CLINICAL RESEARCH STUDY PROTOCOL

Study Title:

Multi-modal Evaluation of a Physical Intervention Approach to Treating Persistent Post-Concussive Symptoms

TBRHSC Research Program Tracking Number:

RP-506-07112017

Version number:

1.5

Version date:

November 30th, 2018

Research Site(s):

Lakehead University

Funding Mechanism:

Funding for this study was obtained from the Northern Ontario Academic Medical Association through their Clinical Innovation Opportunities Fund. Other sources of support include in-kind contributions of time as described in the study budget from the Principal and Co-Investigators (see Appendix 16.6)

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CONFIDENTIALITY STATEMENT

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ABBREVIATIONS/DEFINITIONS

Lakehead University – LU

Northern Ontario School of Medicine – NOSM

Persistent Post-Concussive Symptoms – PCS

Healthy control – HC

Standard of care – SC

Aerobic and balance retraining program – AET

International Physical Activity Questionnaire – IPAQ

Balance Error Scoring System – BESS

Heart rate variability – HRV

1. BACKGROUND / RATIONALE

Each year, 120,000 people sustain a traumatic brain injury (TBI) in Canada[1], with an estimate of 80-90% of TBIs being categorized as mild[2,3]. Mild TBIs, also known as concussions, have been referred to as the silent epidemic in North America, as the incidence is much higher and effects more persistent than once thought. Concussions can result in a variety of long-term cognitive, psychological, and physical symptoms. Self-reported memory and attention complaints are the most common cognitive effects and may persist for several years post-injury[4–6]. It has also been reported that in 75% of all sports-related concussions, athletes experience reduced balance and symptoms of dizziness[7]. These residual symptoms may also negatively impact the ability to engage in regular activities of daily living such as work, sports, and driving. Driving safe is a complex task and requires perception of speed and distance, along with good coordination for steering and braking[8].

After concussion, participants are slower to respond to traffic hazards[8] and this has been related to increased crash frequency[9]. The goal of the proposed study is to examine the effect of an aerobic and balance retraining program (AET) on common persistent symptoms of concussion using measures of cognition and brain function, mental and physical health, and driving performance.

To date, the majority of randomized controlled trials (RCTs) have used rest and psychological approaches to alleviate persistent concussion symptoms and have focused on providing individuals with recovery-related information, reassurance, or education. Most of these studies have found no benefit or reported inconclusive findings[10]. Of the research that has focused on treatment, AET[11] has shown to be promising for overall symptom reduction. The conclusions of these studies, however, are limited by the lack of control groups, biased samples, and the inclusion of TBIs of all severities. In addition, many of the interventions were delivered prior to the period when symptoms are typically considered persistent. Controlled studies are needed to test the specific effects of treatment on the persistent symptoms in a post-concussion syndrome sample lasting greater than one month post-concussion. The intervention we plan to test is AET in a controlled/stepwise exercise training program using RCT methodology. Recent evidence indicates that an active rehabilitation program may be useful for individuals with persistent concussion symptoms[12] and that exercise can also be effective at improving mood[13].

Studies have also shown that levels of brain-derived neurotrophic factor (BDNF) are significantly increased as a result of aerobic exercise in healthy individuals. In particular, preliminary data from our group[14] demonstrated an increase in salivary BDNF levels in a healthy control group following 4 weeks of AET (the same protocol we are proposing). BDNF is a secreted protein that has been shown to play a central role for neural health and brain plasticity[15,16]. BDNF has been demonstrated to be a useful biomarker of brain injury post-concussion[17] with animal research showing significantly reduced levels of BDNF several hours or days after a concussion[18]. Notably, aerobic fitness and BDNF share a relationship that is predictive of memory performance in healthy individuals[19–21]. Also, it is known that executive function and circulating BDNF both decline with age, however, changes in serum BDNF

predicts improvements in cognitive outcomes in response to aerobic exercise in older individuals[22].

This provides strong evidence to further examine this intervention in people who are experiencing residual cognitive and/or physical complaints after concussion, but are otherwise healthy. One of the reasons for the lack of response to treatment in previous studies may be, in part, due to the heavy reliance on subjective self-report measures. Therefore, in addition to obtaining self-report measures of persistent complaints, we plan to obtain objective measures of functioning using sophisticated technology, including event-related potentials (ERP) during computerized cognitive tasks, biomarkers (BDNF), force plate measures of balance, and driving simulation measures of participant reaction times under dual tasking situations.

While self-reported cognitive complaints can persist after concussion, they are rarely detected using traditional neuropsychological tests[23,24]. Using more complex attention and memory tasks, however, slower and less accurate performance can be detected up to several years' post-injury[25–27]. Non-invasive imaging techniques, such as event-related potentials (ERP) can also provide further insight into inefficient neural processing after concussion. ERP is a method of surface electroencephalography (EEG) that non-invasively detects the neural signaling in relation to an event (stimulus or task). In individuals with concussion, ERP studies have previously found deficits in stimulus discrimination[28], and inhibitory control[29] reflected by increased errors and variable response times in behavior as well as reductions in electrical potentials. Previous studies have found decreased amplitude and increased latency following concussion suggesting a decrease in speed and cognitive resources available for attentional processing[29–33].

One of the main goals of recovery from persistent concussive symptoms is the ability to return to daily living. While evaluating performance in daily living activities can be difficult (e.g., driving), we are able to evaluate performance using devices such as driving simulators. Measurements of performance in a simulator (e.g., response time) may become a useful tool as part of a comprehensive assessment for physicians as they recommend return to daily activities.

2. OBJECTIVES / STUDY AIMS

The primary objective of our proposed study is to implement AET to reduce persistent symptoms after concussion. Our secondary objective is to investigate the usefulness of BDNF as a biomarker of persistent concussive symptoms responsiveness to AET.

Our 4 specific goals are to help people with persistent concussive symptoms by:

1. Minimizing the occurrence of persistent cognitive and physical symptoms following concussion.

2. Improving performance and efficiency of neural processing during cognitive tasks.

3. Correlating BDNF levels with severity of symptoms and correlating change in BDNF levels to improvements in physical symptoms and balance.

4. Improving functioning in activities of daily living, such as driving

RATIONALE, SIGNIFICANCE, AND JUSTIFICATION

The clinical significance, rationale, and justification of this collaborative effort is demonstrated by both clinical and research initiatives at treating people with concussion directly in our community. With the recruitment assistance by medical professionals, this project has a strong foundation and the potential to make a direct impact here in Thunder Bay. The group format of the AET is a cost- and time-effective method by which to treat a subgroup of the concussion population who experience long-lasting symptoms. This subgroup is growing as diagnostic protocols are becoming more standardized and the potential persistent effects are becoming general knowledge, especially due to increased media coverage around sport or military related injuries related to concussion. If successful, the AET protocol and salivary BDNF biomarker test may help in the assessment and treatment of persistent concussion symptoms that currently are often treated with rest and education. The findings from the proposed study will help clinicians to also monitor progress to aid in return to play, school, or work decisions, resulting in significant savings to the healthcare system and employer as a result of lost work time. Also, by improving physical health, AET may improve the quality of life.

ASSESSMENT OF OUTCOME/HYPOTHESIS

1. It is anticipated that the concussed participants receiving the AET will exhibit less mental, cognitive, and physical symptoms related to post-concussion syndrome. These signs and symptoms will be measured via the SCAT-3 and the RPSQ scores.

2. It is anticipated that AET will result in increased efficiency of neural processing during cognitive tasks in post measures compared to SC and with less difference than compared to HC compared to pre- intervention comparisons. Cognitive efficiency will be measured by the amplitude and latency of two event related electrical potentials associated with attention and conflict monitoring processing.

3. It is anticipated that concussed participants receiving the AET will exhibit improved balance. This will be measured using the force platform centre of pressure area, displacement, and velocity measures while completing the various static stance positions using the BESS protocol.

4. It is anticipated that concussed participants receiving the AET will exhibit increased improvements in salivary BDNF levels, indicative of an improvement in concussion symptoms. Salivary BDNF will be quantified using the BDNF ELISA assay and changes in pre- vs. post-intervention concentrations will be assessed. Additionally, we hypothesize that lower levels of BDNF upon entry to the study will indicate more pronounced concussive symptoms. This relationship will be determined by correlating the pre-intervention BNDF concentration to measures of the post intervention assessments.

5. It is anticipated that concussed participants receiving the AET will exhibit improved reaction times compared to the SC group during dual tasking scenarios to avoid crashing in dangerous traffic situations.

3. EXPECTED RISKS/ BENEFITS

3.1 Expected Risks

Low intensity aerobic and balance exercise poses minimal risk for healthy individuals. Like all types of exercise, there is a slight risk of sustaining a musculoskeletal injury such as a sprain or strain. There is a small risk, however, when performing aerobic and balance exercises while experiencing PCS; participants may see an increase or worsening of his/her symptoms. In order to minimize this risk, exercise will begin at a very low intensity and gradually increase. All exercise sessions will be monitored by a research team member to ensure that the session is being completed at the proper intensity. Should a participant report any PCS during a session, the session will be stopped immediately. Furthermore, to ensure that participants are healthy enough to participate in exercise, all participants will be medically cleared by Dr. Wark prior to participating in the study.

There is a minor risk that, when using the driving simulator, participants may experience symptoms such as nausea or dizziness. Breaks will be allowed during the assessment in an effort to prevent this. Water will also be readily available during the assessment should the participant require it. If a participant experiences any of these symptoms and is unable to continue, the session will end.

Physical and cognitive assessment, neuroimaging, and biomarker assessment should pose minimal risk to participants.

There is a minor social risk with respect to confidentiality. This risk will be minimized by 'de-identifying' the personal information with codes. All names will be removed from data/samples. All data will be stored in an encrypted file on the secure Sync.com account on a password-protected computer in a locked office at LU. Any hard copies of data such as screening checklists or the IPAQ will be coded and stored in a locked filing cabinet in a secure office at LU (Dr. Zerpa's current office, SB 1007). All saliva samples will be coded and stored in Dr. Lee's secure lab.

The results of this study will be published with aggregate data, that is, data which is combined and summarized so that no individual participant can be identified.

3.2 Expected Benefits

This study may directly benefit participants in the AET and SC group by potentially improving his/her PCS. This study also has benefits to the scientific community and society, in that there is scarcity of research on the effects of an AET program in individuals with PCS.

4. ELIGIBILITY

4.1 Study Setting Description

This study will be taking place at multiple sites at Lakehead University and around Thunder Bay. Participants will be recruited through the use of recruitment flyers (attached, Section 16.1) posted at various locations as well as on social media (Lakehead University School of Kinesiology Twitter and Facebook). Recruitment flyers will also be posted at Fairway Physiotherapy, as well as other local doctor's offices.

Participants will complete informed consent, screening checklist, questionnaires, ImPACT, and physical measures at the School of Kinesiology, Lakehead University.

Saliva will be collected at the School of Kinesiology, Lakehead University

Oddball and Flaker tasks will be completed at Dr. Michael Wesner's Vision Laboratory, Lakehead University

The driving simulation will be completed at the Centre for Research on Safe Driving, Lakehead University

4.2 Study Sample Description

For the experimental group, the population being evaluate is anyone age 18-50 years, at least two weeks post injury, experiencing at least one PCS symptom that is mild in severity, as well as the remaining inclusion criteria (see attached screening checklist, Section 16.3). For the heathy control group, the population being evaluated is anyone age 18-50 years, as well as the remaining inclusion criteria (see attached screening checklist, Section 16.3)

4.3 Justification when a sample includes vulnerable populations or excludes certain populations

Please refer to the exclusion criteria below. Persons who have been previously diagnosed with a psychological/neurological disorder, substance abuse disorder/impairment, or are currently seeking therapy/counselling will be excluded from the study. Participants will also be excluded if he/she verbally states that he/she does not have a valid driver's license and 12 months of driving experience.

4.4 Participant Inclusion Criteria

A participant is eligible for inclusion in the study if the individual meets all of the following criteria:

1. Man or woman aged 18-50 years.

2. Reports at least one PCS symptom that is mild in severity.

3. It has been between two weeks and six months since date of injury.

4. Is able to provide consent in English

4.5 Participant Exclusion Criteria

A participant is ineligible for the study if the individual meets any of the following criteria

1. Has been previously diagnosed with a psychological/neurological disorder
2. Has been previously diagnosed with a substance abuse disorder/impairment,
3. Is currently seeking therapy/counselling for depression,
4. Does not have valid driver's license and 12 months of driving experience.

4.6 Participant Withdrawal Criteria

Withdrawal will occur upon participant request. A participant who wishes to withdraw consent from the study will be asked to specify if he/she wish for any data or samples collected to be withdrawn from the study. Samples and data will be withdrawn in accordance with the participant's wishes.

5. STUDY DESIGN

5.1 Study Design

This study is designed as a randomized controlled trial. Potential PCS participants will be referred to another member of the research team by Dr. Wark. Potential participants will then complete the informed consent process and pre screening checklist. Potential healthy participants will contact the research team directly and set up a time to complete the informed consent, pre screening process, and IPAQ. After being deemed eligible based on the screening criteria (screening checklist attached, section), PCS participants will be randomly assigned to either an AET or standard of care (SC) intervention (see section 7). Using minimization software, each intervention group will be balanced by age and sex. Healthy participants will serve as the control group (HC) and will receive no treatment. Once participants in the SC group have completed the study, the AET will be offered, although it will not be included in the data analysis. Following informed consent, PCS participants will be provided with Garmin VivoSmart HR unit to monitor aerobic activity outside of the study (accelerometer, heart rate monitor, and step counter capabilities). Participants will be required to wear the Garmin units as often as possible for the duration of the study. In place of the Garmin VivoSmart HR unit, participants in the HC group will complete the IPAQ to determine physical activity levels prior to participating in the study,.

All participants will compete a series of pre and post intervention assessments (see section 7.2) over the course of one week at Lakehead University. Following the pre intervention assessments,

participants in the AET group will complete an eight week aerobic and balance retraining program at the School of Kinesiology, Lakehead University (see section 7.2). Participants in the SC group will continue with his/her standard of care for eight weeks. Healthy participants will be instructed not to significantly change his/her lifestyle (diet, physical activity) for the duration of the study weeks. After eight weeks, all participants will complete the assessments once again.

5.2 Number of Participants/Assignment to Treatment Groups

It is anticipated that 60 participants will be recruited into this study. Participant enrollment will be split between the AET, SC, and HC group. There will be 20 participants in each group.

5.3 Duration of Study and Study Timeline

The study is expected to last one year in total following the coordination of the research team and ethics approvals. Note: These dates are subject to change based on the date we begin participant recruitment. The relative timeline will remain the same.

Timeline	Milestone Targets
Sept 2017 - Dec 2017	Obtain ethics approval Coordinate research team
March- Dec 2019	Project start date (March 2018) Recruitment, intervention, data collection
Oct 2019- Dec 2019	Data analysis
Feb 2020	Manuscript completion Conference presentations

5.4 Length of Participation

Participation in this study will last 10 weeks, depending on scheduling of the pre and post intervention assessments. Pre intervention assessments will be conducted at Lakehead University before beginning intervention. The AET intervention will occur three times per week for eight weeks. Each session will last approximately one hour. The SC intervention will be ongoing throughout the eight weeks. The HC group will not complete an intervention. Final assessments will be completed after any intervention has concluded.

6. PARTICIPANT ENROLLMENT

6.1 Participant Identification and Recruitment Procedures

The recruitment will include the use of flyers (attached, Section 16.1) and social media. Recruitment flyers directed at potential participants with PCS will be placed in Dr. Wark's office at Fairway Physiotherapy, as well as other healthcare clinics around Thunder Bay. In order to recruit healthy participants, and to reach the general public, the research team will post the recruitment poster on the Lakehead University School of Kinesiology Facebook page and Twitter page. Posters will also be displayed around Lakehead University and various public spaces around Thunder Bay. If a potential PCS participant expressed interest in participating,

he/she will be referred by his/her healthcare provider, or referred by his/her self to Dr. Wark, who will forward his/her information to the research team if appropriate. If a potential healthy participant is interested in participating, he/she will contact the research team using the contact information on the recruitment posters. An appointment will be set up between he/she and a member of the research team at the Lakehead University School of Kinesiology.

6.2 Procedures for Informed Consent

If a potential participant contacts, or is referred to the research team, an appointment will be set up to complete the informed consent process and pre screening checklist. During this meeting, a research team member with TCPS-2 training, other than Dr. Wark, will go through the information letter and consent form (attached, Section 16.2) with the potential participant. The potential participant will be given at least 24 hours to consider volunteering for the study, as well as ask any questions they may have regarding the study. Potential participants are welcome to contact another member of the research team or any of the listed Research Ethics Boards to ask such questions prior to signing the consent form. If the potential participant wishes to consent to the study, they will indicate this by signing the consent form (attached, 16.3) and providing it to a research team member. The participant will be given a copy of the consent form to take home. The original will be retained by the research team as part of the study file.

6.3 Procedures for Participant Screening

Once informed consent is obtained, a trained member of the research team will determine the potential participant's eligibility using the screening checklist (attached, Section 16.3). If the potential participant meets these criteria, they will be included in the study and given a participant code number. If the potential participant does not meet these criteria, their signed consent form as well as the screening checklist and will be marked as a screen-fail and kept in a "Screen-Fail" binder in a locked filing cabinet in a secure office to be kept for a minimum of five years.

6.4 Procedures for Participant Enrolment /Allocation /Randomization

To achieve adequate enrolment, recruitment flyers will be placed at several locations and clinics around Thunder Bay. Once informed consent has been obtained, and the potential participant has been deemed eligible through the screening process, age and sex of the participant will be used to randomly assign the participant to an intervention group through a process called minimization. This process ensures group sizes are equal and eliminates potential bias that may be introduced which is important for clinical research of small sizes. The NOSM research assistant would then communicate the enrolment and group assignment to Dr. Paolo Sanzo who will administer the AET intervention. The SC intervention will continue under the supervision of the participant's healthcare provider. Participants will be assigned a code number by the research assistant to ensure confidentiality is maintained during the transfer of data or samples between locations.

6.5 Procedures for Participant Retention

If potential PCS participants complete the intervention, they will be allowed to keep the Garmin VivoSmart HR unit. Participants in the HC group will be eligible for a $15 gift card after completion of pre, and post assessments

7. STUDY PROCEDURES

7.1 Time and Events Schedule

Event/Activity/Procedure	Medical appointment	Informed Consent Visit	Pre-intervention assessment A (LU)	Pre-intervention assessment B (LU)	Pre-intervention assessment C (LU)	Pre-intervention assessment D (LU)	AET (3x week)/SC/HC	Post-intervention assessment (A, B, C, D)
Referral	X							
Informed Consent		X						
Screening		X						
ImPACT			X					X
BESS			X					X
Saliva				X				X
Oddball and Flanker task					X			X
Driving Simulation						X		X
Intervention							X	

7.2 Description of Study Procedures, Assessments and Participant Activities

Once participants have been randomized into groups, participants will be scheduled to complete the pre intervention assessments at Lakehead University over a period of one week. These assessments will include a physical, cognitive, neuroimaging, biomarker, and driving behaviour assessmentt. These assessments will also be completed after the intervention in PCS participants, and after eight weeks in HC.

Physical and Cognitive Assessment:

Participants will complete the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) at the School of Kinesiology, Sanders building, Lakehead University. The ImPACT will be used as a standard measure of cognitive abilities including: attention, working memory, processing speed, and reaction time. At a mutually agreed upon date and time, participants will meet a member of the research team at the Lakehead University Sanders Fieldhouse. Before beginning the assessments, a member of the research team will verbally restate the participant's rights and confirm that he/she is still willing to participate in the study.

Participants will then be set up at a computer station, where they will follow the on screen instructions for completing the ImPACT battery. Following completion of the ImPACT battery, participants will be asked to stand in a variety of static positions including: narrow based double leg stance, single leg stance, and tandem stance with one foot behind the other. Participants will perform each stance position with his/her eyes open and closed and on a firm and soft surface using the Balance Error Scoring System (BESS) protocol. Each stance will be performed over an AMTI force platform. This approach will be used to measure participant sway, centre of pressure displacement, and to count for the number of perturbation errors induced during the balance test[34]. The session should last approximately one hour.

Biomarker Assessment:

Brain-derived neurotropic factor (BDNF) will be assessed using a morning saliva sample. Participants will be asked to refrain from brushing his/her teeth, smoking, and consuming food or drink within two hours of the sample collection. Participants will also be asked to avoid alcohol consumption 12 hours prior to sampling. At a mutually agreed upon date and time, the participant will meet a member of the research team at the Sanders building, Lakehead University. Before beginning saliva collection, the member of the research team will verbally restate the participant's rights and confirm that he/she is still willing to participate in the study. Saliva will then be collected from participants in room SB-1025 (biohazard containment level 1) via the passive drool method into a tube, which will then be put on ice and transported to Dr. Lees' lab for processing. Processed saliva samples will be stored until samples have been collected from all participants. If the sample is collected immediately prior to the physical and cognitive assessments, participants will be provided with light refreshments after saliva has been collected.

To analyze salivary samples for BDNF, a sandwich ELISA technique will be used (Mandel, Ozdener, & Utermohlen, 2011). A 96-well microtiter plate (Nunc Maxisorp; VWR, West Chester, PA) will be incubated overnight at four degrees Celsius. In the 96-well plate, a total of 100 µl of monoclonal mouse anti-human BDNF (clone 35928.11; Millipore, Etobicoke, ON) will be diluted to 1 µg/ml in a filter-sterilized phosphate buffered saline (PBS) at a pH of 7.4. The plate will be washed three times, soaking for one minute between washed. It will be washed with tris-buffered saline (TBS) plus 5% tween (TBST), and blocked with 300 µl of 3% bovine serum albumin (BSA) in 0.05% PBST for two and a half hours at room temperature. Samples will then be acidified for 20 minutes to a pH of 3.0 using 1M of HCl. Samples will be neutralized after 20 minutes using 1M NaOH diluted in a 1% BSA buffer in PBST to a ratio of 1:4. Comparison will be made between samples and standards diluted in the same buffer as the samples. These will range from 15.63 to 500 pg/ml using a full-length, homodimeric recombinant BDNF (Peprotech, Rocky Hill, NJ). The plate will then be washed five times, before adding in duplicate 100 µl of sample/standard. At room temperature, the plate will then be incubated at room for two hours with agitation, before being washed five more times. After being washed again, a total of 100 µl of polyclonal chicken anti-human BDNF (2.5 µg/ml;

Promega, Madison, WI) will be added to the plate. After two and a half hours, the plate will be washed five times again. Following this incubation, 100 µl of anti-chicken IgY-HRP (1 µg/ml; Promega) will be added to each well, before being incubated for one hours. The pate will be washed five times after this incubation. A total of 100 µl of room temperature Pierce 1-Step Ultra TMB solution (Pierce Biotechnology, Rockford, IL) will then be added to each well for fifteen minutes. To stop the reaction at fifteen minutes, 100 µl 1M HCl will be added to each well to stop the reaction. The assay will be read at 450 nanometres (nm). Total BDNF (pg/ml) will be calculated by using the standard regression equation provided with the standards. To the research team's knowledge, BDNF is not used as a diagnostic tool, thus no incidental findings are expected.

Neuroimaging:

Neural processing will be assessed by using continuously recorded EEG during the performance of computer based tasks commonly used in experimental psychology for assessing divided attention and inhibitory control. At a mutually agreed upon date and time, participants will meet a member of the research team at the Sander building, Lakehead University. A member of the research team will then escort he/she to Dr. Michael Wesner's Vision Laboratory at Lakehead University. Before beginning the procedures, the member of the research team will verbally restate the participant's rights and confirm that he/she is still willing to participate in the study. Participants will be seated at a desk and fitted with an EEG cap and 32 channels will be prepared with gel. Once all recording sites are ready for recording the participant will be familiarized with the task procedures and equipment. At the desk he/she is seated at, he/she will view a monitor and be provided with a response pad. The order of the tasks presented will be counter-balanced in order to reduce the chance of order effects. Participants will be offered opportunities for breaks in between blocks of each task as well as in between the start of tasks. Event related potential (ER) will be measured for the duration of the tasks. Completion of the session should require two hours.

ODDBALL paradigm:

The Oddball paradigm is a commonly used task to test attention by requiring participants to make a specific response to rare target stimuli amongst more repetitive, distractor stimuli[35]. In this visual version, participants will be provided an instruction at the outset of a block that indicates what the target stimulus for that block will be. During each trial, a stimulus (shape/letter) will be displayed for 200 milliseconds (ms). Participants will be instructed to respond to each stimulus as quickly and accurately as possible with a button press of one of two buttons; a button to denote distractor stimuli, and a button to indicate target stimuli. The interstimulus interval will be variable (1400-1600 ms) to reduce anticipation. Participants will complete 400 trials separated into 5 blocks with an option for rests between each block.

FLANKER task:

The Flanker task is commonly used to test the ability to attend to central relevant information (the direction of an arrow) while disregarding irrelevant distracting stimuli (pairs of flanking arrows presented on either side of the central arrow). To identify the direction of the central arrow, participants will press a left or right button to indicate the direction of the central arrow. Data will be separated into time frames containing the components of interest (the N200 and P300). The session is concluded after completion of the oddball and flanker tests twice.

Behaviour Measure (Driving Simulator):

The performance of participants in a driving simulator will be assessed by measuring his/her reaction time and counting the number of passes and failures when anticipating potentially dangerous traffic situations. Reaction time will also be measured during dual-tasking activities. At a mutually agreed upon date and time, the participant will meet a member of the research team at the Sanders building, Lakehead University. A member of the research team will then escort he/she to the Centre for Research on Safe Driving (Braun Building, room 1024). Before beginning the assessment, the member of the research team will verbally restate the participant's rights and confirm that he/she is still willing to participate in the study. Participants will then be fitted with a POLAR SP0810 heart rate monitor before being introduced to the STISIM Drive® Model 400 driving simulator. Participants will be seated approximately 70% of his/her arm's length from the steering wheel with a backrest inclination of 10° (Majid et al., 2013; Yoo, An, Lee, & Choi, 2013)[36,37]. The simulator will be connected to a PowerLab (16/30) data acquisition unit which will be interfaced with LabChart 7 software. Heart rate (HR), heart rate variability (HRV), and reaction time (RT) will be measured using LabChart 7.

Participants will perform a 10 minute orientation drive to familiarized his/herself with the control and feel of the driving simulator. During the orientation drive, he/she will be exposed to examples of the dual tasking activities so that he/she will know how to successfully respond to the prompts. Once a participant feels comfortable with the simulator, the 20 minute simulation and data collection will begin. The simulation will be based on the Thunder Bay road system with traffic and pedestrians present. Weather will be clear and visibility will not be reduced. Reaction times will be measured during predetermined scenarios and will be recorded from the moment stimulus occurs to the moment the brake is depressed or evasive maneuver performed. Heart rate and HRV will be recorded throughout the duration of the simulation and will be marked at the beginning and end of each dual task scenario and reaction time activity. Participants will be exposed to several scenarios. These scenarios include: Vehicle incursion at intersection, pedestrian incursion from side of the road, sudden braking by a vehicle in front of participant, pedestrian incursion in school zone, braking by a vehicle in front of participant, and animal incursion (attached)

During dual task events, red triangles will be displayed over either of the side mirrors. These triangles will be deactivated by the press of a button on either side of the steering column, accounting for the dual tasking component of the reaction time scenarios. These scenarios will

have a three second threshold for time to react before the scenario will be considered a fail (National Safety Council, 2012; Triggs & Harris, 1982)[38,39].

In the event a participant is unsuccessful during a dual tasking scenario and collides with on screen stimuli, he/she will continue with the simulation with no second chance at completing that specific activity. If a participant begins to experience symptoms of simulator sickness, the scenario will be paused to allow him or her to take a break from the screen and/or have something to drink or eat. The research team member will have water on hand, if required by the participant. When he/she feels ready to proceed, the simulation will be resumed from the point of the original pause. If a participant feels that he/she is unable to continue, the simulation will be stopped and data collection terminated.

Aerobic and Balance Retraining Program:

After completing baseline assessments, PCS participants assigned to the AET intervention will complete an eight week supervised AET program. The program will consist of three sessions per week, approximately 40-60 minutes each. Each session will be completed under the supervision of a trainer with the Canadian Society for Exercise Physiology (CSEP-CPT) certification. At mutually agreed upon dates and times, participants will meet a member of the research team at the Sanders building, room SB-1025. Before beginning the intervention, the member of the research team will verbally restate the participant's rights and confirm that he/she is still willing to participate in the study. Participants will then be outfitted with a Polar F2 heart rate monitor, in order monitor exercise intensity during the session. Exercise intensity for each session will be based on the participant's heart rate reserve (HRR). At the first session, the participants HRR will be calculated using the Karvonen formula; Target Exercise Heart Rate = ((220-Age-Resting Heart Rate) × % Intensity) + Resting Heart Rate. Once the participant's HRR has been calculated, the participant will begin the aerobic component of the session.

The aerobic component of the session will be performed on a cycle ergometer. Participants will begin with a five minute warmup at a self selected speed, which will be used to bring the participant's heart rate to the desired intensity. Intensity for each session will start at 20% of HRR, and increase linearly by 10% for the first four weeks; at week four, participants will be cycling at an intensity of 50%. Weeks five and six will be performed at 55% of HRR, week seven will be performed at 60% of HRR, and week eight will be performed at 65% of HRR. Duration will follow a similar pattern for weeks one to four, beginning at 20 minutes and increasing in five minutes/week increments. At week five, duration will be reduced to 25 minutes, and then increase to 30 minutes for weeks six to eight.

Following completion of the aerobic portion of the session, participants will rest for five minutes before beginning the balance component of the session. Participants will perform three balance exercises (in order) each session: narrow based double leg stance, single leg stance, and tandem stance. Difficulty of these exercises will be progressively increased by modifying the

duration, surface, and whether the participant's eyes are open or closed. For weeks one and two participants will perform the exercises with his/her eyes open; participants will perform each exercise for 15 seconds on a firm service in week one, and on a low density foam block in week two. In weeks three and four, participants will perform the exercises with his/her eyes closed; exercises in week three will be performed on a firm surface, while week four will be performed on a low density foam block. Duration will be increased to twenty seconds per exercise for weeks three and four. Weeks four to eight will follow the same eyes open/closed and surface progression as weeks one to four; eyes open for weeks five and six, eyes closed for weeks seven and eight. Exercises will be performed on a firm surface in weeks five and seven, and on a low density foam block in weeks six and eight. Participants will perform each exercise for 35 seconds in weeks five and six, and 40 seconds in weeks seven and eight. Following the completion of the aerobic and balance components of the session, participants will complete a cool down consisting of a series of static stretches. Each session will conclude after the completion of the cooldown.

After completion of 24 sessions (eight weeks x three-one hour sessions per week), participants will repeat the procedures for the previously described baseline assessments. Similarly, HC and SC participants will complete the baseline assessments again after eight weeks.

8. DATA MANAGEMENT

8.1 Data Collection

A trained member of the research team will obtain age (years), sex, height (cm), and weight (kg), as well as the pre screening form (see attached screening checklist, 16.3). This data will then be uploaded to the sync.com account and completed, if necessary, by Dr. Wark.

Dr. Sanzo will administer the ImPACT and BESS. ImPACT results will be recorded and stored on the secured, password protected, ImPACT Applications, Inc. server. Data will be immediately coded by the researcher. BESS computer data will stored on a secure, password protected computer in Dr. Sanzo's secure office (currently SB-1009).

Dr. Lees will oversee the collection of the saliva sample at the School of Kinesiology, Lakehead University. The research assistant will label the tube with the participant code and will transport it back to NOSM (unless already at NOSM), where it will be immediately processed.

Oddball and Flanker tasks will be overseen by Dr. Lawrence-Dewar and Dr. Wesner. All data will be collected and analyzed in Dr. Wesner's Vision Laboratory at Lakehead University.

The driving simulation will be overseen by Dr. Zerpa at the Centre for Research on Safe Driving and recorded by the STISIM Drive® Model 400 driving simulator.

8.2 Data Management

The research team (Principal Investigator, Co-Investigators and research assistant) has access to all data if necessary. The research assistant will create a code key that will be kept on a secure Sync.com account (see below for further information, access provided through NOSM) in an encrypted file, along with the electronic coded data abstraction files. These files will be kept separate from the code key in order to prevent participant identification.

The hard copy screening checklists will be coded and stored in Dr. Zerpa's current office in a locked filing cabinet at School of Kinesiology, Lakehead University (SB-1007). Electronic copies will be uploaded to the secure Sync.com account.

Saliva samples will be immediately coded and processed/stored in the NOSM laboratory. Results of the saliva analysis will be stored in an encrypted file on a password protected computer in a secure office.

Dr. Sanzo will extract ImPACT data from the ImPACT Applications, Inc. server to a password protected computer in a secure office. Electronic data collected from the BESS will be transferred to a secure USB (for data transfer) and then to a password protected computer in a secure office. All paper and electronic data will be coded and uploaded to the secure Sync.com account.

Electronic data collected from the Oddball and Flanker tasks will be coded to a secure USB (for data transfer) and transferred to a password protected computer in a secure office. Data will then be uploaded to the secure Sync.com account.

Electronic Data collected from the driving simulation will be coded and transferred to a secure USB (for data transfer) and then to a password protected computer in a secure office. Data will then be uploaded to the secure Sync.com account.

Sync.com account details:

The website states the following:

Sync's unique, zero-knowledge storage platform guarantees your privacy by providing end-to-end encryption, and most importantly - only you have access to the encryption keys. We can't read your files. Neither can the NSA.

-Zero-knowledge, end-to-end encryption

-Privacy guarantee (we can't access your files or file metadata)

-2048 bit RSA, 256 bit AES, SSL and TLS encryption

-Files encrypted in transit and at rest

-Share controls, permissions and user administration

-Remote logout

-Remote wipe

-File audit logs

-Account notifications

-Two-factor authentication

9. SPECIMEN MANAGEMENT

A research assistant, will facilitate the collection of the saliva following an establish passive drool protocol. Participants will be instructed to drool though a straw into a collection tube. The samples will be transported Lakehead University School of Kinesiology to NOSM for processing and analysis. Salivary BDNF will be quantified using an established protocol in Dr. Lees' lab, which utilizes an enzyme-linked immunosorbent assay. All samples will be labeled with the participant code number as well as a letter for each time point. For example, A for pre-treatment, B for post-treatment. Samples will be kept until all analysis is completed, after which all labels will be removed and samples will be disposed of as biohazardous waste.

10. DATA / SPECIMEN ANALYSIS

Dr. Lees and the NOSM research assistant will be performing data analysis on the saliva samples at NOSM. Dr. Sanzo, Dr. Lawrence-Deware, Dr. Wesner, and Dr. Zerpa will be performing analysis on the physical and cognitive measures at Lakehead University. The main analysis will be a comparison of the pre- and post-outcomes.

Dr. Paolo Sanzo will perform the analysis of the data collected related to balance from the AMTI force platform and ImPACT neurocognitive assessment. The AMTI force platform measures the ground reaction forces that are generated by a body standing or moving across the plate. The AMTI force plate is also capable of measuring torques about each axis and has six degrees of freedom, which includes three forces (f_z, f_x, and f_y) and three moments (M_z, M_x, and M_y). All of these measures are fed into an AMTI amplifier and converted to digital signals via an analog to digital converter. The information collected by the force platform is then uploaded into BIOSOFT computer software which allows the researcher to view and analyze data following collection. The BIOSOFT computer software calculates the x and y moments of postural sway which are used to compute the variables of interest and produces graphical representations of this data. Descriptive statistics will be calculated to provide the mean and standard deviations for the variables of interest including the area of the centre of pressure, velocity of centre of pressure, length of centre of pressure, and displacement of centre of pressure. The main objective of the analysis is to compare pre- and post-treatment changes in balance. The ImPACT measures components of cognitive functioning including: attention, concentration, reaction time, memory, processing speed, decision making, problem solving, and response variability. The main objective of this component of the analysis will be to compare pre- and post-treatment changes in composite scores for the variables described.

Dr. Carlos Zerpa will perform the analysis on the data collected from the driving simulator. This analysis will include the comparison of people with concussion who will undergo AET to those

going through regular standard of care and healthy control on measures of reaction time for dual and non dual tasking driving events. The analysis will be performed pre and post intervention to examine the interaction effect between group and time on measures of reaction time. The statistical analysis will include descriptive statistics to calculate means and standard deviation for each group for the pre and post test data. A mixed factorial analysis of variance will also be performed with group as the independent factor, time (pre and post intervention) as the repeated measure and reaction times as the dependent variable to examine the effect of the AET.

Preprocessing and analysis may either occur on Dr. Wesner's recording computer using asa-lab software or a separate analysis computer (also password protected) using EEGlab software. Prior to analysis data will be segmented into epochs around each event (trial) presentation. Data will be temporally filtered. Baseline line correction using the 200 ms before the stimulus presentation will be applied. Artifact detection and removal will be applied to remove trials that have been affected by excessive head motion (for example blinking, general body movement). Once preprocess, all the trials from the same condition type will be averaged to create an event-related potential for each condition type. This data, for each participant will be exported for statistical analysis (performed in JASP). Repeated measures ANOVA will be used to determine if there are significant between group and between condition differences.

Missing data will be handled according to the type of data that is missing. For analyses that depend on change (pre- vs post-), if a participant misses an assessment (i.e saliva) we will have to exclude the participant's results for that assessment. If the rest of the assessments were completed pre and post intervention, then they will be included in the data analysis.

There will be no interim analysis.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size Calculation

A priori power analysis was conducted to determine that we would have 80% power at alpha = .05 (two tailed) to detect a medium to large effect size with 12 participants in each group, leaving room for a 13% dropout rate. We therefore propose 20 participants per group.

11.2 Statistical Analysis

The main analysis will be a mixed factorial ANOVA to examine interaction effects between group (AET, SC, and HC) and time (pre- and post-) on measures of ERP, balance, BDNF and reaction time. If an interaction is found between group and time on any of the dependent variables (ERP, balance, BDNF and reaction time), the interaction will be explained using simple main effects. If no interaction is found for any of the dependent variable measures, the main effects for time and groups will examined by a post hoc analysis to determine differences between groups. We anticipate greater change in the AET group compared to SC and HC group.

12. OTHER STUDY ADMINISTRATION CONSIDERATIONS

12.1 Concomitant use of medications or interventions during the course of the study

All relevant concomitant care and interventions are permitted throughout the study.

12.2 Allocation sequence generation and concealment mechanism

To randomize participant group assignment, an online program called QMinim (http://rct.mui.ac.ir/qminim/) will be utilized. This program uses a process called minimization which ensures group sizes are equal and eliminates potential bias that may be introduced which is important for clinical research of small sizes (BMJ 2005;330:843).

12.3 Blinding Procedures

Participants will no be blinded to his/her group assignment. Participants placed into the SC group will be given the option of receiving the AET after completion of the study, although this will not be included in data analysis.

Dr. Lees, Dr. Zerpa, Dr. Lawrence-Dewar, and Dr. Wesner will be blinded from group assignment for data analysis purposes.

12.4 Premature discontinuation or termination of the study

The study sponsor/investigator and the Research Ethics Board reserve the right to terminate this research study at any time. Reasons for termination include but are not limited to:

The occurrence of adverse events poses a potential health risk for participants;

Unsatisfactory participant enrollment;

Investigator request to withdraw from study;

Noncompliance with the protocol or regulatory guidelines are not being followed;

REB decision to terminate or suspend approval for the investigation or Investigator.

12.5 Ancillary and post-trial care

Participation in this study is not expected to cause any harm, and the participant can withdraw at any time. There is no compensation as the participant agrees to the risks outlined in the information letter.

13. QUALITY CONTROL AND QUALITY ASSURANCE

We are able to track adherence to the protocol because the intervention requires a visit which is documented in the data abstraction form. All data will be translated into the data abstraction forms. To promote data quality, all team members will be trained in their duties. All questionnaires to be used are valid (see Section 7.2).

13.1 Data Integrity Measures

See above. All members of the research team are responsible for adhering to the protocol and ensuring data quality.

13.2 Training Study Staff

All members of the research team will be protocol trained. All duties to be performed by members of the research team will be delegated by the Principal Investigator. Appropriate task training will be completed by the PI/research team prior to the study start. All supervisors for the AET program will be certified by the Canadian Society for Exercise Physiology. The NOSM research assistant is TCPS 2 CORE trained in order to administer informed consent. Dr. Lees will supervise the NOSM research assistant who is already trained in all protocols covering the roles of saliva analysis and group assignment.

13.3 Auditing and Monitoring

There is no auditing conduct.

14. REGULATORY CONSIDERATIONS

14.1 Participant privacy and confidentiality

Data will be kept confidential throughout the study through the following measures:

-a key will be created with a list of participant names and their respective codes, in a password protected encrypted document on a secure computer at Lakehead University. This computer will remain in a locked cabinet in a locked office except when in use at one of the research sites, as well as when in transport between sites. Only the research team will have access to the key.

-The key will be kept in a separate file (using a different password) from all original raw data,

- To ensure participant data can be immediately coded following collection, the key will be placed in an encrypted folder in a secure Sync account, (see below for more details) to which only research team members will have access.

- Saliva samples will be coded immediately following the draw

- All data abstraction forms and screening tools will be coded and abstraction forms will only be electronic (saved into password protected folders on secure Sync account),

- No data will leave the collection site uncoded, -Only members of the research team will have access to the data,

- Data will be stored in secure offices on password protected computers at the location they were collected,

- All data published will use aggregate data so no individual person can be identified.

The data will not be disclosed to third parties, and original signed consent forms/coded screening tools will stay in secure filing cabinets in Dr. Zerpa's secure office at the Lakehead University School of Kinesiology (currently number SB 1007). All data will be kept for a minimum of five years, after which it will be destroyed. Any data collected during the screening process (signed consent forms, screening checklists) for a potential participant who does not meet the criteria, and who will therefore not be included in the study, will be securely destroyed in a locked Enviroshred box for confidential shredding.

14.2 Ethical Review

It is the understanding of the sponsor that this protocol as well as appropriate consent procedures will be reviewed and approved by the Thunder Bay Regional Health Science Centre. This board operate in accordance with the current Canadian Regulations. Approval from the board will be obtained before starting the study, and will be documented in a letter to the investigator specifying the date on which the board met and granted the approval. All protocol modifications will be reviewed and approved by the appropriate Research Ethics Boards in accordance with local requirements, before the changes can be implemented. Modifications which eliminate an apparent immediate hazard to participants do not require pre-approval by the Research Ethics Board. Such deviations will be recorded and explained in the annual REB report.

14.3 Scientific Review

The Northern Ontario Academic Medical Association has reviewed this study.

14.4 Institutional Review

This protocol as well as required resources will be reviewed and approved by the Thunder Bay Regional Health Sciences Centre Research Program. Approval must be obtained prior to initiating the study.

14.5 Clinical Trial Registration

This study will be registered as a clinical trial at ClinicalTrials.gov

14.6 Retention of Study Documents

All original signed consent forms and screening checklists will be maintained confidentially at Lakehead University School of Kinesiology in a locked filing cabinet in Dr. Zerpa's secure office (currently SB-1007). To protect participant data, each participant will be given a code. A code key will be created in a password-protected and encrypted file away from raw data. This key will also be placed on the secure Sync.com account. All data abstraction forms will be electronic and coded. They will be stored in an encrypted file on the Sync.com account.. All data will be kept for a minimum of 5 years after which it will be destroyed securely.

14.7 Data Monitoring Committee

There will be no data monitoring committee.

14.8 Unanticipated Problems

All adverse events will be recorded and will be reported appropriately as outlined in the REB guidelines.

14.9 Publication of Data and Protection of Trade Secrets

The results from this study will be published in a peer-reviewed scientific journal as aggregate data. The research team will have access to all coded data until the storage period is complete.

14.10 Dissemination

Participants can inquire about his/her own as well as aggregate study results. Aggregate data will be communicated to healthcare professionals and the public via presentations at local scientific conferences (such as the Northern Heath Research Conference, Northern Constellations, or the Showcase of Healthcare Research) and a publication in a peer-reviewed scientific journal.

All research team members who have contributed intellectual input into the study design and/or interpretation of results, or contributed to data collection and/or analysis will be included as authors. Members of the research team will write any manuscripts resulting from the study.

14.11 Declaration of interests

There are no financial or other competing interests for any member of the research team.

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16. APPENDICES

16.1 Recruitment materials

Do you have symptoms related to a concussion?

Help local researchers examine the effects of exercise on persistent symptoms

Who can participate?

- Adults between 18 and 50 years
- Fluent in English
- No history of neurological disorder
- 2 weeks to 6 months since injury
- Drivers license
- Not currently seeking counselling/therapy for depression

Contact us for more information!

Lakeheadconcussion@gmail.com

Dr. Carlos Zerpa
Assistant Professor
Lakehead University

Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

Lakehead University | School of Kinesiology

Thunder Bay Regional Health Sciences Centre

For more Information about your rights as a research participant, contact the TBRHSC Ethics Board Chair at 684-6422

Are you a healthy individual with no concussion symptoms?

Help local researchers examine the effects of exercise on persistent symptoms

Who can participate?

- Adults between 18 and 50 years
- Fluent in English
- No history of neurological disorder
- Drivers license
- Not currently seeking counselling/therapy for depression

Contact us for more information!

Lakeheadconcussion@gmail.com
Dr. Carlos Zerpa
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Lakehead University

Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario
Lakehead University School of Kinesiology
Thunder Bay Regional Health Sciences Centre

For more Information about your rights as a research participant, contact the TBRHSC Ethics Board Chair at 684-6422

16.2 Informed consent materials

** On Lakehead University, Northern Ontario School of Medicine, and Thunder Bay Regional Health Sciences Centre letterhead**

Healthy control information letter

Principal Investigator:	Dr. Sheryl Wark, Family & Sport Medicine Physician, Fairway Physiotherapy Assistant Professor, Northern Ontario School of Medicine (NOSM) (807-344-5242)
Co-Investigators	Dr. Simon Lees, Associate Professor, NOSM Dr. Paolo Sanzo, Associate Professor, NOSM and Lakehead University, School of Kinesiology Dr. Jane Lawrence-Dewar Dr. Carlos Zerpa, Assistant Professor, Lakehead University, School of Kinesiology Dr. Michael Wesner, Associate Professor, Lakehead University, Psychology Department
Funding provided by:	Northern Ontario Academic Medical Association (NOAMA)

Dear Potential Participant,

We are inviting you to participate in a research study. The name of this study is "A Multi-modal Evaluation of a Physical Intervention Approach to Treating Persistent Post-Concussive Symptoms". Please keep in mind that this is an invitation, and by no means are you required to participate. This study has been funded through the Northern Ontario Academic Medical Association (NOAMA) through their Clinical Innovation Opportunities Fund. We have asked you to participate because you are a healthy individual, 18-50 years of age, free of any psychological/neurological disorder, no history of substance abuse, are not currently undergoing therapy or counselling for depression, and have a valid drivers license

We are a group of researchers and doctors from the Northern Ontario School of Medicine (NOSM) and Lakehead University. The research team includes Dr.

Sheryl Wark, Dr. Simon Lees, Dr. Paolo Sanzo, Dr. Jane Lawrence-Dewar, and Dr. Carlos Zerpa, and Dr. Michael Wesner.

What is the usual treatment?

Treatment of concussions usually involves complete physical and mental rest until symptoms are no longer present. In many people, symptoms of a concussion can resolve in 7-10 days. In a minority of people, these symptoms can last longer than 710 days and may last months or years. In persons who experience long term symptoms, some studies have shown that mental and physical rest may not be beneficial.

Why is this study being done?

Persons with PCS may experience difficulties completing day to day tasks, such as driving, concentrating, or exercising. This reduces a person quality of life and puts a strain on the healthcare system. The goal of the research study is to determine the effectiveness of an aerobic exercise therapy (AET) on PCS, which will include mild aerobic and balance training. An AET program has previously been studied for the treatment of PCS, and results have been promising. As a participant who does not have PCS, if you are participating, you will complete a few initial assessments. These assessments include a computerized concussion test, balance test, reaction test, driving test, and a saliva test over a one week period. After eight weeks, you will complete the same assessments again.

If you would like to participate in this study, an appointment will be set up between you and a member of the research team at Lakehead University. The purpose of this appointment will be to inform you of your rights as a participant and fill out an informed consent form. Over the course of the whole study, you will be asked to participate in up to eight assessment visits, four at the beginning, four at the end (described below), including a computerized concussion test, simple balance test, reaction tests, and driving simulation. Your saliva will also be collected at some point during this week as well.

The ImPACT computerized concussion test and balance test will be conducted at the Sanders building, Lakehead University. For the ImPACT test, you will be seated at a computer station, where you will follow on screen instructions designed to evaluate mental functioning. The ImPACT test should last 30-45 minutes. The balance test will involve single and double leg stances, with and without your eyes closed. The balance test will be performed on a force

platform, which will measure how much your center of mass and center of pressure moves, as well as the speed at which they move. The entire session should last approximately one hour

For the computerized reaction test, you will meet a member of the research team at the Sanders building, Lakehead University, where you will be escorted to Dr. Dr. Michael Wesner's Vision Laboratory at Lakehead University. Here, you will complete two computerized reaction tests while wearing a specialized head cap. This cap will allow us to measure brain activity non-invasively during these tests. The tests will involve a series of visual stimuli on a computer screen, which will require you to press a corresponding button to the stimuli shown. The reaction tests should last approximately two hours.

For the driving simulation, you will meet a member of the research team at the Sanders building, Lakehead University, where you will be escorted to the Centre for Research on Safe Driving in the Braun building, Lakehead University. The simulation will replicate driving conditions of Thunder Bay, and ask you to respond to a series of scenarios including: vehicle entering an intersection, pedestrian running on to the road, sudden braking by a vehicle in front of you, pedestrian running on to the road in a school zone, braking by a vehicle in front of you, and an animal running onto the road. These assessments will also be completed while you are required to perform a second task during the scenario, such as pressing a button when your side mirror is covered. This visit should take less than an hour.

The saliva draw will be completed in the Sanders building, room SB-1025, Lakehead University. For the saliva draw, you will be asked not to brush your teeth, smoke, eat, or drink for 2 hours before saliva collection. You will also be asked not to consume alcohol for 12 hours before saliva collection. You will passively drool into a tube, which will be collected and analysed in a lab for brain-derived neurotrophic factor (BDNF). Higher levels of BDNF have been associated with improvements in mental functioning.

Following the baseline assessments, you will be asked to return after eight weeks to take the tests once again. During this time, you will be instructed not to significantly change your physical activity level. Upon completion of the study, you will be eligible for a $25 gift card.

What will happen during this study?

You will be asked to complete the baseline assessments. After eight weeks, you will be asked to return and complete the assessments again. Below you will find an overview of the study.

Study Overview:

Week	1 & 10				2-9
Event	ImPACT & balance	Reaction test	Driving simulation	Saliva	None
Time Required	1 hour	2 hours	1 hour	15 minutes	No required appointments

How many people will take part in this study?

It is anticipated that 60 participants will be recruited into this study.

Recruitment, data collection and analysis will continue over the span of 6 months. Your direct participation, however, will only last 9-10 weeks depending on scheduling of the preliminary and final assessments.

What are the risks or harms of participating in this study?

No serious side effects or risks such as stroke, heart attack or death are anticipated due to participation in this study. During the driving simulation, there is a small chance that you will experience dizziness or nausea. If this happens, the simulation will be paused to allow you to rest, or stopped completely.

What are the benefits of participating in this study?

The purpose of this study is to gather this information and our research may impact how people suffering from PCS are treated. Research investigating PCS and AET is important work and this study will serve to expand the knowledge in this field.

Can participation in this study end early?

Your participation in this study may end early if you choose to withdraw for any reason. If you wish to withdraw consent from the study, you will be asked to specify if you wish for any data or samples collected to be withdrawn as well. Samples and data will be withdrawn in accordance with your wishes. You are under no obligation to participate in this study, and you may choose to withdraw from it at any point by contacting Dr. Carlos Zerpa (807-343-8940), the primary contact for this study. During the course of the research project, you will be given all information

that is relevant to your decision to continue or withdraw from the study, as well as information on your right to request the withdrawal of collected data.

What are the costs of participating in this study?

There are no fees associated with participation in the research. If you choose to park at the assessment locations, there are fees associated with these parking lots. Parking fees at Lakehead University for study visits will be reimbursed.

What happens if I have a research related injury?

There is no compensation or insurance coverage for research-related injuries, however, we do not anticipate any to occur during your participation in this study. Please note that by consenting to participate in this study, you have not waived any rights to legal recourse in the event of research-related harm**.**

Are study participants paid to participate in this study?

There will be no prorated payments. Parking costs for study visits at Lakehead University will be reimbursed. Upon completion of the study, you will be able to keep the activity monitors.

How will my information be kept confidential?

As described above, all personal data (test scores and saliva samples) that are collected will be de-identified through a coding process, and only the research team will have access to this data and the samples. Collected hard copies of the data will be stored in a secure file cabinet in a locked office. Computer data will be kept on a secure server on a password protected computer. Saliva samples will be stored in a secure laboratory at NOSM until analysis, after which they will be securely disposed of. All data/samples will be stored for a minimum of five years. When the study is finished, we will write up our aggregate results, that is, data which is combined and summarized so that no individual participant can be identified in manuscripts. These manuscripts may then be published in academic journals. We will also present our results at academic conferences. If you are interested in the results of the study, we can arrange to have those results sent to you. Please ask a member of our team; we would be happy to provide them to you. Dr. Carlos Zerpa will be the sponsor for this study, and the research team as a whole will act as study monitors and auditors. These people, as well as the research ethics boards at TBRHSC will be granted access to the information you provide and data collected as a result of your participation in this study for verification of clinical trial procedures/data without violating your confidentiality to the extent permitted by the applicable laws and regulations. A description of

this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Do the investigators have any conflicts of interest?

There will be no commercialization of the study findings by the researchers. There are no real, potential, or perceived conflicts of interest on the part of the researchers, their institutions, or the research sponsors. None of the research team members will receive a fee for your enrollment.

What are the rights of participants in a research study?

If you have any questions regarding this study, please feel free to contact the research team. The primary contact for this study is Dr. Carlos Zerpa and he can be reached at 807- 343-8940; czerpa@lakeheadu.ca. This project has been approved by the ethics board at TBRHSC. If you have any concerns regarding your rights as a research participant, or wish to speak to someone other than a research team member about this research project, you are welcome to contact the:

Chair, Research Ethics Board

Thunder Bay Regional Health Sciences Centre

Phone: 807-684-6422

Fax: 807-684-5904

Email contact for REB: TBR_REO@tbh.net

We understand that you may need some time to consider your participation, so you may take at least 24 hours to assimilate the information provided, pose any questions you may have, and discuss and consider whether you will participate.

We thank you for your time,

Dr. Sheryl Wark,	Dr. Simon Lees,
Dr. Paolo Sanzo,	Dr. Jane Lawrence-Dewar
Dr. Carlos Zerpa	Dr. Jane Lawrence-Dewar
Dr. Michael Wesner	Sarah Niccoli

PCS information letter

Principal Investigator:	Dr. Sheryl Wark, Family & Sport Medicine Physician, Fairway Physiotherapy Assistant Professor, Northern Ontario School of Medicine (NOSM) (807-344-5242)
Co-Investigators	Dr. Simon Lees, Associate Professor, NOSM Dr. Paolo Sanzo, Associate Professor, NOSM and Lakehead University, School of Kinesiology Dr. Jane Lawrence-Dewar, Assistant Professor NOSM, Adjunct Professor Lakehead University, School of Kinesiology Dr. Carlos Zerpa, Assistant Professor, Lakehead University, School of Kinesiology Dr. Michael Wesner, Associate Professor, Lakehead University, Psychology Department
Funding provided by:	Northern Ontario Academic Medical Association (NOAMA)

Dear Potential Participant,

We are inviting you to participate in a research study. The name of this study is "A Multi-modal Evaluation of a Physical Intervention Approach to Treating Persistent Post-Concussive Symptoms". Please keep in mind that this is an invitation, and by no means are you required to participate. This study has been funded through the Northern Ontario Academic Medical Association (NOAMA) through their Clinical Innovation Opportunities Fund. We have asked you to participate because you have been referred by Dr. Wark, are currently experiencing persistent post-concussive symptoms (PCS) and it has been two weeks to six months since the date of injury, are 18-50 years of age, free of any psychological/neurological disorder, no history of substance abuse, are not currently undergoing therapy or counselling for depression, and have a valid drivers license.

We are a group of researchers and doctors from the Northern Ontario School of Medicine (NOSM) and Lakehead University. The research team includes Dr. Sheryl Wark, Dr. Simon Lees, Dr. Paolo Sanzo, Dr. Jane Lawrence-Dewar, Dr. Carlos Zerpa, and Dr. Michael Wesner.

What is the usual treatment?

Treatment of concussions usually involves complete physical and mental rest until symptoms are no longer present. In many people, symptoms of a concussion can resolve in 7-10 days. In a minority of people, these symptoms can last longer than 7-10 days and may last months or years. In persons who experience long term symptoms, some studies have shown that mental and physical rest may not be beneficial.

Why is this study being done?

Persons with PCS may experience difficulties completing day to day tasks, such as driving, concentrating, or exercising. This reduces a person quality of life and puts a strain on the healthcare system. The goal of the research study is to determine the effectiveness of an aerobic exercise therapy (AET) on PCS, which will include mild aerobic and balance training. An AET program has previously been studied for the treatment of PCS, and results have been promising. If you are participating, you will complete a few initial assessments over the course of one week. These assessments include a computerized concussion test, balance test, reaction test, driving test, and a saliva test. Following completion of the assessments, you will complete either an AET or standard of care (SC) intervention for eight weeks. After eight weeks you will repeat the assessments.

If you would like to participate in this study, an appointment will be set up between you and a member of the research team at Lakehead University. The purpose of this appointment will be to inform you of your rights as a participant and fill out an informed consent form. Over the course of the whole study, you will be asked to participate in up to eight assessment visits, four at the beginning, four at the end (described below), including a computerized concussion test, simple balance test, reaction tests, and driving simulation. Your saliva will also be collected at some point during this week as well. If you are in the AET group, you will also be asked to participate in 24 training visits, described below. Additionally, you will be given an activity monitor to be worn on your wrist for the duration of the study.

The ImPACT computerized concussion test and simple balance test will be conducted at the Sanders building, Lakehead University. For the ImPACT test, you will be seated at a computer station, where you will follow on screen instructions designed to evaluate mental functioning. The balance test will involve single and double leg stances, with and without your eyes closed. The balance test will be performed on a force platform, which will measure how much your center of mass and center of pressure moves, as well as the speed at which they move. The entire session should last approximately one hour

For the brain imaging, you will meet a member of the research team at the Sanders building, Lakehead University, where you will be escorted to Dr. Michael Wesner's Vision Laboratory at Lakehead University. Here, you will complete two computer-based reaction tasks while wearing a specialized head cap. This cap will allow us to measure brain activity non-invasively during tasks. In order for the recording electrodes to monitor brain activity, we will place electrode gel at each recording location. The gel may feel slimy and cool at first. Once the

recording sites are ready, the experimenter will review the instructions of the computer based tasks for you. These tasks will require you to make a button press as quickly and accurately as possible when a target image appears on the computer screen. The whole procedure including set up and recordings should last approximately two hours. There is shampoo and towels available at the lab should you want to wash your hair in a sink following the study.

For the driving simulation, you will meet a member of the research team at the Sanders building, Lakehead University, where you will be escorted to the Centre for Research on Safe Driving in the Braun building, Lakehead University. The simulation will replicate driving conditions of Thunder Bay, and ask you to respond to a series of scenarios including: vehicle entering an intersection, pedestrian running on to the road, sudden braking by a vehicle in front of you, pedestrian running on to the road in a school zone, braking by a vehicle in front of you, and an animal running onto the road. These assessments will also be completed while you are required to perform a second task during the scenario, such as pressing a button when your side mirror is covered. This visit should take less than an hour.

The saliva draw will be completed in the Sanders building, room SB-1025, Lakehead University. For the saliva draw, you will be asked not to brush your teeth, smoke, eat, or drink for 2 hours before saliva collection. You will also be asked not to consume alcohol for 12 hours before saliva collection. You will passively drool into a tube, which will be collected and analysed in a lab for brain-derived neurotrophic factor (BDNF). Higher levels of BDNF have been associated with improvements in mental functioning.

Following the baseline assessments, you will be assigned to either the AET group or SC group. If you are assigned to the AET group, you will begin a three days per week, eight week AET intervention. If you are assigned to the SC group, you will continue with your current PCS treatment. All AET sessions will be completed at the Sanders building, Lakehead University, under the supervision of a trainer that has the Canadian Society of Exercise Physiology Certified Personal Trainer (CSEP-CPT) certification. For all sessions, you will wear a heart rate monitor to measure exercise intensity. The aerobic portion of the session will be completed on a stationary bicycle. During week one, you will complete a five minute warmup, followed by 20 minutes of cycling at a low intensity. From week to week, the duration and intensity will be adjusted to gradually increase difficulty.

Following the aerobic portion of each session, you will complete a series of balance exercises. These exercises will be the same as completed during the preliminary test. In week one, difficulty will be kept low. As with the aerobic portion of the session, difficulty will be increased from week to week. Difficulty will be increased by adjusting duration, surface (firm or soft), and if your eyes are open or closed during the exercises. Each session will conclude with a cooldown consisting of static stretching.

After eight weeks you will repeat the baseline testing. If you were in the SC group, you will be offered the AET intervention following completion of the study. You will be able to keep the activity monitors following completion of the study.

What will happen during this study?

You will be randomly assigned to either the AET or the SC group upon consent. We will be using randomization software that will help balance enrolment numbers in each group. Because of this, the chance that you will be placed in either group is not exactly 50/50, but it is still a random assignment. The participants placed in the SC group will be offered the AET once their participation in the study is complete, and this will not be included in data analysis. Below you will find an overview of the study for participants assigned to the AET and SC interventions.

AET Overview

Week	1 & 10				2-9
Event	ImPACT & balance	Reaction test	Driving simulation	Saliva	AET intervention
Time Required	1 hour	2 hours	1 hour	15 minutes	1 hour, 3x per week

SC Overview

Week	1 & 10				2-9
Event	ImPACT & balance	Reaction test	Driving simulation	Saliva	SC intervention
Time Required	1 hour	2 hours	1 hour	15 minutes	No required appointments

How many people will take part in this study?

It is anticipated that 60 participants will be recruited into this study. Recruitment, data collection and analysis will continue over the span of 6 months. Your direct participation, however, will only last 9-10 weeks depending on scheduling of the preliminary and final assessments.

What are the risks or harms of participating in this study?

No serious side effects or risks such as stroke, heart attack or death are anticipated due to participation in this study. During the driving simulation, there is a small chance that you will experience dizziness or nausea. If this happens, the simulation will be paused to allow you to rest, or stopped completely.

Low intensity aerobic and balance exercise has minimal risk for healthy individuals. Like all types of exercise, there is a small risk of experiencing an injury such as a sprain or strain. There is a small risk when performing aerobic and balance exercises while experiencing PCS; participants may see an increase or worsening of his/her symptoms. In order to reduce this risk, exercise will be very easy to begin, and gradually get harder over the eight weeks. All exercise sessions will be monitored by a research team member to ensure that the session is being completed at the proper intensity. Should you report any signs of PCS during a session, the session will be stopped immediately. Furthermore, to ensure that you are healthy enough to participate in exercise, all participants will be medically cleared by Dr. Wark prior to participating in the study.

What are the benefits of participating in this study?

While we are unsure of the direct benefit to you, the participant, there is the Possibility that AET and SC will improve your PCS symptoms. The purpose of this study is to gather this information and our research may impact how people suffering from PCS are treated. Research investigating PCS and AET is important work and this study will serve to expand the knowledge in this field.

Can participation in this study end early?

Your participation in this study may end early if you choose to withdraw for any reason. If you wish to withdraw consent from the study, you will be asked to specify if you wish for any data or samples collected to be withdrawn as well. Samples and data will be withdrawn in accordance with your wishes. We want to assure you that whether you choose to participate or not participate in the study, your medical care will not be affected in any way. You are under no obligation to participate in this study, and you may choose to withdraw from it at any point by contacting Dr. Carlos Zerpa (807-343-8940), the primary contact for this study. Participation, refusal to participate, or withdrawal from participation will not in any way affect your care from Dr. Wark or your primary care physician/healthcare provider. During the course of the research project, you will be given all information that is relevant to your decision to continue or withdraw from the study, as well as information on your right to request the withdrawal of collected data.

What are the costs of participating in this study?

There are no fees associated with participation in the research. If you choose to park at the assessment locations, there are fees associated with these parking lots. Parking fees at Lakehead University for study visits will be reimbursed.

What happens if I have a research related injury?

There is no compensation or insurance coverage for research-related injuries, however, we do not anticipate any to occur during your participation in this study. Please note that by consenting to participate in this study, you have not waived any rights to legal recourse in the event of research-related harm**.**

Are study participants paid to participate in this study?

There will be no prorated payments. Parking costs for study visits at Lakehead University will be reimbursed. Upon completion of the study, you will be able to keep the activity monitors.

How will my information be kept confidential?

As described above, all personal data (test scores and saliva samples) that are collected will be de-identified through a coding process, and only the research team will have access to this data and the samples. Collected hard copies of the data will be stored in a secure file cabinet in a locked office. Computer data will be kept on a secure server on a password protected computer. Saliva samples will be stored in a secure laboratory at NOSM until analysis, after which they will be securely disposed of. All data/samples will be stored for a minimum of five years. When the study is finished, we will write up our aggregate results, that is, data which is combined and summarized so that no individual participant can be identified in manuscripts.

These manuscripts may then be published in academic journals. We will also present our results at academic conferences. If you are interested in the results of the study, we can arrange to have those results sent to you. Please ask a member of our team; we would be happy to provide them to you. Dr. Carlos Zerpa will be the sponsor for this study, and the research team as a whole will act as study monitors and auditors. These people, as well as the research ethics boards at TBRHSC will be granted access to the information you provide and data collected as a result of your participation in this study for verification of clinical trial procedures/data without violating your confidentiality to the extent permitted by the applicable laws and regulations. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Do the investigators have any conflicts of interest?

There will be no commercialization of the study findings by the researchers. There are no real, potential, or perceived conflicts of interest on the part of the researchers, their institutions, or the research sponsors. None of the research team members will receive a fee for your enrollment.

What are the rights of participants in a research study?

If you have any questions regarding this study, please feel free to contact the research team. The primary contact for this study is Dr. Carlos Zerpa and he can be reached at 807- 343-8940; czerpa@lakeheadu.ca. This project has been approved by the ethics board at TBRHSC. If you have any concerns regarding your rights as a research participant, or wish to speak to someone other than a research team member about this research project, you are welcome to contact the:

Chair, Research Ethics Board
Thunder Bay Regional Health Sciences Centre
Phone: 807-684-6422
Fax: 807-684-5904
Email contact for REB: TBR_REO@tbh.net

We understand that you may need some time to consider your participation, so you may take at least 24 hours to assimilate the information provided, pose any questions you may have, and discuss and consider whether you will participate.

We thank you for your time,

Dr. Sheryl Wark,
Dr. Paolo Sanzo,
Dr. Carlos Zerpa
Dr. Michael Wesner
Dr. Simon Lees,
Dr. Jane Lawrence-Dewar
Sarah Niccoli

16.3 Screening checklists

Inclusion/Exclusion Criteria Screening Checklist- PCS

Participant number _____

- Person aged 18-50 years
- Fluent in English
- Experience injury greater than 2 weeks ago?
- Experienced injury less than 6 months ago?
- Not diagnosed with psychological/neurological disorder
- Not diagnosed with depression
- Not currently seeking counselling/therapy for depression
- Has valid drivers license with 12 months driving experience

Inclusion/Exclusion Criteria Screening Checklist- HC

Participant number _____

- o Person aged 18-50 years
- o Fluent in English
- o Not diagnosed with psychological/neurological disorder
- o Not diagnosed with depression
- o Not currently seeking counselling/therapy for depression
- o Has valid drivers license with 12 months driving experience

16.4 Data abstraction form

Participant Number:_____
Consent Date:
_____

Sex (male/female)	
Height (cm)	
Weight (kg)	
Age (in years)	
Date of injury	
Date of first assessment	

Past Medical History	(Y/N)		
Concussion		How many?	
Traumatic brain injury			
Migraine			
ADHD			
Motion sickness			

16.5 International Physical Activity Questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information
More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

16.6 Study budget

Year 9 . 2016-17
version P2 9.0

AHSC AFP Innovation Fund

FORM P2 PROPOSAL BUDGET

PROPOSAL BUDGET BREAKDOWN

Please save as a PDF file before sending to your Governance Organization along with P1. For instructions on how to add or delete rows as required, visit ifpoc.org and view the instruction under the P2 section.

Provide a brief description and justification of all requested budget expenditures with sufficient detail to allow for an assessment of their eligibility. Compensation support for AFP physicians should be in accordance with Governance Organization Guidelines. For personnel expenses: include the position, title and costs for a full time equivalent as well as benefits including salary support for non AFP physicians (if eligible), research assistants, other health care professionals or administrative staff.

List other expenses - refer to local and IFPOC Provincial guidelines for restrictions: "Innovation Funds should be used to support the human resources and infrastructure necessary to implement, test and/or evaluate new concepts and modes of health care delivery. In general, the funds are not intended for equipment; however, the innovative use of equipment could form the basis of a project. Funding may not be used to defray the cost of implantable medical devices or drug trials. While this funding is clearly intended to support innovative clinical care to patients, it is not intended as a substitute for perceived inadequacies in either the OHIP fee schedule or individual institutional funding."

The budget should also specify the contributions (cash or in-kind) of any other funders/contributors.

Please note that "other sources" could include the following:
- AFP funds not provided by Innovation Fund
- Cash contributions from funding bodies such as CIHR, or other partnering organizations such as CCO, or CCN
- Cash contributions from businesses and/or other community organizations
- Cash contributions from practice plans, or other sources

Finally, "other sources" does NOT include in-kind contributions... these should be listed separately on the final page of this budget.

Innovation Fund Project Budget
Project Title

version P2 9.0

Project Lead #1
Name
Dr. Sheryl Wark
Email
swark@nosm.ca
Project Lead #2
Name
Email

AFP Physician Compensation Funded by the Innovation Fund	Year 1	Year 2 (If applicable)	Total
AFP Physician Compensation (list names with time commitment ie .5 day per wk per yr)			$ -
Dr. Sheryl Wark - estimated 32 hours over the year, plus parking and mileage (See note 1)	$ 5,192.00		$ 5,192.00
			$ -
Subtotal - Physician Compensation - A	$ 5,192.00	$ -	$ 5,192.00

AFP Physician Compensation Funded by Other Sources	Year 1	Year 2 (If applicable)	Total
AFP Physician Compensation (list names with time commitment ie .5 day per wk per yr)			$ -

version P2 9.0			$ -
			$ -
Subtotal - Physician Other Compensation - B	$ -	$ -	$ -

Project Staff Compensation Funded by the Innovation Fund (list, describe time and compensation amount and how calculated)			
	Year 1	**Year 2**	**Total**
Graduate Student (See note 2)	$ 6,500.00		$ 6,500.00
Personnel - Research Assistant (See note 3)	$ 12,600.00		
Personnel - Trainers (See note 4)	$ 9,600.00		
Personnel - Driving Simulator Techs (See note 5)	$ 3,000.00		$ 3,000.00
Subtotal - Staff Compensation - C	$ 31,700.00	$ -	$ 31,700.00

Project Staff Compensation Funded by Other Sources (list, describe time and compensation amount and how calculated)			
	Year 1	**Year 2**	**Total**
			$ -
			$ -
Subtotal - Staff Other Compensation - D	$ -	$ -	$ -

Total Compensation (A + B + C + D)	$ 36,892.00	$ -	$ 36,892.00

Expenses Funded by Innovation Fund	Year 1	Year 2	Total
SUPPLIES (itemize components below) **BDNF ELISA -** ELISA components such as antibodies and standards, as well as consumables (microcentrifuge tubes, pipet tips, gloves, ELISA plates). **EEG** - We request $1,800 use and maintenance of the EEG equipment including gel, electrode/cap replacement or repair.	$ 4,108.00		$ 4,108.00
EQUIPMENT (provide justification for equipment purchases of >$2000 in the space below) We are requesting the funds to purchase 60 VivoSmart HR Garmin units which are required for the research team to track phsical activity of the participants outside of the study. These will also be used for participant reimbursement in the study. Participants that complete the study will be allowed to keep the VivoSmart. We are budgeting for an additional 20 units to account for potential loss. Each unit is $90USD - 40% discount when ordered in bulk = $54USD per unit x 80 units = $4,320 x HST (13%) = $4,881.60 USD x 1.32 (current exchange rate) = ~$6,500.	$ 6,500.00		$ 6,500.00
OTHER EXPENSES (itemize accounting services, space rental, lab service, diagnostics, patient reimbursement, etc) **Publications** - $1,500 for publication page charges are requested. **Conferences** - We request $1,000 for the cost of travel to conferences to present study results. Costs include conference registration, airfare, ground transportation, accommodations and food.	$ 2,500.00		$ 2,500.00
Total Expenses	$ 13,108.00	$ -	$ 13,108.00

Expenses Funded by Other Sources	Year 1	Year 2	Total
SUPPLIES (itemize components below)			$ -
EQUIPMENT (provide justification for equipment purchases of >$2000 in the space below)			$ -
OTHER EXPENSES (itemize accounting services, space rental, lab service, diagnostics, patient reimbursement, etc)			$ -
			$ -
			$ -
Total Expenses Funded by Other Sources	$ -	$ -	$ -

Total Budget - All Sources	$ 50,000.00	$ -	$ 50,000.00
Total Budget - Innovation Fund ONLY	$ 50,000.00	$ -	$ 50,000.00

Notes/Budget Assumptions (Provide any additional justification to support expenditures if not referenced on P1)

1. Dr. Sheri Wark will be responsible for evaluation and screening potential participants. We expect that this will take 15 minutes for each potential participant and that we will need to screen 80 potential participants in order to reach the goal of 40 participants with post concussion syndrome. In addition, the research team will have monthly meetings (12 meetings, 1 hour each) to organize and update the team. Also, these meetings will be used for data anlaysis and interpretation in preparation for manuscript writing and conference presentations. This brings the total time to 32 hours for AFP physician compensation. Based on 32 hours for the year, we expect to pay at the $161.00/hour. Based on the 2016 OMA claim guide, this is the rate for >25 hours for the year. In addition, we are estimating $40 to cover parking at lakehead University and mileage to travel to the meetings.

2. One graduate student will be involved in this research project. They will assist with informed consent, data collection data interpretation, and presenttion of findings at conferences and manusript publications. $6500 stipend is in-line with the Lakehead University recommendation to supplement the graduate teaching assistant stipend that they will receive.

3. A 0.25 FTE research assistant is requested to assist in the ethics application, saliva collection, transorting samples to NOSM, preparing samples for storage, perforing ELISA, organizing the arms of the study, assisting in data colection and analysis and manuscript writing. $12,600 is requested to cover the 0.25 FTE, including 20% benefits.

4. Trainers - We will require trainers to run the aerobic exercise therapy (AET) portion of the study (3 one hour sessions per week for 8 weeks, $20/hr = $480 per participant x 20 AET participants = $9,600).

5. Driving Simulator Techs - We will require personnel to run the driving simulator portion of the study (120hr at $25/hr = $3,000).

Optional Section (only fill in if appropriate):		
In-Kind Donations:**		
Source:	**Type:**	**Year provided (1 or 2)?**

version P2 9.0 Dr. Sanzo, Dr. Lees, Dr. Zerpa, and Dr. Lawrence-Dewar; in-kind contribution of time, 10% time commitment (based on ~10% of salary/benefits) - $10,000 each		$40,000 for Year 1

** In-Kind donations are defined internally by your own Governance Organizations.

Please check with your Governance Organization administrator if you are unsure what should be included

Contact information for Governance Organization administrators can be found on

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