ONGOING RESEARCH STUDIES IN THE NEUROSCIENCES PROGRAM

Quarterly Report on the Research Activities Involving a Clinical Research Coordinator

January 1st, 2016 – March 31th, 2016

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1. INTRODUCTION

This report contains up to date information on the ongoing research projects that are supported by the Clinical Research Coordinator (CRC) of the University of British Columbia's (UBC's) Division of Neurosurgery at the Clinical Academic Campus of Vancouver General Hospital (VGH) for the period of January 1st – March 31st, 2016. The main objective of the report is to familiarize the staff of the Division of Neurosurgery of UBC with the current research activities that are being supported by their CRC. The studies that are supported by the CRC in this report are divided into two categories of ongoing studies: prospective studies, and retrospective studies. Additionally, summer student research projects that have applied for funding are included as their own section. The number of studies per category is presented in the table below (Table 1).

Table 1. Number of studies per category.

Number of Ongoing Studies				
Prospective	Retrospective	Inactive or Complete Studies	Summer Studentships	Total
6	4	0	1	11

Detailed description of the purpose, objective, budget and sample size of each study supported by the CRC is presented in the next three sections of this report.

2. ONGOING PROSPECTIVE STUDIES

1. **<u>CSDH study</u>: Timing of Mobilization After Burr Hole Drainage of Chronic Subdural Haematomas: a randomized study – PI: Dr. Akagami**

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Sep '14 Sep '16	142	57	yes	Active	N/A

This is a two treatment arm, randomized, prospective study to minimize re-do burr-hole drainage procedures and any other associated complications in patients with chronic subdural haematomas.

Primary Outcomes:

- Recurrence requiring re-do drainage within the 1st month post-operatively
- Recurrence requiring re-do drainage between the 1st and 3rd months post-operatively

The timing of when to mobilize patients after burr-hole drainage of chronic subdural haematomas remains controversial. Traditionally, patients have been subjected to delayed mobilization in order to allow for the theoretical re-expansion of the brain and to decrease recurrence. Timing of bed rest is not consistent among centres and varies from immediately after to 7 days after surgery.

The objective is to determine optimal timing of mobilization in CSDH patients following a burr-hole drainage.

There are 57 participants enrolled in the CSDH Study, 15 of them were enrolled during the last quarter.

2. **<u>AHCRN REGISTRY</u>: Characterizing Patient Population in the Adult Hydrocephalus Clinical Research Network (AHCRN) – AHCRN Registry– PI: Dr. Zwimpfer**

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Nov '14 no end date	perpetual	46	yes	active	N/A

A multicenter and multinational registry that collects data on adult hydrocephalus patients to characterize the etiology, understand variability, progression, and current treatment practices for hydrocephalus patients.

The overall purpose of the Registry is to establish and maintain a hydrocephalus patient event database for the Clinical Centers of the AHCRN, a research network newly established to investigate clinical management of adult hydrocephalus.

Primary Objectives:

- To describe the natural history and treatment response for adults with previously untreated congenital hydrocephalus

- To describe the assessment and treatment of patients with Normal Pressure Hydrocephalus (NPH)
- To describe the complications associated with shunt surgery
- To determine the role for treatment with Endoscopic Third Ventriculostomy (ETV)

The Registry will provide previously unavailable epidemiological information about hydrocephalus patients seen throughout the participating Clinical Centers. This information will provide the basis for multi-institutional studies to be carried out by the AHCRN that may ultimately improve the clinical care for adults with hydrocephalus throughout the world. The continuing collection of such information serves to provide data necessary for hypothesis generation and study design. Examples of preliminary study designs include, but are not limited to, the following: preliminary power analysis, sample size determination, and recruitment projections. Radiologic imaging data will provide a unique opportunity to assess aspects of adult hydrocephalus diagnosis, management, and outcomes.

Accomplishments of Merit:

- VGH made UBC 1st site to have accomplish Neuropsychological Battery Administration Training
- VGH made UBC 1st site to complete Neuropsychological Battery Administration Quality Control

There are 226 participants enrolled in the AHCRN Registry at all participating sites. Of those, 46 are from the VGH site with 4 patients enrolled in the last quarter.

3. RATE study - Resident Activity Tracker Evaluation Study - PI: Dr. Toyota

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	RDBC BCSPQC MD Financial		Sep 15 Aug 16	60	53	yes	Active	N/A

Medical resident work hour restrictions remains a large topic of debate in the Accreditation Council for Graduate Medical Education; and more importantly, also in the Royal College of Physicians and Surgeons of Canada.

An adequate number of hours of sleep play an important role in medical residents' performance, and quality of life. Factors associated with medical resident fatigue and prolonged work hours include the following: an increase in automobile accidents, negative effect on well-being, an increase in stress, relationship-related stress, and decreased performance in both simulated tasks and standardized tests. Formal changes to resident work-hours regulation have not been imposed for Canadian medical residents. On-call duties vary substantially across medical specialties further complicating the issue. The actual physical demands of resident on-call duties and the impact on sleep duration and number of interruptions have not been comprehensively investigated to date.

This study will be the first in literature to measure average and maximum heart rate, sleep duration and interruptions, and number of steps taken per day in medical resident trainees, across non-surgical and surgical specialties and when the residents are on or off call. Such novel results

will help advance and guide current discussion on resident work hour restriction towards a more comprehensive conclusion.

There are 53 residents currently enrolled in the RATE Study, 18 of them were enrolled during the last quarter.

4. **<u>TOCA 511 Study</u> - A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma – PI: Dr. Toyota**

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Tocagen		Apr 16 Sep 19	170 in Phase 2; 200 in Phase 3	N/A	CREB Approved VCHRI Pending	Not started yet	N/A

Name of Investigational Product: Toca 511, a retroviral replicating vector (RRV) expressing a yeast-derived, codon-optimized cytosine deaminase (CD) prodrug-activator gene, in combination with Toca FC (flucytosine) extended-release tablets.

Methodology: This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus standard of care (SOC) that comprises Investigator's choice of either single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of glioblastoma or anaplastic astrocytoma. Subjects will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC or control. Repeat scans will be obtained every 6 weeks for the first year and every 3 months after that.

The ethics application has been approved by CREB and the VCHRI approval is pending.

5. **<u>QoL aneurysm study</u> - Quality of life in patients diagnosed with unruptured cerebral aneurysm: prospective single-center series - PI: Dr. Gooderham**

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Jan 16 Dec 17	150	N/A	Pending	Pre-submission	N/A

Aneurysms may require endovascular or microsurgical treatment if ruptured, growing, symptomatic or of significant size. The goal of prophylactic treatment of an aneurysm is to increase the number of years with good quality of life.

The main goal of the present study is to identify how does the diagnosis of an unruptured cerebral aneurysm and its subsequent treatment impact quality of life as measured by SF-36 and EQ5D in patients. We aim to quantify if the impact in quality of life varies overtime. We aim to verify if the choice of technique (endovascular vs microsurgical) has an impact on quality of life

in the short and long term. We will explore the relationship with other variables such as gender, medical comorbidities, aneurysm location, and postoperative complications.

Quality of life will be assessed via the SF-36 and the EQ5D tool at time 0 (time of diagnosis) and at 1 year for patients with an untreated cerebral aneurysm. Quality of life will be assessed via the SF-36 tool at time 0 (time of diagnosis), 6-8 weeks postoperative follow-up and at 1-year postoperative follow-up in the patients who have been treated. The latter group will be divided in 2 sub-groups: endovascular and microsurgical (clipping).

Ultimately, we will compare quality of life in untreated unruptured cerebral aneurysms patients with general population at time 0 and 1 year. We will compare quality of life in coiled unruptured cerebral aneurysm patients at time 0, 6-8 weeks and at 1 year. We will compare quality of life in clipped unruptured cerebral aneurysm patients at time 0, 6-8 weeks and at 1 year. We will compare quality of life between clipped and coiled patients at time 0, 6-8 weeks and at 1 year.

6. <u>LAANTERN Registry</u> - PI Dr. Toyota

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Monteris		Jan 16 Dec 19	150	2	yes	active	N/A

The NeuroBlate® System (NBS) is a minimally invasive robotic laser thermotherapy tool that is being manufactured by Monteris Medical. It employs a pulsed surgical laser to deliver targeted energy to abnormal brain tissue. To further understand performance and utilization of NBS in current standard of care, post-market multi-center registry called LAANTERN (Laser Ablation of Abnormal Neurological Tissue using Robotic Neuroblate system) is designed to collect baseline, procedural and follow-up data on patients that are already scheduled to be treated with NBS in observational manner for publication purposes.

This is a multi-center registry that will include data collection at baseline (prior to NeuroBlate® procedure, which is also referred as the index procedure), during index procedure, discharge and up to 24-month follow-up. Up to 1,000 patients may be enrolled at up to 50 study sites. Most of the enrollment will occur prospectively; however, the data collection for patients who already underwent a procedure with NBS may also take place retrospectively. For example, if the patient already had a NBS procedure, he/she may be approached about study participation. If the patient agrees to participate in the study, the data collection will be initiated once Informed Consent Form (ICF) is signed (e.g., demographics, procedure, and discharge data will be collected retrospectively and future follow-up visits collected prospectively).

3. ONGOING RETROSPECTIVE STUDIES

1. Biomarkers in Malignant Brain Tumors Study - PI: Dr Toyota

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
June 15 August 16	Obtained	151/151	Active	N/A	N/A

Objective:

To conduct a retrospective clinical chart review of our institution's glioblastoma cases to compare the predictive and prognostic value of molecular markers to that of traditional histological diagnoses.

This is a retrospective chart review involving charts of patients with glioblastoma treated at VGH from 2010-2014. We have created a database to register basic patient demographics, treatment protocols and outcome. Specific to our study, we classified the tumors by classic histologic description and grading as well as new cutting edge diagnostic molecular and genetic analysis.

Based on this database, we will stratify the patients into outcome categories based on classical grading and newer molecular markers. A statistical analysis of this data will then be conducted in order to compare the predictive value of these classic histologic methods with the newer methods for patient outcomes.

Quinn Parker was a summer student who had obtained UBC SSRP funding for the summer. The chart review has been completed, and we await statistical analysis.

2. QoL Retrospective study - Quality of Life after Surgery in Patients with Pituitary Tumors and Acromegaly – PI: Dr. Akagami

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrollment	Status	Abstract/Paper/ Manuscript	Funding
Dec 15 Dec 16	yes	63	active	N/A	N/A

Patients with pituitary tumors have been previously noted to report decreased quality of life (QoL). These studies have used a variety of validated questionnaires (such as SF36 and AcroQoL) to assess the physical, cognitive and psychological well-being of patients affected by functional and non-functional tumors. Predictably, QoL is variably affected by different types and extents of tumor. Studies which have focused on patients with acromegaly have generally shown improvement of QoL after treatment (GH<2ng/ml). However, it is not clear whether the improvement of QoL is primarily driven by the correction of hormonal imbalances. In fact, a recent study from Korea found that AcroQoL scores were similar between patients with controlled and uncontrolled disease.

This will be a retrospective review of QoL after pituitary surgery in patients with acromegaly. Any patient that lacks the SF36 questionnaire will be contacted, consented and given a copy to complete. All charts of patients who have previously undergone this procedure with Dr. Akagami shall be assessed. Multivariate analysis will be used to determine the factors which most impact QoL improvement post-operatively.

3. **<u>3D Segmentation Study</u>** - Computational 3D Segmentation of Cerebral Vasculature for Evaluation of Cerebral Aneurysms , PI: Dr. Goodherman– ***New study this quarter***

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrollment	Status	Abstract/Paper/ Manuscript	Funding
Jan 10 Dec 15	CREB Approved; VCHRI Pending	500	VCHRI Review	N/A	None

The primary objective of this study is to develop computer software using advanced imaging analysis techniques that can accurately detect cerebral aneurysms on CTA scans. The secondary objective of this study is to develop computer software that can detect changes in the size and shape of aneurysms over time in the same patient.

We hypothesize that advanced imaging analysis techniques will be able to be applied to CTA scans to successfully and accurately detect cerebral aneurysms and compare their size and shape at different points in time in the same patient.

4. **Trigeminal Schwannoma Study:** Review of Trigeminal Schwannoma Surgical Resections at Vancouver General Hospital, PI: Dr Akagami**,** ***New study this quarter***,

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrollment	Status	Abstract/Paper/ Manuscript	Funding
Mar 16 Feb 17	CREB/VCHRI Approved	30	Active	N/A	N/A

This is a retrospective review of trigeminal schwannomas that were operated on by Dr. R. Akagami at Vancouver General Hospital between 2001-2015 with an open craniotomy approach. Our aim is to characterize the clinical presentation against imaging findings, and document the natural history of the TS tumours with respect to management strategy that includes surgical resection, radiotherapy, and observation.

We have two objectives. First, we will attempt to characterize the patients' trigeminal schwannoma anatomy with respect to location in middle and posterior cranial fossae, and then investigate their outcomes following transcranial resection of tumour by Dr. R. Akagami. We hope to correlate the patient's clinical presentation with the tumour anatomy with respect to sensory and motor symptoms, and then compare these against those of the findings in literature.

4. INACTIVE OR COMPLETE STUDIES

None this quarter.

5. SUMMER STUDENTS

1. **AHCRN summer student project:** Collection and Submission of Clinical, CSF and Radiological Data of Patients Being Assessed at Vancouver General Hospital Adult Hydrocephalus Clinic as Part of the Adult Hydrocephalus Clinical Research Network (AHCRN)

PI:	Dr. Charles Haw
Student	Mr. Nicholas Salterio, Y1 B.Sc.
Project Supervisor:	Dr. Thomas J. Zwimpfer
Funding	VGH Foundation Hydrocephalus Fund