of ethics to IRB and HRPO, establishment of

	operating guidelines and oversaw the setup of study at sites through communication with investigators and supervision of clinical trial coordinator at SCHN. This included overseeing creation of recruitment and study databases, ordering of materials, submitting technical reports.

Name:	Melissa Rouel/Jennifer Lorenzo
Project Role:	Clinical trial coordinator SCHN
Nearest person month worked	3.15
Contribution to project	Assist with preparation and submission of ethics to IRB and HRPO, obtaining invoices and ordering study materials at SCHN, creation of study database and recruitment date base, preparing study urine kits and actigraph kits, creation of actigraph database and managing actigraph software, preparing files for recruitment.

Name:	Jonathan Payne
Project Role:	Coinvestigator and site-PI at MCRI (Royal Children's Hospital RCH)Melbourne)
Nearest person month worked	1.2
Contribution to project	Monthly meetings with PI and overseen setup of project at Royal Children's Hospital site in Melbourne. Supervision of RCH clinical trial coordinator. Creation of operation guidelines at RCH. Submission of local governance approval at RCH.

Name:	Kristina Haebich
Project Role:	RCH clinical trial coordinator
Nearest person month worked	4.2
Contribution to project	Assisted with preparation of application to governance approval,

	assisted with setting up study at Melbourne site including obtaining relevant invoices and ordering. Participation in monthly meetings with site-PI and monthly meetings with co-investigator meetings with Sydney team. Study file step up. Familiarization of study protocol, assessment battery and operation guidelines.

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

Nothing to report.

What other organizations were involved as partners?

Nothing to report

8. Special Reporting Requirements

Nothing to report

9. Appendices

Nothing to report.