



a place of mind



ONGOING RESEARCH STUDIES IN THE DIVISION OF PEDIATRIC NEUROLOGY

JANUARY 1, 2022 TO MARCH 31, 2022

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Our Vision:

To become a national and international leader in the provision of leading edge care for children and youth with neurological disorders, conducting research, applying technology to improve patient care, obtaining superior clinical outcomes and sharing information through peer reviewed publications and educational programs.

Our Mission:

To improve the neurological health of children and youth in B.C. through compassionate, leading edge care, education and research, and to implement advances in pediatric neuroscience, particularly those that significantly improve patient outcomes.

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1. INTRODUCTION

This report contains up to date information on the ongoing research projects in the Division of Pediatric Neurology for the period of January 1, 2022 to March 31, 2022. The main objective of the report is to familiarize the members of Pediatric Neurology with the current research activities. The studies presented in the report are divided into two major categories: ongoing prospective studies and retrospective studies. Each study category is further divided in 4 subcategories: Epilepsy, Brain Injuries / Inflammation, Developmental Malformation / Neuromuscular Diseases and Neuro-oncology. The number of studies per category and subcategory is presented in the table below.

Number of Ongoing Studies in the Divisions of Pediatric Neurology			
Category	Prospective	Retrospective	Total
Epilepsy	31 (2 new)	18 (1closed)	49
Brain Injuries/Inflammation	5 (1 new)	0	5
Developmental Malformations/ Neuromuscular Diseases	11 (1 new, 2 closed)	5	16
Neuro-oncology	0	4	4
QA projects	1	0	1
Total	48	27	75

Detailed description of the purpose, objectives, budget and sample size of each study is presented in the next two sections of this report.

2. ONGOING PROSPECTIVE STUDIES

2.1. EPILEPSY

1. fMRI Study - PI: Dr. Bjornson

Multi-Site Pediatric Network for fMRI Mapping in Childhood Epilepsy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	2006 ongoing	200	168	yes	active	Abstract, 45 th Annual Congress of CNSF, June 2010

The purpose of this study is to establish the utility of functional Magnetic Resonance Imaging (fMRI) to identify atypical language in childhood localization related epilepsy, by using a variety of language paradigms that have already been tested in normal children and patients with epilepsy.

The study objectives include:

- To establish the network infrastructure for multi-site collection and management of functional imaging data linked to a database of common assessments and measures;
- To establish the feasibility of conducting multi-site fMRI by identifying patients with atypical language, and to provide pilot data necessary to conduct a large scale study to compare fMRI findings to invasive methods (IAT, ECS, surgical outcome).

To achieve our goals, we will establish an imaging consortium with web based access and central data storage. A multi-centre, cross sectional prospective study will use fMRI to study patients undergoing epilepsy surgery. A web based system will be established that will allow entry of clinical variables and imaging data. Clinical data will be collected as part of routine evaluation for chronic epilepsy in children considered for epilepsy surgery. The Inclusion Criteria are:

- Patients undergoing comprehensive epilepsy evaluation;
- Children between 3-19 years of age.

There are 168 subjects enrolled in the study, with one enrolment in the last quarter.

2. EEG-MEG/EEG-fMRI Epilepsy Study – PI: Dr Bjornson/ Dr Williams

Pediatric Integrating Neurophysiology with Neuroimaging for Pediatric Epilepsy Connectomics

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Internal funds	60K	2018 2022	10	7	yes	active	N/A

The aim of the study is to establish the feasibility of using EEG-MEG and EEG-fMRI to localize inter-ictal spike related activity. We will begin data collection with data obtained from prescribed protocols. We will assess the applicability of multimodal imaging methods using standard study paradigms already tested in clinical practice. Studies will be performed with children and adolescents (7 to 17 years and verbal) with specific epilepsy clinical profiles determined as part of routine clinical care. As a consequence, all children will have clinical, EEG, structural MRI and

neuropsychological assessments. Children will be excluded if they have contraindications to MR scanning or are unable to cooperate and complete study tasks.

MEG and EEG-fMRI literatures suggest that both methods may make positive contributions to the pre-surgical work-up; however, it remains unclear as to why the findings remain so mixed. Only testing both the MEG and EEG-fMRI paradigms with representative groups drawn from the population of pediatric epilepsy patients at BCCH will determine the utility of both methodologies for children with medication-resistant epilepsies in the province of British Columbia.

The study has been approved and is active. *Two adult control subjects and five children have been enrolled in the study. There were no enrolments in the last quarter.*

3. Lorcaserin Dravet Syndrome Study – PI: Dr. Boelman

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	Eisai	29K/pt 19K site fees	2021-2024	3-5 @ BCCH	0	yes	active	

This is a multicenter, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group adjunctive therapy study in subjects with Dravet syndrome. The study will consist of a Core Study and open-label Extension Phase.

Core Study

Primary Objective

- The primary objective of the study is to demonstrate that lorcaserin has superior efficacy compared to placebo on percent change in frequency of convulsive seizures per 28 days in subjects with Dravet syndrome.

Secondary Objectives

- To evaluate whether lorcaserin has superior efficacy compared to placebo on the 50% responder rate (percent of subjects with at least 50% reduction in frequency of convulsive seizures per 28 days compared to baseline)
- To evaluate whether lorcaserin has superior efficacy compared to placebo on the proportion of subjects who are free from convulsive seizures
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To evaluate the safety and tolerability of lorcaserin in subjects with Dravet syndrome

Extension Phase:

- To evaluate the safety and tolerability of lorcaserin
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of convulsive seizures
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of each type of seizure

- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are free from convulsive seizures
- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are seizure-free
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of clusters
- To summarize the efficacy of lorcaserin as measured by CGIC
- To summarize the efficacy of lorcaserin as measured by on quality of life

There are no patients enrolled yet in this clinical trial.

4. Lorcaserin Extended Access Program Study – PI: Dr. Boelman

Extended Access Program and Retrospective Chart Review for Lorcaserin in Dravet Syndrome and Other Refractory Epilepsies

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Eisai	19K/pt 18K site fees	2022-2028	5 @ BCCH	0	yes	active	

This protocol includes an Extended Access Program (EAP) for patients who have completed the Lorcaserin Dravet Sy study described above, and who, based on the treating physician’s judgment, had a clinical benefit.

The primary objective is to provide continued access of lorcaserin to patients with Dravet syndrome and other refractory epilepsies.

Secondary Objectives:

- To summarize the efficacy of lorcaserin as measured by percent change in frequency of convulsive seizures
- To summarize the efficacy of lorcaserin as measured by the 50% responder rate (percent of patients with at least 50% reduction in frequency of convulsive seizures per 28 days) compared to baseline
- To summarize the efficacy of lorcaserin as measured by the proportion of patients who are free from convulsive seizures
- To summarize the efficacy of lorcaserin as measured by percent change in total seizure frequency
- To summarize the efficacy of lorcaserin as measured by the 50% responder rate (percent of patients with at least 50% reduction in total seizure frequency per 28 days) compared to baseline
- To summarize the efficacy of lorcaserin as measured by the proportion of patients who are seizure-free
- To summarize the retention rate of patients started on lorcaserin
- To evaluate the safety and tolerability of lorcaserin

The study is REB approved, however the institutional approval is pending Lab approval. Lab will start reviewing new applications in May, due to the initiation of CST at the BCCH site.

5. **TAK-935-3001-Dravet Syndrome Study** – PI: Dr. Boelman-*new study this quarter*

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome (DS)

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Takeda	22K/pt 23K site fees	2022-2028	3-5 @ BCCH	0	No	Not started yet	

The purpose of this Phase 3 clinical trial is to evaluate the safety, tolerability, and efficacy of soticlestat as an adjunctive therapy in pediatric patients and young adults with Dravet Syndrome (DS).

Soticlestat is a first-in-class small molecule inhibitor of cholesterol-24-hydroxylase (CH24H) in the brain. Soticlestat has shown antiseizure efficacy in nonclinical studies, including models relevant to the rare developmental epileptic encephalopathies (DEEs) that are inadequately treated by current adjunctive antiepileptic drugs.

Primary Objectives:

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).
- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.

Research Design:

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and young adult subjects with DS. The treatment period is approximately 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.

This study consists of the following periods:

- 4- to 6-week screening/baseline period.
- 16-week treatment period (4-week titration period and 12-week maintenance period)
- 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or phone call.

The study is under REB review, and hasn't started yet.

6. **STXBP1 Registry** – PI: Dr. Boelman

A National STXBP1 Registry and Family Resource

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no			2018-2023	50	21	yes	active	N/A

We wish to establish a secure Canadian registry & family resource for patients who are affected by STXBP1 gene mutations. These mutations cause a rare neurodevelopmental disorder that starts in early childhood with drug-resistant epilepsy, a movement disorder, intellectual disability & autism spectrum disorder. With very few patients known to us across the country, we do not have a complete characterization of this disorder, nor are there any personalized treatments or any family support or patient advocacy groups in Canada.

The registry will facilitate a better understanding of how we can make the greatest impact on the patients' quality of life by understanding the experiences across the lifespan from the patients, their families & clinicians. We hope to facilitate a sense of belonging for patients & their caregivers that may foster them reaching out to each other for support, advocacy & the sharing of ideas. *There are 21 enrolments, with no enrolments in the last quarter.*

7. Angelman Syndrome Study - PI: Dr. Boelman

A Prospective Natural History Study of Angelman Syndrome for Therapeutic Development

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCH	10,000	2020 2026	250 total 15 @ BCCH	13	yes	active	N/A

The purpose of the study is to increase our understanding of the long-term natural history of Angelman Syndrome (AS) and obtain AS-specific norms for outcome measures that can be used in AS clinical trials, ultimately improving the care of individuals with AS.

We hypothesize that through this study, we will collect data so as to better determine appropriate outcome measures and endpoints for clinical trials.

Primary objective: To analyze the changes over time in sleep disturbance, adaptive functioning, maladaptive behaviors, and anxiety in a cohort of children and adults with AS.

Secondary objectives include, but are not limited to, the analyses of the prevalence of medical complications such as seizures, ages at which specific developmental milestones are achieved, prevalence of behavioral traits that are not necessarily maladaptive at different ages, changes in facial characteristics over time, as well as changes in levels of parental stress and quality of life for the family over time.

This is a longitudinal observational investigation into the natural history, morbidities, and mortality of Angelman syndrome (AS).

There are 13 subjects enrolled in the study, with 1 enrolment in the last quarter.

8. Black Light Study – PI: Dr. Connolly/Lagace

Commercial Hand-held Black Light to Facilitate Screening for Neurocutaneous Disorders

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
No			2021 - 2023	10	8	yes	active	N/A

The purpose of this pilot study is to show that a commercial hand-held black light is non-inferior to a Wood’s lamp to identify hypomelanotic lesions in fair skin patients with known neurocutaneous disorders.

The primary hypothesis is that a commercial hand-held black light is non-inferior to a Wood’s lamp to identify hypomelanotic lesions in light skin patients with known neurocutaneous disorders. The secondary hypothesis is that a commercial hand-held black light is equivalent to a Wood’s lamp to identify hypomelanotic lesions in fair skin patients with known neurocutaneous disorder.

The primary objective is to identify if a commercial hand-held black light can identify all the hypomelanotic lesions identified with a Wood’s lamp to demonstrate non-inferiority of commercial hand-held black light to Wood’s lamp. The second objective is to demonstrate the equivalence of commercial hand-held black light to Wood’s lamp. The third objective is to report descriptive epidemiological data about hypomelanotic lesions in TSC patients. The primary end points will be the skin tone and the number and size of hypomelanotic lesions identified under normal lighting and with a Wood’s lamp and a commercial hand-held black light. Secondary end points will include age, pre or post puberty status, sex, diagnosis and if there is a genetic confirmation of diagnosis.

This will be a comparative randomized descriptive pilot study where each patient will be his/her own control. Since TSC is a neurocutaneous disease with hypomelanotic lesions, we will recruit patients attending the TSC Clinic at BC Children’s Hospital.

There are 8 subjects enrolled in the study, with no enrollments in the last quarter.

9. BBD in Epilepsy Study – PI: Dr. Afshar/Dr. Connolly

Prevalence of Bladder and Bowel Dysfunction (BBD) in pediatric patients with Epilepsy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
no			2021 - 2023	50	8	Yes	active	N/A

Functional disorders of the lower urinary tract and bowel known as Bladder and Bowel Dysfunction (BBD) are one of the most common reasons for outpatient referrals to pediatric urologists. Diagnosis and management of BBD in a timely manner is important to prevent future complications such as recurrent urinary tract infections and renal failure and to improve the quality of life of the affected children and their families. It is suggested that the neurological pathways that regulate bladder and bowel control might be disturbed in children with epilepsy. Based on this, we expect the frequency of BBD in children with epilepsy to be higher than the general population (2-20%). However, overlapping presentation between epilepsy and BBD (e.g., urinary incontinence around the time of epilepsy or urinary problems associated with anti-seizure medications) makes the diagnosis of BBD in this group of pediatric patients more challenging. This study is the first to use a validated tool to determine what percentage of children with epilepsy are affected by BBD at the same time.

Purpose: To improve the diagnosis and management of BBD in children with epilepsy.

Hypothesis:

- The prevalence of BBD in children with epilepsy is higher than 20%
- There is an association between BBD and anti-seizure medications.

Objective: To determine the prevalence of BBD in pediatric patients with epilepsy

Specific Aims:

- To determine the prevalence of BBD based on the type of epilepsy.
- To determine the association of anti-seizure medications and prevalence of BBD.

There are 8 subjects enrolled in the study, with no enrollments in the last quarter.

10. XPF-009-301 EPIK study – PI: Dr. Connolly-new study this quarter

A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects with KCNQ2 Developmental and Epileptic Encephalopathy of EPX-100 (Clemizole Hydrochloride) as Adjunctive Therapy in Patients with Dravet Syndrome

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/Paper/Manuscript
Yes	Xenon	51K/pt, 25K start up fees	2022-2026	2-3	0	pending	Not started yet	N/A

The purpose of this study is to evaluate the safety, tolerability, and efficacy of XEN496, in infants and children with KCNQ2-DEE, given the strong mechanistic rationale for ezogabine use in this unique form of epileptic encephalopathy.

Hypothesis: Patients treated with XEN496 will demonstrate a decrease in seizure frequency from baseline compared to the placebo in pediatric patients with KCNQ2-DEE.

Primary objective: To evaluate the efficacy of XEN496 as adjunctive therapy in reducing seizure frequency compared to placebo in pediatric patients with KCNQ2-DEE.

Key Secondary objective: To evaluate the proportion of pediatric patients with KCNQ2-DEE who achieve a $\geq 50\%$ reduction from baseline in seizure frequency when taking XEN496, compared with placebo.

Additional Secondary objective: To evaluate Caregiver Global Impression of Change (CaGI-C) and Caregiver Global Impression of Severity (CaGI-S) scores in pediatric patients with KCNQ2-DEE taking XEN496, compared with placebo.

Research Design: Approximately 40 participants will be randomized in a blinded manner to either the XEN496 or placebo treatment group in a 1:1 ratio. Participants, caregivers, outcomes assessors/adjudicators, investigators, and sponsor will be blinded to treatment allocation.

The study has been submitted to REB. The review/approval process is in progress.

11. ARGUS Trial – PI: Dr. Connolly

A 20-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of EPX-100 (Clemizole Hydrochloride) as Adjunctive Therapy in Patients with Dravet Syndrome

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/Paper/Manuscript
Yes	Epygenix Therapeutics	86.4K/pt, 36K start up	2022-2026	2-3	0	pending	Not started yet	N/A

This is a 20-Week Multicenter, randomized, double-blind, placebo-controlled, dose escalation design of EPX-100 (Clemizole HCl) as adjunctive therapy in Patients with Dravet Syndrome.

The primary objective is to evaluate the efficacy of EPX-100 orally in divided doses as adjunctive therapy compared with placebo in participants with Dravet Syndrome, in terms of the mean percent change in countable convulsive seizure frequency (CCSF1) in the Titration and Maintenance (T+M) periods relative to baseline.

Secondary Objectives:

- To evaluate the difference between EPX-100 vs placebo in proportion of participants with >50% reduction in the median countable convulsive seizure frequency between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week maintenance Period.
- To evaluate the difference between EPX-100 vs placebo in proportion of participants with >25% reduction in the median countable convulsive seizure frequency between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week Maintenance Period.
- To compare the difference between EPX-100 vs placebo in the number of countable convulsive seizure-free days during the final 4-week Maintenance Phase vs the Observational Phase.
- To describe the difference between EPX-100 vs placebo in the reduction in episodes of status epilepticus¹, between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week maintenance Phase.
- To evaluate the median difference between EPX-100 vs placebo in the percent change per 28-day frequency of all seizures I the final 4-weeks of the 12-week treatment period (Maintenance Phase) relative to the baseline (4-week Observational Phase).
- To compare the incidence of rescue antiepileptic drug (AED) use between treatment arms, as measured by the number of days on rescue AEDs during the 12-week Maintenance Phase as compared with the 4-week Observational Phase.
- To describe improvement in Clinical Global Impression (CGI).
- To describe changes in Quality of Life in Childhood Epilepsy short form (QOLCE-55).
- To describe changes in Targeted Behavior using Visual Analog Scales (VAS).
- To describe change in the Sleep Disturbance Scale for Children (SDSC) by treatment arm and by each scheduled visit.
- To evaluate the safety of EPX-100 orally in divided doses as adjunctive therapy compared with placebo.
- To determine the PK profile of EPX-100 in plasma during the during the Titration Phase, Maintenance Phase and Open-Label Extension Phase.

The REB has deferred the study, and re-submission has been made.

12. Flunarizine Study – PI: Dr. Connolly

Flunarizine for Treatment Resistant Absence Epilepsy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Xenon Pharma	132,600	2019-2021	20	9	Yes	active	N/A

This is an open label, single-center phase 2 study to evaluate the potential clinical efficacy, safety and tolerability of flunarizine administered as adjunctive treatment in patients diagnosed with treatment resistant absence epilepsy. It is hypothesized that patients treated with flunarizine will

tolerate the study drug safely and demonstrate a decrease in total number of absence seizures per week compared to a baseline period. Seizure frequency will be documented via seizure diaries and side effects and safety will be closely monitored. This study will inform the feasibility and utility of conducting a larger clinical trial.

The primary objective is to assess the efficacy, safety and tolerability of flunarizine compared to a baseline period on absence seizures in patients with treatment refractory epilepsy taking a minimum of one anti-seizure medication (ASM).

The secondary objectives are to evaluate EEG changes in patients with absence epilepsy; to evaluate changes in quality of life for patients; and to evaluate global impression change and clinical impression of change.

The study is active. A total of 9 subjects have been enrolled so far. Five subjects completed the study as per protocol, three subjects were withdrawn from the study, and 1 subject was a screen failure due to increase of the seizures. *There were no enrolments during the last quarter.* The SickKids Hospital has been included as an additional centre for the study. They have been already approved, and the contract has been finalized.

13. Dravet Syndrome & LGS Study (1900) – PI: Dr. Connolly

An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Zogenix	25K start-up funds 32K/pt	2019-2023	8@ BCCH	7	yes	active	N/A

This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with rare seizure disorders, epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with LGS who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time.

Objectives:

The primary objective of the study is to assess the long-term safety and tolerability of ZX008.

The key secondary objectives of the study are:

- To assess the effect of ZX008 on the following effectiveness measures:
- Investigator assessment of convulsive seizure response
- Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the investigator
- CGI-I rating, as assessed by the parent/caregiver
- Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by the investigator - Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by the parent/caregiver

Subject will be eligible to participate in this trial for up to 36-months, or until ZX008 is approved in a subject’s country of residence and listed on a patient’s health plan formulary. Thus, the maximum duration for participation is 36 months. *Seven subjects have been enrolled in the study.* The enrolment is completed. The follow-up of the subjects enrolled is as per the study protocol.

14. QOL Study - SickKids – PI: Dr. Connolly

Efficacy Impact of Pediatric Epilepsy Surgery on Health-Related Quality of Life

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	CIHR	270/study visit	2014-2022	50@ BCCH	29	Yes	completed enrolment	N/A

Epilepsy in children often has catastrophic consequences on multiple domains of health-related quality of life (HRQL). Medically refractory epilepsy refers to poorly controlled epilepsy in spite of treatment with two or more antiepileptic drugs. The two main treatments for medically refractory epilepsy are medical treatment with antiepileptic drugs or surgery.

Primary Objectives:

- To assess HRQL over two years in children with medically refractory epilepsy, comparing two treatment groups: surgery and medical therapy.
- To evaluate the mediating and moderating factors for changes in HRQL following treatment.
- To identify the baseline characteristics predicting HRQL in children at two years after surgery.

Secondary Objective is to assess whether changes in the children’s HRQL following epilepsy surgery will be associated with changes in family factors.

Inclusion criteria

- Age 4 – 18 years (the HRQL instrument has been validated in this age range)
- Medically refractory localization-related epilepsy (assessed by clinical semiology and/or electroencephalography)

There are 29 subjects enrolled at BCCH, with no enrolments in the last quarter. There are 20 active subjects, and 9 subjects withdrew from the study. The enrolment has been completed and closed. The active subjects have been completing the questionnaires as per protocol.

15. ANAVEX2-73-RS-003 Rett Syndrome Study – PI: Dr. Datta

A Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of ANAVEX2-73 in Patients with Rett Sy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Anavex Life Sciences Corp.	30K/pt 26K site fees	2021-2024	5 @ BCCH	2	yes	active	

This international Phase 2 efficacy, tolerability, and safety study design is a double-blind, randomized, placebo-controlled, 12-week dose titration study of ANAVEX2-73 oral solution in the treatment of patients with RTT between 5 and 17 years of age. Approximately 84 participants of the study with a voluntary option for all patients to continue in a 48-week open-label extension.

Primary Endpoints

- Recording of Adverse Events (AEs); graded AEs according to common Terminology Criteria for Adverse Events (CTCAE) V5.0.
- Physical and neurological examination.
- Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], and oral body temperature).
- 12-lead ECG; three consecutive ECGs where participants should be in a resting position for ≥ 5 minutes prior to each ECG evaluation.
- Clinical laboratory tests (hematology including routine clotting tests; clinical chemistry including full liver function tests and lipid panel; CYP polymorphisms; and urinalysis).
- Concomitant medication log.
- PK of ANAVEX2-73 and ANAVEX19-144.

Co-Primary Efficacy Endpoints:

The co-primary efficacy endpoints will be the change from baseline to End of Treatment (EOT) in the modified intent-to-treat (mITT) population in the following measures:

- Rett Syndrome Behaviour Questionnaire (RSBQ) total score, and
- Clinical Global Impression - Improvement Scale (CGI-I) score

The mITT population is defined as all randomized patients who receive at least 1 dose of study medication.

Secondary endpoints include a range of efficacy (clinical, quality of life) and PK measures.

- RSBQ Emotional Factor-Pediatric (subset of the RSBQ)
- Clinical Global Impression - Improvement Scale (CGI-I)
- Anxiety, Depression, and Mood Scale (ADAMS)
- Children's Sleep Habits Questionnaire (CSHQ)
- Seizure frequency via seizure diary
- Motor Behavioral Assessment-7 dynamic pediatric items (MBA-Ped7)
- Visual Analog Scale (VAS) of the top three concerns a family has for their daughter
- Rett Syndrome Caregiver Inventory Assessment (RTT CIA)
- Child Health Questionnaire-Parent Form 50 (CHQ-PF50)
- Population PK of ANAVEX2-73 and its active metabolite, ANAVEX19-144, integrated to safety, tolerability and efficacy assessments.

Exploratory endpoints include a variety of genomic and biochemical measures and analyses of relevance to safety and efficacy.

- Glutamate plasma concentration.
- GABA plasma concentration.
- Other Amino Acid plasma concentrations.
- Exploratory DNA and RNA profiles.
- Analyses of efficacy endpoints in the subgroups of subjects without the SIGMAR1 (rs1800866) or COMT (rs113895332/rs61143203) sequence variations.
- Pharmacodynamics (PD); PK-PD relationships will be explored for safety, tolerability, and efficacy endpoints.

Patients will be randomized into 2 arms to receive placebo or ANVEX2-73 for a total of 12 weeks during the period of blinded titration and safety monitoring. Upon completion, all patients will be offered the option of participating in an additional 48-week OLE. Study drug will be provided to the patients/caregivers in 120 ml bottles that are labelled in a blinded fashion, containing a solution of either Placebo or 5 mg/ml ANAVEX2-73. Open-label product will be provided for the OLE study. Safety Reviews will occur on site or at home at Weeks 0, 4 and 12 during the 12-week double-blind period, and at Weeks 0, 12, 24, 36 and 48 during the OLE, and any other time, if medically indicated.

The study is active, with 2 enrollments in the last quarter.

16. mTOR Study - PI: Dr. Datta

Treatment of Medically Refractory Epilepsy due to Focal Cortical Dysplasia with mTOR inhibitors

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	RDF BCCHF	3,500 20K	2019-2023	6	0	yes	active	

Summary: We are proposing an open-label pilot study looking at the efficacy of mammalian target of rapamycin (mTOR) inhibitor, sirolimus, for the treatment of acute seizure exacerbation secondary to a focal cortical dysplasia in children who are awaiting imminent epilepsy surgery.

Purpose: The purpose of this study is to measure if mTOR inhibitor, sirolimus reduces seizure frequency by effecting mTOR signalling (an electrical activity signal in the brain) in patients with Focal Cortical Dysplasia (FCD) with treatment resistant epilepsy (TRE) who will be undergoing respective epilepsy surgery.

Hypothesis: Since patients with FCD have been shown to have excess mTOR signalling brain activity, and it has been shown to be effective in patients with TSC, mTOR inhibitors may be useful in reducing seizure frequency in patients with FCD who are admitted to hospital with extreme TRE prior to surgery.

Methods: This is a single center open-label pilot study of patients with FCD and TRE over 1 year. Patients 5 months to 6 years, with FCD, which is confirmed on MRI, who are undergoing pre-surgical investigations, not responding to AEDs (failed >6) and requiring admission for seizure control will be included.

The study is active with no enrolments so far.

17. Brain Differences in Children with Rett Syndrome - PI: Dr Weber/Dr Datta

Functional, Metabolic, and Structural MRI Findings in Rett Syndrome

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript

yes	Catalist grant	20K	2021 2024	20	0	no	Not started yet	
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Background: Rett Syndrome (RTT) is a severe genetic brain disorder that typically manifests in females due to de novo mutations in the methyl-CpG-binding protein 2 gene (MECP2). Patients usually have normal early growth and development until 6 to 18 months of age, followed by a slowing of development, loss of purposeful hand movements, distinctive hand movements and deceleration of brain and head growth. Although there is a spectrum of clinical severity, common symptoms involve neurologic (seizures, movement disorders), cardiac (arrhythmias), gastrointestinal (poor feeding, gastroparesis), orthopaedic (scoliosis) and autonomic systems. Further research is necessary to understand anatomical, metabolic, and functional changes in the brains of children with RTT, and to link these changes with measures of genetics, disease progression and clinical features.

The primary aim of this study will be to investigate WM architectural and metabolic differences between girls with RTT (aged 5-12 years; n = 10) compared to healthy age-matched girls (aged 5-12 years; n = 5-10), as well as explore the relationship between these WM measures and RTT clinical severity scores, age, genetic MECP2 mutations, and seizures. Secondary aims will explore novel functional abnormalities in RTT and its association with severity, age, genetic mutations, and seizures.

Hypothesis 1: Reductions in fractional anisotropy (FA), as measured using DTI, in the genu and splenium of the corpus callosum and external capsule will be found in girls with RTT compared to controls. FA will be found to decrease with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

Hypothesis 2: Single voxel spectroscopy measures of NAA will be reduced in frontal lobe white matter, while mI and Glx will be increased. NAA, mI and Glx will be found to be correlated with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

Hypothesis 3: Resting state blood oxygen level dependent (BOLD) MRI measures of functional connectivity and brain dynamics complexity (Hurst exponent) will reveal reduced connectivity and efficiency of information processing (respectively) with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

This research will help identify the structural, metabolic and functional differences between girls with RTT and their healthy counterparts. These findings will be linked to specific MECP2 mutations and clinical severity, allowing for a greater understanding of the specific causes of RTT, and paving the way for future targeted therapies.

The Rett Sy patients (cases for the study) will undergo General Anesthesia for the MRI. We have included co-investigators from the Department of Anesthesia. Due to unforeseen challenges, the study is still under REB's review. The actual subject enrolment will be initiated upon REB's approval.

18. tDCS Study - PI: Dr. Datta

Transcranial direct current stimulation (tDCS) for treatment of pediatric focal refractory epilepsy not amenable to epilepsy surgery: a feasibility pilot study at BCCH

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript

no	N/A	0	2018-2022	6	6	yes	active	
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Summary: This is an open-label pilot study to investigate the feasibility of transcranial direct current stimulation (tDCS) in the pediatric population at BC Children’s Hospital with treatment resistant focal seizures, who have been evaluated for epilepsy surgery and are deemed not to be epilepsy surgery candidates. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that has been shown to suppress regional cortical excitability, using electrodes through the scalp to stimulate the nervous system. It has also been shown to reduce inter-ictal epileptiform discharges (IEDs) and frequency of seizures in some clinical studies, including pediatric studies.

Method: We will include 6 children, adolescents and young adults, aged 6-21 years, with focal treatment resistant epilepsy, who are not amenable to epilepsy surgery.

There are 6 subjects enrolled so far. Five subjects have completed the treatment; one subject withdrew from the study. It was decided to wrap up the enrolment and perform the analyses of the already enrolled participants.

19. NIH Toolbox Study - PI: Dr. Datta/Dr Panenka

Determining Associations between Epileptiform Discharges, Cognition, and Emotional Functioning in Children with Epilepsy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Catalist Grant	22K	2018-2021	210	112	yes	active	

Overview: Early detection of cognitive and emotional dysfunction in pediatric epilepsy is critical for improving outcomes. The proposed study aims to use a novel assessment tool, the ‘National Institutes of Health Toolbox’, to characterize cognitive functioning in pediatric idiopathic epilepsy and to investigate how cognitive and emotional functioning are impacted by inter-ictal seizure activity.

Study Goals and Objectives: This study will systematically screen children with idiopathic epilepsies (IE) for cognitive and emotional deficits using the NIH Toolbox and standardized psychological screening tools. Our goal is to investigate the impact of inter-ictal epileptiform discharges (IEDs) features on cognitive and emotional functioning in patients with IGE. Based on the above reviewed evidence, we hypothesize:

- Children with IE will exhibit global and domain-specific cognitive impairments compared to same-aged peers.
- A higher frequency of IEDs will be associated with poorer global cognitive functioning (i.e., cognitive composite score) and increased symptoms of depression and anxiety.
- Location of IEDs will be associated with different profiles of cognitive functioning.

Implications: If practicality and feasibility are demonstrated, this project will immediately change care for children in the BC epilepsy service as the NIH Toolbox is then likely to be adopted into clinical care. This study will also increase our understanding of how IEDs contribute to cognitive and emotional dysfunction in epilepsy, and has the potential to inform therapies that will ultimately improve outcomes for affected children.

There are 112 subjects enrolled in the study, with no enrolment in the last quarter.

20. Alexander Disease study - PI: Dr. Demos

A Phase 1-3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ION373 in Patients with Alexander Disease

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Ionis Pharmaceuticals	62K/pt 19K start-ups	2021 2026	2-4	0	no	Not started yet	

This is a registration supporting (Phase 1-3), double-blind, randomized, placebo-controlled study conducted at multiple centers.

The primary objective is to evaluate the efficacy of ION373 in improving or stabilizing gross motor function in patients with Alexander disease.

The secondary objective is to further evaluate the efficacy of ION373 in improving or stabilizing disease manifestations across the full range of affected domains (gross and fine motor, communication, swallowing, autonomic and/or other gastrointestinal functions, nutritional/growth status) in patients with Alexander disease.

The exploratory efficacy objective is to explore the effects of ION373 in additional disease specific clinical manifestations, such as orthostatic hypotension (OH) and macrocephaly, and in exploratory disease progression biomarkers.

The pharmacokinetic objective is to characterize the pharmacokinetics (PK) of ION373 in cerebrospinal fluid (CSF), plasma and urine in patients with Alexander disease.

The safety objective is to evaluate the safety and tolerability of ION373 in patients with Alexander disease.

This study is composed of 2 periods – a Double-Blind Treatment Period and an Open-Label Treatment Period – each with a duration of 60 weeks.

The REB has deferred the study once. Re-submission has been made and the REB review is in progress.

21. Epilepsy & Genomics study - PI: Dr. Demos

Pediatric Epilepsy: Using Genomics to Improve Patient Care and Outcomes

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Alva Foundation UBC Vancouver Foundation	100,000 45,000 50,000	2014 2022	300	266	yes	active	multiple abstracts, papers

Current methods of genetic testing in Canada limit doctors' ability to identify genetic disorders implicated in epilepsy in a timely fashion, and it's likely that some go undiagnosed. Modern genomic technologies such as next-generation sequencing (NGS), specifically whole exome sequencing (WES), allows for simultaneous sequencing of many genes or exons (coding region of DNA) all at one time. Compared to current standards of genetic testing in Canada, the use of whole exome sequencing would allow for earlier diagnosis of single gene disorders causing epilepsy and thus earlier institution of appropriate treatment which could have a positive impact on outcome.

Overall Objectives

Performing WES technology in infants and young children with epilepsy of unknown cause will likely increase numbers identified to have a single gene disorder causing epilepsy and allow for more rapid diagnosis of a single gene disorder which in turn will allow for earlier intervention with a specific treatment plan based on genetic cause. The latter will likely lead to better outcomes for children and their families. WES may also reduce costs associated with current testing strategies which often involve extensive investigations in children with epilepsy of unknown cause.

A total of 160 eligible patients (and their parents) between the ages of 0 and 18 years attending the Pediatric Neurology Clinic at BC Children's Hospital or admitted to BC Children's Hospital will be invited to participate in this study. Genetic counselling will be offered to all families, both pre- and post-testing. In this study, new genetic technologies will efficiently analyse the genes of participating children to learn more about the cause of their epilepsy and how it can be treated.

There are 266 subjects enrolled in the main study, including 7 siblings. There are 12 withdrawn and 37 excluded subjects, with 217 active subjects. 17 trios were sent for whole genome sequencing. This main study is no longer enrolling. The 17 trios for Whole Genome Sequencing are being analysed with a collaboration with the Rare Disease Discovery Hub at BCCHRI.

There are two sub-studies associated with this study. Both sub-studies have been REB approved. Sub-study 1 named: "Clinical Whole Exome Sequencing" is focused on identifying gene variants and gene candidates associated with epilepsy in children who have seizures and epilepsy and have undergone whole exome sequencing through clinical investigations. *There are 70 subjects currently enrolled in sub-study 1, 2 of them enrolled in the last quarter, and the sub-study is actively enrolling.* Sub-study 2 is named "Parents of Children Who Have Undergone Genetic Testing for Epilepsy" and is focused on interviewing parents of participants in the main study who have been told their child's WES results, to determine the importance of genetic testing in parents' decision-making regarding their children's epilepsy treatment, and care. *There are 28 subjects currently enrolled in sub-study 2, with no enrolments in the last quarter, and the sub-study 2 is actively enrolling.*

Exome re-analysis: Re-analyzing research exome sequencing data in unsolved cases to identify candidate genetic variants responsible for patient's phenotype. These patients are recruited under EPGEN study and have undergone exome sequencing on research basis.

We have started a regular Genomics rounds every month to discuss genetic causes of epilepsy in our patients.

22. IDIC 15 Registry - PI: Dr. Demos

The Isodicentric chromosome 15 (Idic (15)) registry of British Columbia, Canada

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript

No	N/A		2015 2025	50	0	yes	active	N/A
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Current Isodicentric chromosome 15 (Idic(15)) is a rare chromosomal disorder in which affected people have additional genetic material derived from chromosome 15.

Hypothesis: The development of a provincial Idic(15) registry will provide the patient numbers and clinical data necessary to facilitate research, including potentially breakthrough therapeutic translational research, and will allow for ongoing accurate education of affected patients/families and medical professionals on this disorder.

Objective: The purpose of this registry is to learn more about the rare chromosomal disorder Isodicentric chromosome 15 with the goal of improving the future for patients with Idic(15) through the enablement and support of research. The registry will compile de-identified clinical data that will further researchers understanding of the disorder, enabling the identification of important research questions and the planning of future studies.

The study is active, however there are no enrolled subjects yet.

23. CAE- Pharmacogenomics-PI: Dr. Demos/Dr Hebbbar

Investigating Treatment-Resistance to Ethosuximide in Childhood Absence Epilepsy by Genome-Wide Association Study

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCCHRI Seed grants		2020 2023	250-300	37	yes	active	

Purpose: In this study, we would like to investigate clinical and contributing genomic factors that may influence treatment response to ethosuximide in patients with childhood absence epilepsy.

Hypothesis: Common polymorphisms in genes directly or indirectly associated with etiology, pathogenesis, and drug metabolism of ethosuximide, along with clinical features manifesting in childhood absence epilepsy could be associated with variable treatment response and seizure outcome.

Objectives:

1. Evaluate clinical factors associated with treatment response to ethosuximide in patients with childhood absence epilepsy treated with ethosuximide.
2. To compare common genomic polymorphisms in childhood absence epilepsy patients who respond to ethosuximide versus non-responders.

Sample size: Our hospital records from 2018 to 2020 (2 years) revealed a total of 159 documented cases of typical absence seizures. This number is expected to be lower than the reality as the software often overlooks the actual clinical data. We consulted a statistician for sample size calculation. The sample size of 289 is calculated based on the main outcome of treatment resistance with an anticipated rate of 15% to ethosuximide. Based on these two indications, we estimate that 270-300 patients will meet the inclusion and exclusion criteria.

Analysis of results: We will perform Chi-Square and Fisher's exact tests for group comparisons. A p-value less than 0.05 will be considered significant. Relations between outcomes and variables

will be analyzed by using the multivariate logistic regression model. GWAS specific statistical analysis will be carried out for genomic data analysis.

There are 37 subjects enrolled in the study, with 8 of them enrolled in last quarter.

24. pSERG Study - PI: Dr. Huh

Pediatric status epilepticus research group (pSERG). Multicenter outcome in pediatric status epilepticus

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	PERF-Boston Children's	3000 start-up 200/subject	2016 – no end date to registry	100 patients 10 @ BCCH	7	yes	completed enrollment	N/A

This is a prospective observational study based on the pSERG network. pSERG includes 11 leading Children's Hospital in the US. pSERG prospectively collects demographic, diagnostic, and detailed patient information from non-competing pediatric hospitals across the United States on pediatric patients with SE. The pSERG was developed to meet the need of a large multicenter data registry for pediatric convulsive status epilepticus.

The rationale of this study is to construct an electronic, web-based data-entry sheet and database, determine feasibility of prospective observational outcome data collection, determine variability, adjusters for severity of outcome data, predict outcome of pediatric status epilepticus, facilitate genetic investigation in a thoroughly phenotyped cohort of status epilepticus study participants, and follow patients longitudinally.

Inclusion criteria:

- 1) Age 1 month to 21 years;
- 2) Convulsive seizures at onset;
- 3) Failure of two or more antiepileptic drugs (AEDs) or requirement of any kind of continuous infusion of AEDs to abort seizures.

Aims:

- 1) Develop a prospective status epilepticus registry among eleven tertiary care pediatric hospitals in the United States focused on standardized status epilepticus outcome assessment.
- 2) Develop a database of patients who present with SE that do not go on to develop rSE as a control group. Using the web-based data entry form, we will acquire demographic and standardized clinical data (time to treatment, medications utilized, length of stay, additional diagnoses, comorbidities, etc), EEG, and neuroimaging to discern unique risk factors for the development of rSE.
- 3) Determine illness severity adjusters of outcome and outcome predictors in pediatric status epilepticus.
- 4) Develop a repository for biological specimens from patients with status epilepticus (control group) and refractory status epilepticus (rSE).

The data collection will be ongoing. There is no end date to this registry. We will follow up patients enrolled in the pSERG study 2 and 5 years after admission, and subsequently in 5 year intervals thereafter. The study follow-up may be extended.

There are 7 subjects enrolled in the study, and the enrolment has been completed.

25. CARE-E Study – PI: Dr. Huh

Cannabidiol in Children with Refractory Epileptic Encephalopathy: A Phase 1 Open Label Dose Escalation Study (CARE-E).

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Saskatchewan Health Research Foundation	\$4,500 start-up \$4,000/patient	2016 – 2022	7	7	yes	completed	N/A

This is an open label dose escalation study. The overall study is being conducted and sponsored by the University of Saskatchewan. The medical marijuana (Cannabis) Herbal Extract used in this study will be produced from the CanniMed® brand of Marijuana for Medical Purposes Regulations (MMPR) product produced by Prairie Plant Systems Inc. (PPS) who are based in Saskatoon, Saskatchewan. PPS is providing technical assistance with the production of the Cannabis Herbal Extract, but is not providing financial assistance to perform this study.

The purpose of this research study is to assess the safety and tolerability (how well a person deals with side effects) of a CBD-enriched Cannabis Herbal Extract (the study drug) in a small group of children with refractory epileptic encephalopathy. This is a pilot study, which means that it is a small-scale preliminary study. Because of the small number of participants in this pilot study, this study will not be able to determine the effectiveness of the study drug. Instead, it is hoped that the results of this study will allow us to determine appropriate dosage regimens for children, and to allow for larger clinical trials to take place.

This study will also look at:

1. The pharmacokinetics (what the body does to a drug) of the study drug;
2. How effective the study drug is at decreasing the number and duration of seizures;
3. The effect of the study drug on developmental functioning of study participants;
4. Measuring the general well-being of study participants using quality of life questionnaires.

The study was expected to enrol approximately 30 participants from 5 Canadian sites (University of Saskatchewan, University of Alberta, University of Manitoba, Université de Montréal and the University of British Columbia).

There are 7 subjects enrolled at BCCH, all of them completed the study visits according to the protocol. The data cleaning and monitoring is still underway.

26. CEEG Consortium - PI: Dr. Huh

A Critical Care EEG Monitoring Research Consortium

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A	N/A	2016 2025	All eligible	0	yes	active	N/A

The goal of this project is to collect and analyze de-identified clinical and EEG data obtained as part of routine clinical care at each center. This information will serve as preliminary data and inform the design of future studies with the following aims over the next 10 years. This is a non-interventional, observational study of patients who are undergoing cEEG monitoring in the ICU. Patients receiving video-EEG monitoring for non-emergent or non-acute reasons (e.g. characterization of chronic seizures) will be excluded from the study. ICU cEEG monitoring will be performed as clinically indicated and patients will be treated according to local standards of care at the discretion of the clinical care team. This study makes use of data already being collected as part of routine clinical care and does not involve patient or family contact. The study involves critically ill patients most of whom will not be capable of giving informed consent during their acute illness. *The study is active, without pediatric reports available so far.*

27. EPBiome Study – PI: Dr. Huh/Dr. Parfyonov

Leveraging the gut microbiota in pediatric refractory epilepsy: Safety and feasibility of oligofructose-enriched inulin supplementation for dysbiosis and seizure control

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Garfield Weston	149,206	2019-2022	75	14	yes	active	N/A

This is a two parts study: (A) Randomized, open-label, pilot study, and (B) randomized double-blind. Primary objectives include:

- To evaluate inter- and intra-patient variability in gut microbiome in epilepsy patients
- To evaluate the tolerability of inulin administration alone or in combination with the KD in patients with epilepsy
- To assess the feasibility of sample collection in this population

Secondary objectives include:

- Effects of inulin on the GM of children on KD
- Effects of inulin on seizure frequency in children with refractory epilepsy

Randomized 1:1 to receive inulin while on KD, or proceed with KD alone. The treatment duration will be 3 months, and the sample size is 75. REB submission was made to amend the study visits to be virtual instead of on site visits. *There are 14 subjects enrolled in the study, 2 in the KD arm, 6 in the epilepsy arm, and 6 controls. Seven subjects were enrolled in the last quarter.*

28. Ketogenic Diet in Infantile Spasms Study – PI: Dr. Huh

A Prospective Study of the Efficacy and Tolerability of the Ketogenic Diet in infants with Epileptic Spasms after Failure of Vigabatrin and/or Steroids

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	RDF	3,500	2018-2021	6	1	yes	active	N/A

The aim of this prospective study is to evaluate the efficacy and tolerability of the early use of the KD in infants with West Syndrome (WS) who are refractory to conventional treatments (ACTH/oral prednisolone and vigabatrin), and to monitor the safety of the KD and one-year neurodevelopment outcome. Infants will start the KD within two weeks after the failure of

vigabatrin and/or steroid therapy. The information obtained from this study will be used to optimize treatment in WS aiming to improve outcomes and thus determine whether and when the KD should be used. *There was 1 enrolment in the last quarter.*

29. VNS study - PI: Dr. Dewi Schrader; Co-PI: Dr. Connolly

Predicting Seizure Responsiveness to Neuromodulation Using Connectomic Profiling (Vagus Nerve Stimulation [VNS] Study)

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	SickKids/ CIHR	2020-2025	10	1	Yes	active	N/A

Medically intractable epilepsy is a form of epilepsy that does not get better with medication. Children with poorly controlled epilepsy may be treated with a surgical procedure called vagal nerve stimulation (VNS). VNS involves putting a device called a pulse generator inside the body which sends regular mild electrical pulses to calm down irregular brain activity that leads to seizures. The study aims to look at how VNS therapy affects seizures and health-related quality of life – quality of life questionnaires will be administered to both parents and patient, and MRI imaging will be used to quantify the effects of VNS. *There was 1 enrolment in the last quarter.*

30. COVID-19 Antibody Study - PI: Dr. Schrader

Rapid Generation of COVID-19 Therapeutics from Pediatric Donors

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	AbCellera	82K	2020 - 2022	20	21	yes	completed	

Purpose: AbCellera has built the world’s leading technology for antibody discovery and is at the forefront of developing antibody-based drugs. In this study, they will deploy this technology against the ongoing COVID-19 pandemic.

The objectives are:

- To determine B cell and antibody immunity to coronaviruses, with focus on COVID-19
- To identify antibodies that neutralize COVID-19 for use as prophylactics or therapeutics
- To identify antibodies that bind to COVID-19, for use in diagnostic tests or as tool antibodies e.g. for manufacturing release tests for vaccines against COVID-19

We propose to identify children and young adults who have recovered from a COVID-19 infection. AbCellera will screen isolated B cells and/or antibodies from the blood, sera or plasma of these anonymized donors, in order to identify antibodies against antigens to which they may have been previously exposed, including SARS-CoV-2.

We expect to enrol 5-20 subjects during one year period. We will identify and contact children and

young adults who were diagnosed with COVID-19. Blood will be drawn from individuals who consent to participate in the study at the C&W COVID-19 Collection Centre. Samples will be anonymized and sent to AbCellera. AbCellera will screen samples and identify antibodies that bind to SARS-CoV-2. Sequence data for SARS-CoV-2 relevant for that specific participant will be requested from the BC Centre for Disease Control (BCCDC). Further characterization and desired antibody properties will be defined based on the application. The current unmet need is for diagnostics, prophylactics and therapeutics. *A total of 21 subjects have been enrolled in the study, 20 subjects completed the study, 1 subject was withdrawn. The enrolment has been completed, all samples sent for analysis, and the study results are pending.* The sponsor will provide the study results in June 2022.

31. In Silico Study - PI: Dr. Schrader

Connectome-informed simulations of pediatric epilepsy surgery

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled		Approvals	Status	Abstract/Paper/Manuscript
yes	SickKids Foundation	295K	2017-2022	50 (35 cases, 15 controls)	17 cases 9 controls		Yes	Active	

Overall hypothesis is that preoperative MRI markers alone are not sufficient to predict outcome of childhood epilepsy surgery, which is *per se* an invasive procedure that induces a cascade of degenerative and plastic brain changes. Instead, preoperative indicators of outcome should be combined with models that simulate consequences of a given surgical approach based on empirical data.

Objective 1 will integrate preoperative markers and data on the actual surgery (resection extent obtained from postoperative MRI). Multi-parameter MRI will map atrophy, gliosis, and myelin changes, directly testing whether anomalies outside the resected area predict seizure relapse. Conversely, pattern analysis of memory and language fMRI will localize regions critical for performance, and test whether their resection relates to postoperative cognitive decline.

Objective 2 will longitudinally analyze feature change from pre- to postoperative MRI, mapping degeneration and functional reorganization in non-resected areas. We will develop a connectome-based framework that simulates postsurgical brain reorganization. Simulations of surgical effects are expected to improve predictive models developed in *Objective 1*.

There are 9 controls and 17 cases enrolled at BCCH, with no enrolments in the last quarter.

2.2. BRAIN INJURIES/INFLAMMATION

1. Advanced neuroimaging in pediatric stroke study - PI: Dr. Bjornson

Advanced neuroimaging in Pediatric Stroke, Pathophysiology of injury and repair in children with focal brain ischemia

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Brain Canada	27,000	2017 - 2022	90 total, 15/BCCH	19	yes	active	

Research in pediatric stroke has lagged far behind adult stroke due to a lack of use of advanced brain imaging including MRI. Post-stroke recovery is much better in the developing brain (infants and children) compared with the mature brain (adults). Insights from MRI and other brain imaging have a tremendous ability to inform us on the reasons and mechanisms for the increased recovery in the developing child's brain. Tracking the brain's anatomic and functional changes from the time of acute stroke during the first year of recovery in children suffering stroke will allow us to better understand the mechanisms of stroke injury and repair, predict outcome, and develop new strategies for brain protection and rehabilitation.

The purpose of this study is to discover mechanisms of injury and repair in children with stroke and correlate these with better and worse neurodevelopmental outcomes. The overall objective of this study is to discover mechanisms of injury and repair in children with stroke and correlate these with better and worse neurodevelopmental outcomes. Study design:

This is a prospective observational study. Each case participant will undergo MR imaging 4 times over 12 months. Each control participant will be undergo 2 hours of MR scanning, as either one or two scan sessions. The total number of study participants is 90. At BCCH, we aim for 15 study participants. *There are 16 adult controls and 3 cases enrolled in the study, with no enrolments in the last quarter.*

2. IPSS Study - International Paediatric Stroke Study; PI: Dr. Bjornson

International Pediatric Stroke Study

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	N/A	2006 2025	100	79	Yes	Ongoing	N/A

The purpose of this study is to obtain preliminary data from large multi-center studies assessing sub-types, outcomes and current treatments for newborns and children with stroke. Due to the relative rarity of childhood stroke, sufficient numbers of patients to provide the necessary power can only be achieved with multi-center and multi-national approaches.

The overall objective is to develop and conduct clinical trials in childhood stroke.

The specific aims are:

Objective 1: To ascertain in a prospective cohort study the numbers of newborns and children with ischemic stroke, their stroke sub-types and risk factors, their current treatments and outcomes within the participating centers. These data will provide the rationale and feasibility data for the study group to design and implement the initial RCT's in paediatric stroke as well as other fundable grant proposals.

Objective 2: To develop and institute standardized protocols for (1) diagnosis, (2) investigation of risk factors, (3) antithrombotic therapies and (4) outcome assessment of neonates and children with arterial ischemic stroke and sinovenous thrombosis

Objective 3: To develop standardized data forms and an appropriate database with web-based data entry from multiple study sites.

Objective 4: Submit successful grant applications for additional funding of IPSS multi-centre studies.

This prospective study will enrol newborns and children with ischemic stroke born at or referred to BC Children's Hospital. This study will then follow these newborns at 3 and 12 months post stroke. *There are 79 subjects enrolled in the study so far, with 2 enrollments in the last quarter.*

3. CFRIF Scans for Protocol Development - PI: Dr. Bjornson

Child & Family Research Imaging Facility - Scans for Protocol Development

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	N/A	2012 - 2021	200	60	Yes	Ongoing	N/A

The purpose of this study is to develop and optimize magnetic resonance (MR) imaging protocols for the 3.0 Tesla scanner located on the UBC Oak Street campus at the Children's & Women's Health Centre of BC.

Hypothesis: After optimization, we expect that the CFRIF will be able to safely and efficiently supply high-quality MR data for individual research studies.

Justification: MRI studies will enhance quantitative and dynamic assessments of tissue structure, microstructure, metabolism and function which ultimately improve early diagnosis and provide new information for treatment. Thus sequences need to be optimized and equipment tested and calibrated. We therefore require practice scans on volunteers to establish appropriate MRI scan protocols and computational approaches before we can host research studies.

Objectives: To maintain a high standard of quality, ensure safety and efficiency by developing and optimizing magnetic resonance (MR) imaging protocols for the new 3.0 Tesla scanner located on the UBC Oak Street campus at the Children's & Women's Health Centre of BC.

The study is active with 60 subjects enrolled, no enrolments during the last quarter.

4. PIBD (Pediatric Inflammatory Brain Disease) database – PI: Dr Schrader *new project this quarter*

Cerebral Brain inflammation in pediatric diseases: Development of a cross-specialty collaborative research program

Funding	Source	Amount \$	Study period	Approvals	Status	Abstract/ Paper/
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						Manuscript
yes	BCCHRI infrastructu re award	65K	2022 - 2024	QI/QA No approvals needed	active	N/A

This pilot study will develop a cross-disciplinary research approach at BCCH for the study of patients with pediatric inflammatory brain diseases (PIBD). It will benchmark the scope of the problem of PIBD across our campus and demonstrate in a pilot cohort the feasibility of patient recruitment to a centralized research registry. Participants with diagnoses of systemic lupus erythematosus, systemic autoinflammatory diseases, central inflammatory or autoimmune diseases, and obsessive-compulsive disorder will be recruited to this registry over the funding period. Cross-sectional assessments will include (a) clinician-reported disease activity or severity; (b) screening for emotional and behavioural problems and executive dysfunction; (c) patient-reported outcome measures for anxiety, depressive symptoms, stress, cognitive function, fatigue, mobility, sleep, and pain; (d) health-related quality of life; and (e) screening for adversity and resilience factors. Scores for validated outcome measures will be compared to normative population data. Exploratory analyses will evaluate associations among outcome measures. Patient/family perspectives on registry participation as well as future linked biological sample collection and neuroimaging will be determined by a study-specific questionnaire. This study will demonstrate proof-of-principle in the development of clinical and translational research capacity across pediatric subspecialties, with the goal of catalyzing new research and improving care for children with diseases affecting the brain with an inflammatory background.

The QI/QA RedCap database has been developed, and the data entry will start shortly.

5. Metagenomics and cytokine CSF Study – PI: Dr. Patel/Dr Schrader

Cerebral Fluid Metagenomics and Cytokine Profiling in Pediatric Patients with CNS Inflammation.

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Lawson	10K	2018 2022	114	27	yes	active	N/A

The purpose of this study is to characterize the causes of inflammation in patients with encephalitis through comprehensive pathogen detection method (metagenomics) and by quantifying the expression of inflammatory cytokines in cerebral spinal fluid (CSF) of children with encephalitis.

Inclusion criteria:

- 1) Age 1 month to 21 years;
- 2) Convulsive seizures at onset;
- 3) Failure of two or more antiepileptic drugs (AEDs) or requirement of any kind of continuous infusion of AEDs to abort seizures.

Specific Aims

- To define the virome (i.e., entire viral community) and microbiome (the broader community of microorganisms including viruses and bacteria) in a case-control study; including 30 CSF samples of cases with known CNS infection, 42 CSF samples of cases with IBrainD with unidentified infection and 42 CSF samples of controls with non-inflammatory CNS disorders.

- To characterize inflammation through cytokine and chemokine profiling in CSF samples of cases and controls.
- To describe the presenting clinical, EEG and neuroimaging features of cases and controls in order to define clinical phenotype and outcome in relation to aims (1) and (2).

There are 27 subjects enrolled, with no enrolments in last quarter. 19 CSF collected so far. The study has not re-started yet.

2.3. DEVELOPMENTAL MALFORMATION / NEUROMUSCULAR DISEASES

1. CNDR Registry - The Canadian Neuromuscular Disease Registry - PI: Dr. Selby

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Marigold Foundation, Jesse's Journey.	9,000/year	2011-2025	400 @ BCCH	384	yes	active	N/A

Neuromuscular Diseases (NMDs) are comprised of a group of disorders involving the central and peripheral nervous systems (brain, spinal cord, nerve roots, plexi, peripheral nerves, etc.) and smooth and/or skeletal muscle. Lack of epidemiologic data on NMDs in Canada, combined with the recognition that small, single-centre clinical studies provide inadequate sample sizes to study NMDs, and the growing international interest in NMD registries, suggest that a new, more comprehensive approach is needed in Canada. The CNDR will create a national framework to provide mutual accessibility between patients and medical scientists to facilitate clinical studies on a national level while providing access to patients from all across Canada including those in remote areas with limited access to specialized neurologic care.

The primary objective of this study is to improve the future for Neuromuscular Disease (NMD) patients through the enablement and support of research into potential treatments.

Secondary Objectives include:

- Enhancing the understanding of NMD epidemiology in Canada
- To understand variations in disease management in Canada
- Foster collaborative research initiatives amongst Canadian investigators
- Identify important research questions
- Create a tool for clinical knowledge translation allowing more uniform standards of care in Canada
- Attract international trial opportunities by making Canada more congruent with the international neuromuscular (NM) community

There are 384 subjects enrolled at BCCH site in this registry, with 3 enrolments in the last quarter.

2. Pfizer PF-06939926 Study - PI: Dr. Selby

A phase 3, randomized, double-blind, placebo-controlled study of PF-06939926 in DMD.

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Pfizer	112K/pt 24K start-up fees	2020-2026	2 @ BCCH	0	yes	To be activated shortly	N/A

The purpose of the study is to demonstrate the safety and efficacy of PF-06939926 treatment

in participants with DMD to support regulatory review for marketing authorization. The primary objective of the study is to demonstrate superior efficacy of treatment with PF-06939926 as compared to placebo based on change from Baseline in the North Star Ambulatory Assessment (NSAA).

This is a Phase 3, global, multi-center, randomized, double-blind, placebo-controlled study in ambulatory male participants, ages ≥ 4 to < 8 years, with a genetic diagnosis of DMD who are on a stable daily regimen of glucocorticoids. Eligible participants will be randomized into Cohort 1 or Cohort 2 in a 2:1 fashion and stratified by their age at Screening (< 6 or ≥ 6 years old). Study enrollment will be managed to ensure that no more than 69 participants are randomized in either of the Screening age strata. Cohort 1 (approximately 66 participants) will receive a single dose of PF-06939926 on Day 1 (Visit 3) and a single dose of placebo at Day 390 (Visit 20). Cohort 2 (approximately 33 participants) will receive a single dose of placebo on Day 1 (Visit 3) and a single dose of PF-06939926 at Day 390 (Visit 20), if they remain eligible.

Intervention Groups and Duration

In the context of this study, treatment will consist of two single intravenous infusions, one of PF-06939926 and one of placebo. PF-06939926 will be administered as a dose of $2E+14$ vg/kg. The term investigational product (IP) is used to refer to either PF-06939926 or placebo. A single intravenous infusion of IP will be delivered over approximately 2 to 4 hours with the timing and sequence as follows:

- Cohort 1 will receive a single dose of PF-06939926 on Day 1 (Visit 3) and a single dose of placebo at Day 390 (Visit 20);
- Cohort 2 will receive a single dose of placebo on Day 1 (Visit 3) and a single dose of PF-06939926 at Day 390 (Visit 20), if they remain eligible.

All participants will be followed for 5 years after the administration of PF-06939926 such that total time on study will be approximately 5 years for Cohort 1 and 6 years for Cohort 2.

The study will be closing shortly at BCCH site, due to adverse events in subjects at other participating sites.

3. Biogen CS11 Study - PI: Dr. Selby

An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract / Paper/ Manuscript
yes	Biogen	75K/pt 29K start-up fees	2016 2023	5 @ BCCH	4	yes	active	N/A

This randomized, double-blind, sham-procedure controlled study will test the clinical efficacy, safety, tolerability, and pharmacokinetics of intrathecal ISIS 396443 over 13 months.

The primary objective is to evaluate the long-term safety and tolerability of ISIS 396443 administered intrathecally (IT) to patients with SMA who previously participated in investigational studies of ISIS 396443. The secondary objective is to examine the long-term efficacy of ISIS 396443 administered intrathecally to patients with SMA who previously participated in

investigational studies of ISIS 396443. The tertiary objective is to examine the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ISIS 396443 administered intrathecally to patients with SMA who previously participated in investigational studies of ISIS 396443.

The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of ISIS 396443 (12 mg) administered as intrathecal injections by lumbar puncture (LP) in subjects who previously participated in investigational studies of ISIS 396443. Up to 274 subjects who previously participated in investigational studies may be eligible to enroll into this study. The sample size is based solely on the number of subjects enrolled in ISIS 396443-CS3B, ISIS 396443-CS4 and ISIS 396443-CS12 studies who may be eligible for participation in this study. *There are 4 subjects enrolled in the study.* One subject has been transferred to BCCH from another site. The enrollment has been completed. The sponsor announced the study closure in 2023.

4. Biogen DEVOTE Study - PI: Dr. Selby

An Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	Biogen	49K/patient 20K start-up fees	2021 2025	3 @ BCCH	0	yes	active	N/A

This is a 3-part (Parts A, B, and C) study in which participants will be followed for approximately 10 months after the first dose of study treatment. Following the completion of this study, all eligible participants may elect to enroll in a separate open-label long-term extension study, pending study approval by ethics committees and the appropriate regulatory authorities. In regards to participants rolling over from Part B, this will be done without unblinding the participant's treatment group.

Part A will be conducted in participants with later-onset SMA who are 2 to 15 years of age, inclusive, for the purpose of evaluating adverse events (AEs). Part B will include participants with both infantile-onset SMA (≤ 7 months of age) and later-onset SMA (2 to < 10 years of age). Part C will enrol participants of all ages with SMA who have been receiving nusinersen treatment for at least 1 year prior to entry in this study. This part is designed to evaluate the safety of transitioning participants from the currently approved dosing regimen to the high dosing regimen in a representative patient population.

Primary Objective: To examine the clinical efficacy of nusinersen administered intrathecally at higher and less frequent doses to participants with SMA. Primary Objective is to evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized myasthenia gravis (gMG) based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

Secondary Objectives:

- To examine the safety and tolerability of nusinersen administered intrathecally at higher and less frequent doses to participants with SMA
- To examine the effect of nusinersen administered at higher and less frequent doses compared to the currently approved dose in participants with SMA.

The study is active. There are no enrolments yet.

5. FGL-3019-094 Study - PI: Dr. Selby- *closed study this quarter*

A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in ambulatory subjects with Duchenne Muscular Dystrophy (DMD)

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	FibroGen Inc.	124.8K/patient 27.3K start-up fees	2022 2026	2-3 @ BCCH	0	N/A	N/A	N/A

This is a global, randomized, double-blind, trial of pamrevlumab or placebo in combination with systemic corticosteroids in subjects with Duchenne muscular dystrophy, aged 6 to <12 years (ambulatory subjects only). Approximately 70 subjects will be randomized at a 1:1 ratio to Arm A (pamrevlumab + systemic deflazacort or equivalent potency of corticosteroids administered orally) or Arm B (placebo+ systemic deflazacort or equivalent potency of corticosteroids administered orally), respectively.

Study Objective: To evaluate the efficacy and safety of pamrevlumab versus placebo in combination with systemic corticosteroids administered every two weeks in ambulatory subjects with Duchenne muscular dystrophy (age 6 to <12 years).

Dose and Mode of Administration:

Pamrevlumab (or placebo): 35 mg/kg IV, Day 0 and every 2 weeks thereafter with the last dose at week 52. Subjects will receive up to 27 infusions over the course of the main study.

Systemic Corticosteroids: Systemic deflazacort or equivalent potency of corticosteroids administered orally.

The sponsor walked away, and the study has been inactivated at our site.

6. Italfarmaco Study – PI: Dr. Selby

Randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	Italfarmaco	32K/patient 44K start-up fees	2018 2021	5 @ BCCH	10	yes	active	N/A

The Primary objective:

- To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD subjects.

Secondary objectives:

- To assess the safety and tolerability of givinostat versus placebo administered chronically in DMD subjects.
- To evaluate the pharmacokinetic (PK) profile of givinostat administered chronically in the target population;
- To evaluate the impact on quality of life and activities of daily living of givinostat versus placebo administered chronically.

Secondary exploratory objectives:

- To evaluate the correlation between PK profile of givinostat and pharmacodynamics (PD) data;
- To explore whether the effects of givinostat versus placebo administered chronically may be related to the type of DMD mutation or to the biomarkers.

There are 10 subjects enrolled in the study, 6 of them were screen failures because they didn't meet the inclusion criteria. Four participants have completed the study and transitioned to the open label study. The enrolment has been completed.

The study was audited by the sponsor, and we passed the audit successfully. The auditor stated that in her 30 years of experience, this is the first audit completed without any findings.

7. Italfarmaco Open Label Study – PI: Dr. Selby

Open label, long-term safety, tolerability, and efficacy study of GIVINOSTAT in all DMD patients who have been previously treated in one of the GIVINOSTAT studies

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	Italfarmaco	18K/patient 50K start-up fees	2020 2025	5 @ BCCH	4	yes	active	N/A

The Primary objective:

- To assess the long-term safety and tolerability of GIVINOSTAT in patients with DMD following core protocols program and with naïve GIVINOSTAT DMD subjects, i.e. subjects screened in study DSC/14/2357/48 who met:
 - all the inclusion criteria and none of the exclusion criteria, and
 - never been randomized because the enrollment in the off-target group was completed.

Secondary objectives:

- To evaluate the effects of long-term administration of GIVINOSTAT on muscular function and strength;
- To evaluate the effects of long-term administration of GIVINOSTAT on respiratory function;
- To evaluate the impact on daily activities and quality of life following longterm administration of GIVINOSTAT.

There are 4 subjects enrolled in the study. The enrolment has been completed. The study patients are followed up according to the protocol.

8. Vision DMD Study - PI: Dr. Selby *closed this quarter*

A Phase IIb Randomized, Double-blind, Parallel Group, Placebo- and Active-controlled Study with Double-Blind Extension to Assess the Efficacy and Safety of Vamorolone in Ambulant Boys with Duchenne Muscular Dystrophy (DMD)

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	ReveraGen.	16,500 start-up fees 28K/subject	2018 2022	6	6	yes	closed	N/A

This Phase IIb study is a randomized, double-blind, parallel group, placebo and active-controlled study to evaluate the efficacy, safety, PD, and population PK of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg versus prednisone 0.75 mg/kg/day and placebo over a Treatment Period of 24 weeks, and to evaluate persistence of effect over a Treatment Period of 48 weeks in ambulant boys ages 4 to <7 years with DMD.

Primary objectives include:

- To compare the efficacy of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 24-week treatment period vs. placebo in ambulant boys ages 4 to <7 years with DMD,
- To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg in ambulant boys ages 4 to <7 years with DMD.

There are 6 subjects enrolled in this study, and the enrolment was completed. Five subjects completed the study and transitioned to the OL Expanded Access study, one subject was withdrawn due to adverse event. The study was closed this quarter.

9. VBP15-006 Study - PI: Dr. Selby – *new study this quarter*

A Phase II Open-Label, Multiple Dose Study to Assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys ages 2 to <4 years and 7 to <18 years with Duchenne Muscular Dystrophy (DMD)

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	ReveraGen.	13K/pt 13K start-ups	2022 2025	6	2	yes	active	N/A

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, physical functioning, and sleep-wake activity of vamorolone over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

Primary Objective: To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD.

Secondary Objectives:

1. To evaluate the pharmacokinetics (PK) of vamorolone administered orally in boys ages 2 to <4 and 7 to <18 years with DMD.
2. To confirm the vamorolone exposure in boys ages 2 to < 4 and 7 to 18 years with DMD at 2.0 and 6.0 mg/kg and to adjust the doses if appropriate to achieve similar vamorolone AUCs across the entire pediatric age range.

Research design: The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a 4-week open-label Dose-tapering Period (Weeks 13-16) for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study.

The study has been approved by REB, and is currently opened for enrolment. *Two subjects have been enrolled in the last quarter.*

10. Vamorolone OL Expanded Access Study - PI: Dr. Selby

An Open-Label, Expanded Access Protocol for Boys with Duchenne Muscular Dystrophy who have Completed the Long-Term Extension (VBP15-LTE) or VBP15-004 Studies

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
yes	ReveraGen.	10K	2019-2023	6	7	yes	active	N/A

The intent of this protocol is to provide continued access to vamorolone for subjects who have completed the VBP15-004 protocol during the time that VBP15-004 is ongoing, and while a new drug application for vamorolone is under preparation and review. The patients will receive standard of care treatment and procedures for management of DMD. The condition of the subjects will be monitored by their treating physician, according to standard of care clinical practice. Adverse events (AEs) and Serious adverse events (SAEs) must be reported in the OpenClinica eCRF. Approximately 30-40 subjects in Canada will be eligible for enrolment, 4-5 of them at BCCH. *There are 7 subjects enrolled so far, 5 of them transitioned from the Vision DMD study, and 2 subjects got transferred from Calgary. The enrolment has been completed. The study patients are being followed up according to the protocol.*

11. PTC-016 Study – PI: Dr. Selby

An open-label, safety study for previously treated ataluren (ptc124) patients with nonsense mutation dystrophinopathy

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript

yes	PTC Therapeutics Inc.	19,485 start-up 3,556/subject	2017 2027	160 total 5 @ BCCH	5	yes	active	N/A
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The objective of this study is to assess the safety and tolerability of 10, 10, 20 mg/kg ataluren in subjects with nmDBMD who had prior exposure to ataluren in a PTC sponsored clinical trial or treatment plan.

The patient is required to complete a visit at the clinical research facility every 48 weeks. Every 24 weeks the patient is required to visit their local PCP for a weight check. A study drug shipment will be sent to the patient/caregiver's home every 12 weeks. Phone conversations by the investigator site will be conducted every 12 weeks (post-drug dispensing) to confirm drug receipt and to monitor and capture adverse events and use of concomitant medications

There are 5 subjects enrolled in this study. One of them withdrew from the study. The enrolment has been completed. Patients are followed up according to the study protocol.

2.4. NEURO-ONCOLOGY

3. ONGOING RETROSPECTIVE STUDIES

3.1. EPILEPSY

1. ShutEye study - PI: Dr. Boelman/Dr Jeffers

Eye-Closure Induced Paroxysms on First EEG as Diagnostic for Eyelid Myoclonia with Absences and Pharmacoresistant Epilepsy.

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2015-2022	yes	100	active	N/A	N/A

The purpose of this study is to identify, via retrospective review of charts and EEG reports, ECP as a sensitive and specific EEG feature of EMA which can be identified on the first EEG study of children presenting with CAE-like epilepsy. This information will inform future designation of epilepsies presenting as either EMA or CAE. The utility of this information lies in the circumvention of pharmacoresistance.

The primary hypothesis of this study is that ECP is a sensitive and specific EEG feature of EMA that can be identified in the first EEG study of children presenting with CAE-like epilepsy. The secondary hypothesis is that ECP predicts pharmacoresistance.

This study is a retrospective chart and EEG review of cases of EMA diagnosed between 2005-2015, compared with a matched control group of patients diagnosed with childhood absence epilepsy on their first EEG study at BC Children's Hospital. *The study is active.*

2. Adult TSC study - PI: Dr. Connolly

Clinical characteristics and multidisciplinary care for adults with tuberous sclerosis complex

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	42 at BCCH	active	N/A	N/A

The overall goal of this study is to examine a large series of adults with TSC (tuberous sclerosis complex) at multiple centres (University of Montreal, University of Toronto, University of Ottawa, and Western University in London, Ontario, and University of British Columbia - BCCH). We hypothesize that children most severely affected with TSC unfortunately are less likely to survive into adulthood. In addition, cases of TSC that are diagnosed only in adulthood are often more mildly affected individuals.

Objectives:

- Describe the clinical characteristics of adults with TSC who are followed at the BCCH TSC clinic.
- Describe the quality of the multidisciplinary care provided to people with TSC and the degree to which this follows current consensus recommendations.

The chart review has been completed for the BCCH site. .

3. CC following VNS in children with LGS study - PI: Dr Connolly

The added value of Corpus Callosotomy (CC) following Vagal Nerve Stimulator (VNS) implantation in children with Lennox-Gastaut Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021- 2023	yes	5-6	active	N/A	N/A

Goals:

- The primary goal is to assess the efficacy of CC following prior VNS in children with LGS.
- The secondary goal is to assess the safety of CC following prior VNS.

Study design: This is a multicenter, multinational retrospective study. All LGS patients who had VNS procedure performed followed by CC between January 1, 1990 to August 18, 2021 at BC Children’s Hospital (BCCH) will be identified. Epidemiological and clinical data will be collected by review of patient records by the study investigators and the study coordinator. *The chart review has been completed at this site.*

4. Clinical experience with Briv. at BCCH study - PI: Dr. Datta

Clinical Experience with Brivateracetam in the Pediatric Population at BC Children’s Hospital

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2023	yes	10	active	N/A	N/A

The safety and efficacy of brivaracetam has not been established in patients younger than 16 years of age. However, as with many new anti-seizure drugs on the market, it is often used off-label in children, especially in those with treatment resistant epilepsy who have not responded to other medications. Open-label post-marketing studies can be very important to clinicians by providing additional information on efficacy and safety of the newer drugs in the “everyday” clinical setting. In addition, children are a unique population that may respond differently to a drug than adults. Therefore, we would like to review the experience with this new anti-seizure medication for pediatric patients treated at BC Children’s Hospital. All patients prescribed Brivateracetam between July, 2018 and June 2020 at BC Children’s Hospital (BCCH) will be identified. A retrospective case series will be performed. Responder rate will be defined as the proportion of patients who experience a 50% reduction in seizure frequency, retention on treatment and adverse effects leading to withdrawal. All patients treated with brivateracetam at BCCH from July 1, 2018 to June 1 2020. There will be approximately 10 patients included in the study. *The study is active.*

5. CBD Postal Code Study - PI: Dr. Datta

The socio-demographic impact on the use of CBD for pediatric epilepsy in British Columbia

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2023	yes	131	active	N/A	N/A

Purpose: Although there is recent evidence that CBD can be effective for the treatment of seizures, at present, the cost is not covered for patients, unlike other anti-seizure medications. The purpose of this study is to determine if CBD use, including duration of use, dosage (mg/kg), the formulation, and benefit from CBD for pediatric epilepsy varies among different socio-demographic areas. This will be determined by correlating clinical data with postal codes linked to census data, using Statistic Canada’s Postal Code Conversion File.

Hypothesis: The use of good formulation of CBD, longer duration of use and sustained benefit of CBD will be more prevalent in more affluent neighbourhoods, as at present, the cost is not covered for families, unlike other anti-seizure medications.

A retrospective chart review of children with epilepsy who are on CBD or have trialled CBD from 2014 to June 1, 2021. Patients will be identified from the EEG database. We anticipate to include 131 patients in this study. *A total of 111 charts have been reviewed so far.*

6. Trisomy 21 patients multicentre study - PI: Dr. Datta

Multi-centre study retrospective study: Comparison of treatment-response of Trisomy 21 patients with infantile spasms to first-line vigabatrin or hormonal therapies

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2024	pending	100 25@ BCCH	active	N/A	N/A

Purpose: In this retrospective study, patients with Trisomy 21 syndrome with infantile spasms will be reviewed from the time frame of January 1, 2000 to June 1, 2021. The purpose of this study will be to compare the treatment response of first-line vigabatrin to first-line hormonal therapy for patients with Trisomy 21 and infantile spasms.

Hypothesis: T21 patients treated with hormonal therapy first-line for infantile spasms will have a better treatment response than patients treated with vigabatrin first-line. Better treatment response includes: 1) shorter time frame for clinical and EEG resolution of infantile spasms, 2) reduced occurrence of infantile spasm relapse, and 3) less subsequent epilepsy.

Methodology: A retrospective multi-center chart review of children with T21 and infantile spasms from January 1, 2000 to June 1, 2021. Including all centers, we anticipate to include 100 patients in this study; 50 treated with first-line hormonal therapy and 50 treated with first-line vigabatrin. Specifically, from BC Children's Hospital (BCCH), we anticipate 25 children. *The study is active.*

7. Five Year JAE Study - PI: Dr. Datta

Five year follow up of patients with juvenile absence epilepsy and EEG prognostic features

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	1000	active	N/A	N/A

The purpose of the study is to determine if there are clinical and EEG predictors to determine the prognosis of patients with juvenile absence epilepsy 5 years after diagnosis.

We hypothesize that most patients with juvenile JAE will require anti-seizure medications for seizure-control at 5 years. Approximately half will have good seizure control with medication. Those that had a trial of weaning off medications will have a high risk of seizure relapse and may not have the same response to an anti-seizure medication after re-initiation. A small percentage will be seizure free after weaning medications.

The outcome measures at 5 years will include: 1) number of patients requiring seizure medications, 2) number of patients who are seizure-free on medication, 3) number of patients who are seizure-free off medication, 4) number of patients continuing medication after an attempted wean off

medication, and 5) number of patients who are treatment-resistant. *The chart review is in progress.*

8. Pooled Perampanel Analysis study - PI: Dr. Datta

Global pooled analysis of perampanel real-world data

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	30	active	N/A	N/A

The purpose of the pooled analysis will be to evaluate the effectiveness and safety/tolerability of perampanel in patients with epilepsy. The primary endpoints include:

- 1-year retention rate
- 1-year seizure-freedom rate (≥ 6 months)
- Incidence and types of adverse events (adverse events will be categorized using MedDRA classification)

The study population includes patients treated with PER at BCCH and ACH from July, 2014 to February 2015. There will be approximately 30 patients included in the study. *The chart review is in progress.*

9. Focal Spikes Study - PI: Dr. Datta

The location of focal spikes on EEG to predict epilepsy and neuro-development

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	1000	active	N/A	N/A

A retrospective chart review and analysis of existing EEG data available at BC Children’s Hospital (BCCH).

Purpose: The purpose of the study is to determine the significance of focal pediatric EEG spikes in various localizations (frontal, temporal, midline, parietal and occipital lobes) to predict the risk of epilepsy, neuro-imaging abnormalities, and neuropsychiatric co-morbidities, such as developmental delay and difficulties with school performance.

Hypothesis: Patients with frontal spikes will have a significantly higher risk of developing epilepsy than those with focal spikes in other regions.

Although EEG findings may be important in children to predict subsequent epilepsy after a first unprovoked seizure, their significance can be improved when associated with imaging findings. We anticipate more focal lesion in the frontal and temporal lobe and more diffuse or non-localized imaging abnormalities in other lobes.

We anticipate a high degree of neuro-psychiatric co-morbidities in patients with focal spikes, especially frontal and temporal spikes (due to connections with the pre-frontal cortex and limbic systems), including in those without seizures. *The chart review is in progress.*

10. ESL Study - PI: Dr.Datta

Clinical experience with eslicarbazepine after trials of carbamazepine and oxcarbazepine in children in two Canadian centers

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	30	active	N/A	N/A

Purpose: The purpose of the study is to assess the efficacy, safety and tolerability of ESL in patients transitioning from CBZ or OXC to ESL due to lack of efficacy, poor tolerability or poor compliance, by performing a retrospective chart review of children treated with ESL in two Canadian Pediatric tertiary care centers.

Hypothesis: ESL will be efficacious and generally well tolerated in pediatric patients transitioning from CBZ or OXC in clinical practice due to inadequate seizure control or intolerable AEs with these agents.

Population: All patients treated with ESL at BCCH and Children’s Hospital of Winnipeg will be included. There will be approximately 30 patients included in the study. The date range of the charts to be included in this research proposal is from 1999 to 2020. *The chart review is in progress*

11. LKS & ESES Study - PI: Dr. Datta –new ESES component added to this study

Long-term follow up of electro-clinical features of patients with Landau-Kleffner Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	30	active	N/A	N/A

Purpose: The aim of the study is to retrospectively analyze the electro-clinical features, etiology, treatment, and prognosis of patients with Landau–Kleffner syndrome (LKS) and ESES with a long-term follow-up from 2-20 years.

Hypothesis: Patients treated with LKS and ESES will likely good have good prognosis regarding seizure control and improvements on EEG at follow-up. However, despite seizure control, they may continue to have language, behavioral, sleep and cognitive issues long-term. Adequate and early treatment may reduce or prevent some of the language and cognitive deterioration.

Methodology: A retrospective EEG, database and chart review of children with LKS and ESES who had an EEG at BCCH from 1992 to January 2020. *The study is active.*

12. Down Syndrome study - PI: Dr. Datta/Dr. MacDonald-closed this quarter

Clinical and electrographic features of epilepsy in Down Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2019-2022	yes	20	active	N/A	N/A

This study will review all Down syndrome patients aged 0-19 who have had an EEG recording at BC Children’s Hospital from January 1992 to July 2019. The purpose of this study will be to describe clinical features, including age of seizure onset, semiology of seizure, number of medications trialed, comorbidities, neuro-developmental and seizure outcomes and EEG characteristics in order to aid clinicians with a more complete overview of the clinical and electroencephalographic features of Down syndrome. We will also determine if there are EEG findings that can predict clinical outcome. The results from this study will provide information on the EEG features of patients with DS and seizures. The findings will potentially provide

information on the natural history of EEGs and seizures in patients with DS over several decades and inform clinicians about potential EEG findings that can predict clinical outcome. *The chart review is ongoing.*

13. SUDEP 2019 study - PI: Dr. Datta

The relationships of Spike wave index count on EEG and Sudden Unexpected Death in Epilepsy

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2022	yes	60	active	N/A	N/A

This study is a retrospective chart review and analysis of existing EEG data available at BC Children’s Hospital. The purpose of the is to determine if the quantity of inter-ictal spikes on EEG can be predictive of Sudden Unexpected Death in Epilepsy (SUDEP). Inter-ictal spikes are brief paroxysmal electrographic discharges observed between spontaneous recurrent seizures in epileptic patients. They provide information about localization of seizures and a high number of spikes can be suggestive of sub-optimal seizure control.

We hypothesize that patients with SUDEP will have a significantly higher quantity of inter-ictal spikes, (SWI) in comparison to control patients with treatment resistant epilepsy who did not die of SUDEP, as in increased quantity of inter-ictal spikes can be suggestive of sub-optimal seizure control In addition, as previously reported by some, we expect post-ictal suppression (voltage attenuation on the EEG after a seizure lasting for 1 second or more) will correlate with an increased incidence of SUDEP.

The results from this study will provide additional risk factors or predictors for SUDEP, a condition where little is still known, especially in the pediatric population. *The chart review is in progress.*

14. KD Age Spasms Study - PI: Dr. Datta

Response to the Ketogenic Diet in refractory infantile/epileptic spasms

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2018 - 2022	yes		active	N/A	N/A

Retrospective chart review of patients with infantile/epileptic spasms treated with the ketogenic diet at BC Children’s Hospital (BCCH). No patient contact.

The purpose of the study is to determine if the efficacy of the ketogenic diet (KD) in refractory infantile/epileptic spasms (IS/ES) varies depending on the age the KD is initiated and if hypsarrhythmia is present on EEG or not. We will identify all patients with refractory IS/ES treated with the KD at BCCH from January 1, 2012 to September 15, 2018, to determine if the age at initiation of KD and presence of hypsarrhythmia will predict the degree of response in reducing or eliminating seizures.

Hypothesis

Based on our clinical experience and review of the literature, we hypothesize that in IS/ES refractory to first line therapies, the KD is not as effective when initiated under the age of 12 months, regardless of etiology. However, if the diet is initiated in patients older than 12 months, there will be better response with seizure freedom or >50% reduction in seizures.

Research Design & Methodology

A retrospective chart review for all patients with infantile or epileptic spasms treated with the ketogenic diet by the BC Children's Epilepsy Service from January 2012 - September 2018 will be performed. *The chart review is in progress.*

15. School Study - PI: Dr. Datta

School Performance at the time of the first EEG and Follow-up

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2023	yes		active		N/A

Purpose: The purpose of the study is to determine if there are differences in school performance difficulties between patients with seizures and patients without seizures at the time of a first EEG. For patients with 2 to 4 year follow-up at BCCH, we also aim to determine if school performance changes over time and if school difficulties are more prevalent in patients with seizures compared to children without seizures (with other chronic medical conditions). Finally, we want to compare children with seizures and children without seizures, but psychiatric disorders with 2-4 years of follow-up at BCCH to see determine if there is a difference in school performance difficulties at baseline and follow-up between these two groups. Chronic psychiatric disorders include mood, psychotic, eating disorders, etc.

Hypothesis: Approximately 30% of patients who have a first EEG will have confirmed seizures. The remainder of patients will not have seizures, but will have an EEG to characterize various paroxysmal events, such as headaches, movement disorders, psychiatric conditions or to assess level of consciousness.

At the time of the EEG, it is hypothesized that approximately a third of children with and without seizures will have difficulties with school performance. However, at 2-4 years, children with seizures will have significantly more school performance difficulties, related to various aspects, including ongoing seizures, seizure medications and missed school days than children without seizures, but other chronic medical conditions. Subsequently, children with seizures and children with psychiatric disorders that are followed at BC Children's Hospital for 2-4 years will be compared. It is hypothesized that children with seizures and chronic psychiatric disorders will have similar levels of difficulties with school performance at baseline and follow-up.

A retrospective EEG, database and chart review of children who had a first EEG at BCCH from 2015 to 2017 who are of school age. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. *The study was approved and initiated this quarter.*

16. Parietal Spikes Study - PI: Dr. Datta

Predictive Value of Parietal Spikes on EEG in the Pediatric Population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021 - 2023	yes	400	active		N/A

The purpose of the study is to determine the frequency and predictive value of parietal spikes on EEG in the pediatric population. There is currently little data on the significance of parietal

spikes on EEG. We will identify EEG's of pediatric patients with isolated parietal spikes over 20 years at BCCH and compare them to a control group (a random sample of patients who had an EEG at BCCH) to determine if isolated parietal spikes can help to predict clinical, seizure and developmental outcome.

A retrospective EEG, database and chart review of children who had an EEG with isolated parietal spikes. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. We will include 200 study patients and 200 control patients. *The study was approved and initiated this quarter.*

17. Brivateracetam Study - PI: Dr. Datta

Clinical Experience with Brivateracetam in the Pediatric Population in two Canadian Centers

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/Paper/Manuscript	Funding
2018 - 2022	yes	4	active		N/A

Brivaracetam was granted FDA approval as an add-on therapy in February 2016. It is indicated as adjunctive therapy for treating adults and adolescents 16 years of age or older with epilepsy. The safety and efficacy of brivaracetam has not been established in patients younger than 16 years of age. We would like to review the experience with this new anti-seizure medication for pediatric patients treated at BC Children's Hospital and Alberta Children's Hospital. All patients prescribed Brivateracetam between February, 2016 and July, 2018 at BC Children's Hospital (BCCH) and Alberta Children's Hospital (ACH) will be identified. A retrospective case series will be performed. *The chart review is underway.*

18. MRI FCD Epilepsy Study – PI: Dr Schrader

The use of advanced MRI analysis techniques to improve the detection of focal cortical dysplasia in children with partial epilepsy on clinical scans.

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/Manuscript	Funding
2020-2022	yes	200	active	N/A	N/A

The purpose of this study is to improve the detection of FCD in children with pharmaco-resistant epilepsy using advanced image processing techniques. We anticipate that these techniques will improve FCD detection, particularly in “MRI-negative” cases. We hypothesize that FCD's that are missed on visual inspection of MRI of the developing brain will be detected by advanced MRI analysis techniques.

The specific aims include:

- To determine if the advanced automated MRI techniques designed for the detection of focal cortical dysplasia in adults can be applied to the developing brain by testing them on MRI-positive cases of histopathologically-proven focal cortical dysplasia in children. To determine if these advanced MRI techniques can be used to identify histopathologically proven areas of focal cortical dysplasia that were previously missed on visual inspection of conventional MRI.
- To determine if the application of these advanced MRI techniques to new cases of refractory partial epilepsy improves the detection of focal cortical dysplasia.

Research design: We will apply methods that were previously developed in the Neuroimaging of Epilepsy Laboratory to existing clinical MRI scans. *The study is active.*

3.2. BRAIN INJURIES/INFLAMMATION

3.3. DEVELOPMENTAL MALFORMATION / NEUROMUSCULAR DISEASES

1. Muscle Gene Panel Testing Study – PI: Dr Selby

Retrospective analysis of diagnostic outcome of muscle gene panel testing in children presenting with suspected neuromuscular disease at BCCH

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2019 - 2022	yes	150	active	N/A	N/A

The purpose of this study is to examine the diagnostic outcome of muscle gene panel testing and determine the associated impacts on clinical management for children presenting with a possible neuromuscular disease at BCCH.

We hypothesize that the introduction of muscle gene panel testing has increased the proportion of patients with a definitive genetic molecular diagnosis and that identification of new genetic diagnoses has altered clinical management.

The objectives are to quantify the proportion of patients for which muscle gene panel testing provided a definitive diagnosis and to determine whether early genetic testing shortens the diagnostic process and/or changes management in patients presenting with suspected neuromuscular disease.

Analysis of Data: Genetic testing results will be categorized based on whether they provide definitive causal mutations, variants of unknown significance, non-causal (benign) mutations or no abnormality found. The genetic results will then be incorporated into the clinical context where we will determine whether the genetic diagnosis is congruent with the clinical phenotype. We will also review the sequence of diagnostic investigations to determine when in the diagnostic process the patient received genetic testing, and if genetic testing altered clinical management. *The study is active.*

2. Impact of Genetic Testing Study – PI: Dr Selby

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2020 - 2023	yes	180	active	N/A	N/A

The purpose of this study is to examine the impact of genetic testing on the diagnosis and further investigations completed in children with suspected neuromuscular disorders who have presented at BCCH between 01 May 2017 and 20 May 2020.

We hypothesize that the introduction of genetic testing early on in the diagnostic odyssey increases the proportion of patients who can be given a definitive diagnoses, improves our understanding of the expanded phenotype and genotype in neuromuscular diseases in childhood and allows for improved management and clinical care.

This study serves as a retrospective analysis in patients presenting at BCCH with a suspected neuromuscular disorder, including a review of their diagnostic journey and the rate of positive diagnosis that the muscle gene panel performed at Sherbrooke Genomic Medicine has allowed, and also the additional ability to get whole exome sequencing and in some cases whole genome

sequencing and how this has also further expanded our understanding and contributed to our interpretation of the pathological findings on muscle biopsy. We also understand that due to limitations in our current knowledge base, genetic testing will yield variants of uncertain significance (VUS), which currently have unknown pathogenicity. The diagnostic yield of these variants will need to be reviewed over time as our collective knowledge base expands.

Primary outcome measure: Determining the diagnostic yield of the gene panel testing (i.e. the percentage of patients for which a definitive diagnosis was reached after genetic testing).

Secondary outcome measures:

- 1) time taken to reach diagnosis
- 2) investigations required to reach diagnosis
- 3) outcomes of diagnosis in terms of changes in clinical management. *The study is active.*

3. AFP Study – PI: Dr Selby

Acute Flaccid Paralysis in Canadian Children: Evaluation of etiological factors and response to therapy

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/Manuscript	Funding
2018-2022	yes	6	active	N/A	N/A

Between the months of August and October 2014, a cluster of children suffering from acute onset flaccid paresis was identified in North America, all with MRI findings suggestive of poliomyelitis. Despite the relatively uniform clinical presentation and MRI findings, no single specific pathogen has been implicated. Because of the uncertainty regarding pathogenesis, the optimal treatment in the acute phase remains unknown. To identify the clinical features and characteristics of the non-polio/enterovirus-associated acute flaccid limb weakness cases in Canada in 2014, we conducted a comprehensive chart review study and reported the clinical spectrum and neuroimaging findings, treatments and clinical outcomes in children presenting to participating Canadian institutions with this clinical phenomenon. After their initial episode, a majority of the patients had recovered completely by the time of their last clinic follow-up but a few still had persistent deficits or disability.

Since the late summer of 2018, there has been an apparent increase in the number of children presenting with acute limb weakness in several Canadian provinces, including Ontario, Quebec and Manitoba. To extend our previous study of enterovirus associated-AFP, we will conduct a retrospective chart review of patients in the AFP cohort in 2014 as well as the recent AFP cases in Canada. Findings from this study will help provide insights into the epidemiology and clinical implications of enterovirus infection in pediatric AFP.

The aim of the study is:

- To perform detailed clinical review of a large cohort of well characterized, geographically diverse pediatric patients with non-polio AFP.
- To perform detailed assessments of demographic and clinical information.
- To establish a detailed demographic and clinical patient database. *The study is active.*

4. Nusinersen respiratory outcomes study – PI: Dr. Wright/Dr. Selby

Respiratory outcomes in children with 5q Spinal Muscular Atrophy types 1 and 2 treated with nusinersen

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2020-2022	yes	23	active	N/A	N/A

The aim of the study is to determine whether respiratory health is improved in patients with SMA treated with nusinersen. As nusinersen therapy has been found to result in significantly improved motor function, we hypothesise that its use will also be associated with improvement in markers of respiratory health, and hospitalization for respiratory illness. This will be a retrospective observational chart review of children <18 years of age diagnosed with SMA managed at BCCH and treated with nusinersen from January 1st 2016 to April 30th 2020. *The study is active.*

5. Lipids study – PI: Dr Selby

Abnormal lipids in Children with Duchenne Muscular Dystrophy: A contributing factor to muscle weakness

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2021-2024	yes	70	active	N/A	N/A

The purpose of this retrospective study is to characterize the frequency and type of dyslipidemia in a cohort of children in British Columbia with DMD and to determine the relationship with DMD disease severity, specific genetic mutation and treatment received. We will also review markers of liver function and liver ultrasound findings where available.

Hypothesis: We hypothesize that children with DMD will have high rates of dyslipidemia and demonstrate evidence of a primary dyslipidemia.

Objectives:

- To describe the frequency and type of dyslipidemia at presentation and during treatment in children with DMD.
- To describe markers of fatty liver disease (liver enzymes, liver ultrasound findings) in children with DMD.
- To explore the relationship between the observed genetic mutations in these children with DMD, level of physical ability and any observed lipid abnormalities.

This study is a retrospective chart review of all patients with DMD followed in the BCCH neuromuscular diseases program at BC Children’s Hospital that have had a lipid panel performed as part of their care. *The study is approved by REB, and the chart review is underway.*

3.4. NEURO-ONCOLOGY

1. Ependymoma Study 2014 - PI: Dr. Hukin

Discerning treatment implications of ependymoma subgroups

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
2014-2022	yes	80	active	N/A	no

Ependymoma is the third most common brain tumour of childhood. It arises anywhere along the neuroaxis. Recent integrative genomics have revealed that several distinct subgroups of ependymoma exist, particularly in the posterior fossa, where two distinct subgroups termed PFA (Posterior Fossa A) and PFB (Posterior Fossa B) exist. These two subgroups have very different clinical outcomes and genomic landscapes.

Objective: We would like to evaluate whether adjuvant radiation therapy is beneficial in patients with PFA ependymoma who underwent subtotal resection.

Hypothesis: We have preliminary data that suggest that PFA ependymoma with subtotal resection have poor survival whether they receive radiation therapy or not. Moreover, we have preliminary data that suggests that PFB ependymoma are commonly salvageable at the time of recurrence whether they received radiation at diagnosis or not. This suggests that a proportion of PFB's may not require any additional therapy after surgery.

Methods: In order to extend these findings, we are assembling a validation cohort of de-identified clinically annotated cases diagnosed up to 2014 (age, extent of resection, pattern of recurrence, treatment, event free survival and overall survival) to determine if these findings are applicable across several centres. *The study is active.*

2. Infant relapse medulloblastoma study – PI: Dr. Hukin

Can we salvage young children with relapse medulloblastoma after initial radiation sparing approaches?

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A.	N/A	2020 2023	70 total 10 @ BCCH	0	yes	active	N/A

Background and Rationale: The management of medulloblastoma in very young children remains a challenge for neuro-oncologists in large part because of the greater vulnerability of the developing brain to radiotherapy related toxicity. Innovative strategies based on high dose chemotherapy, use of intrathecal chemotherapy, modified field or dose of adjuvant radiation have been used to delay or avoid craniospinal irradiation to minimize the risk of deleterious neurocognitive impairment in survivors.

Objectives: By assembling a large cohort of young children with relapsed medulloblastoma following initial radiation sparing approach, we aim:

Primary objectives:

- To describe their progression-free survival and overall survival following salvage therapies
- To describe the potential prognostic factors (clinical, therapeutics, pathology and molecular) associated with successful salvage therapy

Secondary objectives:

- To describe the pattern of relapse after initial radiation sparing strategies
- To report the rate of palliative management without any cancer-directed therapy at time of relapse in this young age group
- To report on the toxicity profile of these salvage therapies focusing on the neurocognitive outcome and hearing toxicity.

Study population

We will take advantage of our Canadian Pediatric Brain Tumor Consortium which includes 16 Canadian pediatric centers with pediatric oncologists involved in pediatric neuro-oncology research to undertake the study at the national level. While Johnston et al previously described 96 cases of infant with medulloblastoma diagnosed in Canada between 1990 and 2005(10), and knowing that approximately half of them relapsed, we estimated we could collect information on 40 Canadian young patients with relapse medulloblastoma for the period of 1995-2017. We estimate based on preliminary contact we could gather an additional 30 patients for a total expected 70 patients meeting our study criteria described below:

- Patient aged between 0 to 6 years at time initial diagnosis of medulloblastoma
- Primary diagnosis of medulloblastoma between 1995 and 2017
- Radiological evidence of relapse medulloblastoma, with or without pathology proven diagnosis of relapse
- Patient treated with infant brain tumor strategies defined by any upfront therapies with the exception of those including upfront craniospinal irradiation. *The study is active.*

3. Male β HCG study – PI: Dr. Hukin

Testosterone Levels in β HCG-secreting CNS Germ Cell Tumors

Funding	Source	Amount \$	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
no	N/A.	N/A	2021-2024	35 total 2-5 @ BCCH	0	yes	active	N/A

Background: Central nervous system (CNS) germ cell tumors are a subset of brain tumors classified on the basis of histological and immunohistochemical features. 'Secreting' germ cell tumors are characterized by elevated levels of alpha-fetoprotein (AFP) or beta-human chorionic gonadotrophin (beta-HCG) secreted into the serum and/or cerebral spinal fluid. Despite the histologically malignant nature of CNS germ cell tumors, symptoms may be present for many months or, at times, years prior to diagnosis.

Purpose & Objectives: To retrospectively collect cases of beta-HCG-secreting CNS germ cell tumors in males that presented with precocious puberty and/or had inappropriately elevated testosterone levels at presentation for their level of puberty.

We are proposing to retrospectively collect and publish a case series of male patients with beta-HCG-secreting CNS germ cell tumors that presented with precocious puberty and/or had inappropriately elevated testosterone levels at presentation for their level of puberty. As this is a rare tumor, we anticipate no more than 35 relevant patients to be identified for this case series from all collaborators. The main PI is Dr Holly Lindsay from Baylor College of Medicine in Houston, Texas. *The study is active.*

4. Molecular Profiling of Ependymoma Study - PI. Dr. Hukin

Molecular Profiling of Ependymoma: Identification and Characterization of Candidate Biomarkers and Regulatory Genes

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
2017-2022	yes	sample size will be determined based on tissue availability	active		

The objective of this study is to retrospectively determine the prevalence of visual disturbances (eye movement, pupillary, and visual field), due to pineal lesions and their treatments in the pediatric population. The manuscript has been accepted in the Journal of Neurosurgery Pediatrics. *The study is active.*

3.5. QUALITY ASSURANCE PROJECTS

1. Biobanking study - PI: Dr. Vercauteren/ Co-investigators Dr. Demos, Dr. Connolly

Collection and banking of biological specimens and collection of clinical data from children with neurological disorders

Funding	Source	Amount (\$)	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A		2014 2024	All eligible	391	yes	active	N/A

BCCH Pediatric Neurology BioBank supports procedures related to the collection of biological specimens (biospecimens) and patient clinical information for research purposes. Both biospecimens and clinical information will be collected from patients who are referred to or regularly attend the C&W Pediatric Neurology clinic. In most cases patients will only be approached once regarding the donation of biospecimens to the C&W Neurology BioBank, however there is the possibility that patients could be asked at other time points throughout their treatment. Participants will always be informed about the collection of biospecimens for BioBanking purposes and can refuse further donations or withdrawal from the BioBank at anytime. In addition patients will be asked to give their permission to be contacted in the future regarding other research that may involve filling out questionnaires or the collection of additional biospecimens. Physicians and scientists of C&W and CFRI/other institutions may use biospecimens from the BCCH Pediatric Neurology BioBank after approval of their research project by the C&W Pediatric Neurology BioBank Scientific Committee, ECMO and CW REB

There are 391 subjects from Pediatric Neurology who consented to have their biospecimens banked.