RESEARCH STUDIES IN EPILEPSY
PEDIATRIC NEUROLOGY
BC CHILDREN'S HOPSITAL

Prepared by

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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.

Table of Contents:

1. INTRODUCTION

This report contains up to date information on the ongoing research projects in epilepsy in the Division of Pediatric Neurology at present.

2. ONGOING EPILEPSY PROSPECTIVE STUDIES

1. Flunarizine Study – PI: Dr. Mary 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	110,500	2019 2021	20	4	Yes	active	N/A

This is a 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. There are 4 subjects enrolled in the study so far. One subject was withdrawn from the study due to increase of the seizures.

2. XPF-008-201 study– PI: Dr. Mary Connolly

A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of XEN1101 as Adjunctive Therapy in Focal-onset Epilepsy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Xenon Pharma	42K start-up funds 24K/patient	2019 - 2023	5@ BCCH		yes	active	N/A

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the clinical efficacy, safety and tolerability of increasing doses of XEN1101 administered as adjunctive treatment in adult patients diagnosed with focal epilepsy.

Hypothesis: Patients treated with XEN1101 will demonstrate a greater decrease in total focal seizure frequency per 4 weeks from baseline compared to the double-blind period, versus patients treated with placebo.

Objectives: Primary:

- To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency in adults with focal epilepsy taking 1-3 antiepileptic drugs (AEDs)
- To assess the safety and tolerability of XEN1101 in adults with focal epilepsy taking 1-3 AEDs

Secondary:

- To evaluate the 50% XEN1101 response rates in comparison to placebo
- To evaluate trends in focal seizure frequency over time in the treatment period
- To assess the effect of XEN1101 vs. placebo on seizure severity and impact in adults with focal epilepsy taking 1-3 AEDs

Total study duration per patient estimated to be 24 weeks or approximately 6 months. The study was approved; the SIV has been scheduled for February 4, 2020.

3. Dravet Syndrome Study(1503) – PI: Dr. Mary Connolly

An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Zogenix	$21K start-up funds $24,300 /patient	2017-2021	7@ BCCH	9	Yes	active	N/A

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 relative to the pre-ZX008 baseline on the following effectiveness measures
    - The change in the frequency of convulsive seizures
    - The proportion of subjects who achieve a ≥40%, ≥50%, and ≥75% reduction in convulsive seizure frequency
    - The longest convulsive seizure-free interval
    - The percentage of convulsive seizure-free days
    - The non-convulsive seizure frequency
    - The convulsive + non-convulsive seizure frequency
- To estimate the incidence of the following on subjects receiving ZX008:
    - Use of rescue medication
    - Hospitalization to treat seizures
    - Status epilepticus.

- To assess the effect of ZX008 relative to the pre-ZX008 baseline on the following quality of life (QoL) measures:
    - Quality of Life in Childhood Epilepsy (QOLCE) score
    - Pediatric Quality of Life Inventory™ (PedsQL) score
    - QoL of the parent/caregiver using the EQ-5D-5L scale
    - Affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS).
- To assess the effect of ZX008 on the following QoL measures:
    - Clinical Global Impression – Improvement rating, as assessed by the principal investigator
    - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver

Number of patients: Up to approximately 310 subjects will be enrolled from the core studies.

There are 9 subjects enrolled at BCCH, seven of them active, two withdrawn due to increased seizure activity and side effects.

4. Lennox-Gastaut Syndrome Study(1601) – PI: Dr. Mary Connolly

A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Multicenter, Randomized, Double-blind, Parallel Group, Placebocontrolled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS, Followed by Part 2: An Open-Label Extension Trial to Assess Long-Term Safety of ZX008 in Children and Adults with LGS

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Zogenix	$20,000 start-up funds $65K/patient	2018 2020	4-5@ BCCH	4	Yes	active	N/A

This is an international multicenter study being conducted in two parts. Part 1 is a double-blind, parallel-group, placebo-controlled, study to assess the efficacy and safety of two doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. The primary study endpoint is assessed from Part 1 data. Part 2 will be an open-label, flexible-dose extension for subjects completing Part 1 of the study.

Objectives:
The primary objective of Part 1 is:

- To evaluate the effect of ZX008 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with Lennox-Gastaut syndrome (LGS) based on the change in frequency of seizures that result in drops between baseline and the combined Titration and Maintenance Periods (T+M)

The key secondary objectives of Part 1 are:

- To evaluate the effect of ZX008 0.2 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops between baseline and T+M

- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo.

The primary objective of Part 2 is:

- To assess the long-term safety and tolerability of ZX008 in children and adults with LGS with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, suicidality, cognition (BRIEF), vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight, and BMI.

The secondary objectives of Part 2 are:

- To assess the effect of ZX008 relative to the baseline
- To determine the incidence of the following on subjects receiving ZX008:

Four subjects consented and screened up to dat. All four subjects withdrew from the study due to side effects.

5. Dravet Syndrome & LGS Study(1900) – PI: Dr. Mary 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/patient	2019-2023	8@ BCCH	0	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. The first study patient will be enrolled beginning of February 2020.

6. QOL Study - SickKids – PI: Dr. Mary 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	2014-2020	50@ BCCH	23	Yes	active	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 23 subjects enrolled at BCCH. There are 14 active subjects, and 9 subjects withdrew from the study.

7. pSERG Study – PI: Dr. Linda 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 Childre n's	3000 start-up 200/subjec t	2016 – no end date to registry	100 patients 10 @ BCCH	7	yes	active	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, co-morbidities, 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,.

8. CARE-E Study – PI: Dr. Linda 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 – 2020	7	7	yes	active	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 will enrol approximately 30 participants from 5 Canadian sites (University of Saskatchewan, University of Alberta, University of Manitoba, Universite de Montreal and the University of British Columbia). The study doctor expects to enrol around 6 participants locally. The study duration is 12 months.

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

9. EPBiome Study – PI: Dr. Linda Huh/Dr Maksim 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	0	yes	active	N/A

This is a two part 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. The study is active, with no enrollments yet.

10. Ketogenic Diet in Infantile Spasms Study – PI: Dr. Linda 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	2018-2020	6	0	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. The study is active, and there were no enrolments yet.

11. Epilepsy & Genomics study - PI: Dr. Michelle 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 2019	300	263	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. The study has been funded by the Alva Foundation.

There are 263 subjects enrolled in the study. A total of 213 participants have WES results so far. There are 36 withdrawals so far, and 227 active participants. 17 trios were sent for whole-genome sequencing.

12. 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 2019	10	6	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 4 children have been enrolled in the study. There were no enrollments in the last quarter.***

13. fMRI Study - PI: Dr. Bruce 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 2019	200	150	yes	active	Abstract, 45th 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 150 subjects enrolled in the study.

14. CEEG Consortium - PI: Dr. Linda 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.

15. PEG Study - PI: Dr. Cyrus Boelman

Personalized Medicine in the Treatment of Epilepsy: Identification of Genes Predisposing to the Disease and to Resistance to Anti-epileptic Treatments

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Genome Canada Genome Quebec OBI	250/pt	2016 20120	200	25	yes	complete d	N/A

The main goal of this research project is to identify further genetic mutations responsible for various forms of epilepsy and to understand the impact of genetic analysis and whole genome sequencing on the tests requested during the patient's monitoring and treatment. The sequencing will be used for each participant in the project, to study a subset of the participant's genes or their entire genome. A further goal of this project is to develop understanding of the genetic factors that influence the response to anti-epileptic medications (pharmacologic response) at an individualized, or personalized, level.

Up to 200 eligible patients (and their parents and/or affected relatives, in some cases) of any age 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. The study has been approved. There are 25 subjects enrolled in the study. The enrolment has been completed across all sites.

16. In Silico Study - PI: Dr. Dewi Schrader

Connectome-informed simulations of pediatric epilepsy surgery

Funding	Source	Amou nt $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	SickKids Foundation	295K	2017-2020	50 (35 cases, 15 controls)	11 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 11 cases enrolled at BCCH.

17. Seizure Action Plan - PI: Dr. Mary Connolly

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
0	NA	NA	One year	200	209	yes	Active	2

Hypothesis: We expect to find that the majority of patients at increased risk of prolonged seizures or clusters of seizures will have a written seizure action plan, and that the majority of parents and caregivers will be interested in a seizure action plan mobile application.

Phase 1 Objectives: The purpose of our project is to improve the pre-hospital treatment of status epilepticus by ensuring that every child in British Columbia with epilepsy has an individualized seizure action plan in paper format and/or electronically.

In phase I of our project, which is outlined in this study protocol, we would like to achieve the following three objectives:

1. To determine the current prevalence of written seizure action plans in epilepsy patients at BC Children's Hospital. This will identify whether or not there is a current gap in their management that should be addressed.
2. To identify epilepsy patients at risk of not having a written seizure action plan. We will compare the characteristics (including seizure type, epilepsy syndrome, history of status epilepticus, and treatments) of epilepsy patients who currently have a seizure action plan with those who do not have one.
3. To evaluate patient and parent/caregiver interest in an electronic version of their child's seizure action plan via a mobile application. This will guide the second phase of our project by helping us determine whether there would be value in designing a Seizure Action Plan mobile application and, if so, which features would be most helpful for users.

Phase 2 Objectives: Design, implement and evaluate a seizure action plan template which can be displayed in paper format and/or electronically in the form of a mobile application.

A total of 209 participants have been enrolled in the study. Off 209 participants, 12 are excluded due to ineligibility.

Abstract was accepted for the American Epilepsy Society Meeting - New Orleans. Presentation, UBC Neurology Residents Day, and Brain, Behaviour and Development Research Day – at BCCHRI. The study has been completed.

18. <u>mTOR Study</u> – 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	3,500	2019-2021	6	0	yes	active	

Summary: We are proposing an open-label pilot study looking at the efficacy of mammalian target of rapamycin (mTOR) inhitibor, 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 enrollments so far.

19. 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	2018-2019	6	6	yes	active	

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. Four subjects have completed the treatment, and one subject withdrew from the study.

20. 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	2018-2020	210	91	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 were 91 subjects enrolled in the study.

21. 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 2020	50	10	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 10 enrollments.

3. ONGOING RETROSPECTIVE EPILEPSY STUDIES

1. KD BCCH study - PI: Dr Connolly

Outpatient initiation of the ketogenic diet: The BC Children's Hospital Experience

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2014-2021	yes	130	active	N/A	N/A

HYPOTHESIS: The KD is an effective non-pharmacologic therapy for pediatric treatment resistant epilepsy that can be initiated safely and effectively on an outpatient basis.

OBJECTIVES: The primary objective of this study was to review the safety of initiating the KD as an outpatient at our centre. The secondary objective of this study is to describe the efficacy of the KD in our patient population. We will analyze demographic and clinical findings in patients who respond to the KD in order to identify and specify any possible differences or predictive factors of those who respond compared to non-responders.

STUDY DESIGN: This is a retrospective chart review study of all patients initiated on the KD as an outpatient at BCCH between January 1996 and January 2014. The chart review is completed.

2. Epilepsy & Autism study - PI: Dr Connolly

Analysis of the clinical and electrical features of children with essential autism

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2017-2021	yes	150-200	active	N/A	N/A

The purpose of this study is to describe in detail the clinical, neurologic and electrical features of children with both autism spectrum disorder and epilepsy. The subjects of this study are 5 infants with SCN2A mutations with neonatal epileptic encephalopathy who are admitted at the 4 participating sites. The chart review has been completed.

Hypothesis: Children with autism and epilepsy may manifest a specific pattern of electrophysiologic anomalies related to specific candidate genes for autism that may be important in understanding mechanism of epilepsy in this population.

Objectives:

- To review the details of the clinical and EEG features of epilepsy in patients with autism spectrum disorders
- To characterize the response to anti-epileptic drugs, ketogenic diet, epilepsy surgery
- To assess the prognosis for seizure control in patients with epilepsy and autism
- To review causes of epilepsy and autism

Methods: The clinical and EEG databases and the genetics ASD database will be searched for patients with autism and epilepsy. The medical records, EEG data and neuroimaging, neurometabolic and genetics investigations will be retrospectively reviewed. A detailed analysis of the clinical features of the epileptic seizures, interictal and ictal EEG features and other available information such as neuroimaging, response to treatment and outcome.
The study has been approved and chart review is underway.

3. Infantile Spasm study - PI: Dr Connolly/Dr Xu

Retrospective review of patients diagnosed with infantile spasm at BCCH between 1990 – 2013

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2013-2021	yes	260	active	presented	N/A

Purpose and objectives:

- Review clinical, neuroradiological and EEG characteristics of patients with infantile spasms (IS) admitted to British Columbia's Children's Hospital from 1990 to 2013
- Review etiology, treatment response and the utility of surgery for treatment of infantile spasms
- Compare efficacy with ACTH, vigabatrin, ketogenic diet and other anti-seizure medications, safety profiles and side effects.
- Describe long-term prognoses of infantile spasm with different etiologies
- Review economic consequences of IS and implications for health improvement

The subjects of this study consisted of patients with IS at BCCH between the years 1990 and 2013. The chart review has been completed.

4. CAE study - PI: Dr Connolly/Dr Michoulas

Treatment-Resistant Seizures in Childhood Absence Epilepsy

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2013-2021	yes	130-150	active	N/A	N/A

Objectives: The primary objective of this study is to determine the occurrence of treatment-resistant CAE in patients followed through the epilepsy clinic at BC Children's Hospital. The secondary objective of this study is to analyze demographic, clinical and EEG findings in CAE in order to identify and specify any possible differences or predictive factors of treatment resistance.

Hypothesis: Treatment-resistant CAE is not uncommon. A combination of one or several demographic, clinical and electrographic factors may help predict which patients with typical childhood absence epilepsy will be treatment-resistant.

This will be a retrospective chart review study of all patients with a clinical diagnosis of CAE followed through the epilepsy clinic at BCCH between 1999 and 2012 with a minimum 1 year follow-up. The study is active, and the chart review is ongoing.

5. MRI in epilepsy study - PI: Dr Connolly/Dr Schrader

The Use of Advanced, Automated Magnetic Resonance Image Processing Techniques for the Detection of Focal Epileptogenic Lesions in Children

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2009-2021	yes	200	active	N/A	N/A

The purpose of this study is to test the sensitivity and specificity of Advanced, Automated Magnetic Resonance Image processing techniques to detect epileptogenic lesions on MR scans

of pediatric epilepsy patients that were acquired over the last 10 years at the BC Children's Hospital. We anticipate that these techniques will improve the treatment of focal epilepsy by increasing our ability to detect epileptogenic lesions in children.

Specific Aims

- To determine if the Advanced, Automated MR image processing techniques designed for the detection of epileptogenic lesions in adults can be applied to the developing brain by testing them on pediatric cases of histopathologically proven lesions that were identified by visual inspection of the pre-operative conventional MRI.
- To determine if Advanced, Automated MR image processing techniques can be used to identify histopathologically proven lesions that were previously undetected on visual inspection of pre-operative conventional MRI.

We estimate that there are over 100 children in the BC Children's Hospital Epilepsy database with MRI of sufficient quality for advanced, automated analysis. MRI data for all the patients will undergo advanced analysis at the Neuroimaging of Epilepsy Laboratory, part of the McConnell Brain Imaging Centre at the Montreal Neurological Institute, by Dr Bernasconi and Dr Schrader. We will use methods that were previously developed in Dr Bernasconi's laboratory for the analysis of epileptogenic lesions in adults. The study is active.

6. AFP Study – PI: Dr Selby

Acute Flaccid Paralysis in Canadian Children: Evaluation of etiological factors and response to therapy - PI: Dr. Selby

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2018-2021	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 has been approved at BCCH site.

7. EEG Autism study - PI: Dr Datta

Epileptiform Abnormalities in Children with Autistic Spectrum Disorder

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2013-2019	yes	1500	active	N/A	N/A

Purpose: In this study, we propose to examine the type, frequency and location of epileptiform abnormalities present in children with a diagnosis of autism spectrum disorder and determine how these findings differ populations of children with other neurodevelopmental diagnoses. We will use the database at the BCCH, established in 1992. The study has been closed this quarter.

8. Down Syndrome study - PI: Dr Datta/Dr MacDonald

Clinical and electrographic features of epilepsy in Down Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2019-2021	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.

9. KD Age Spasms Study - PI: Dr. Anita 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 - 2021	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.

Purpose

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 hypsarrythmia 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 hysparrythmia 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 study has been approved and chart review is in progress.

10. 4PW Study - PI: Dr. Anita Datta

Significance of hypnogogic atypical spike wave discharges on EEG in the pediatric population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2017 - 2021	yes		active		N/A

Purpose: The purpose of the study is to determine the frequency and predictive value of inter-ictal atypical spike wave discharges or bifrontal fragments that are seen on EEG in the pediatric population usually upon falling asleep or awakening.

A retrospective EEG, database and chart review of children who had an EEG with hyponongic bifrontal generalized fragments and subsequent follow up EEG between 12-24 months. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. The study is active.

11. Occipital Spikes Study - PI: Dr. Anita Datta

Clinical Features of Patients with Occipital Spikes on EEG in the Pediatric Population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2018 - 2020	yes	500	active		N/A

Retrospective chart review and analysis of existing EEG data available at BC Children's Hospital (BCCH); No patient contact.

Purpose

The purpose of the study is to determine the frequency and clinical features of occipital spikes on EEG in the pediatric population. We will identify EEG's of pediatric patients with occipital

epileptiform discharges over the past 20 years at BCCH and determine if there are any differences compared to a group of age and sex matched controls referred to our EEG lab who have EEGs for various indications. We want to determine if the presence of occipital discharges on EEG and certain EEG characteristics can help to predict clinical outcome. We would also like to examine the evolution of occipital spikes on recurrent EEG's.

A retrospective EEG, database and chart review of children who had an EEG with only occipital spikes and subsequent follow up EEG between 12-24 months. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. We will include 250 study patients and 250 control patients. The chart review is underway.

12. Brivateracetam Study - PI: Dr. Anita 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 - 2019	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.