theAlfred

# Ethics Committee

## Certificate of Approval of Amendments

This is to certify that amendments to

Project: **60472** (Local reference: **10/20**) **A Therapeutic Intervention, Open Label Study to Compare the Efficacy and Safety of Graded Exercise Compared to Passive Stretching in Subjects Who Have Sustained a Mild Traumatic Brain Injury**

Coordinating Principal Investigator:
**Dr Sandy Schultz**

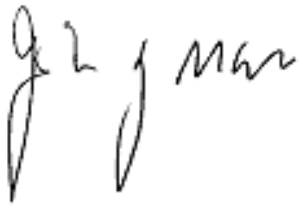
Amendment:
**Amendments to Protocol – change in email address for submission of SAEs, baseline period during testing increased to 5 minutes; changes to PICFs; and addition of new supporting documents**

Attachments:
Protocol – Summary of Changes dated **July 2020**
Protocol version **4** dated **30-Jul-2020**
MASTER Participant Information Sheet & Consent Form version **7** dated **19-Aug-2020**
(Alfred Health Local Governance version dated 19-Aug-2020)
MASTER Participant Information Sheet & Consent Form (Parent/Guardian) **version 6** dated **19-Aug-2020**
(Alfred Health Local Governance version dated 19-Aug-2020)
Certificate of Insurance dated **29-Jul-2020**
Caretaker4 User Manual **version 8** dated **19-Apr-2018**
Study Device Cleaning Requirements version **1** dated **26-Feb-2020**

have been approved under the National Mutual Acceptance (NMA) scheme in accordance with your amendment application dated **7-Aug-2020** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

**SPECIAL CONDITION:** All research projects approved by the Alfred Hospital Ethics Committee are subject to, and must be carried out in compliance with, the most recent applicable COVID-19 government and relevant institution's restrictions.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.



**Professor John J. McNeil**
**Chair, Ethics Committee**

Date: **1-Sep-2020**

*All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).*

*The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).*

# Participant Information Sheet/Consent Form

**Interventional Study** - *Adult providing own consent*

*Alfred Health*

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

## Part 1 What does my participation involve?

### 1 Introduction

You are invited to take part in this research project. This is because you have mild traumatic brain injury, which is also known as concussion. The research project is testing new ways to assess and treat initially diagnosed concussion. The new treatment is called graded exercise, which is exercise that is gradually increased in intensity. The devices being researched are:

- The i-Touch application called ClearPlay©, the i-Touch application is used with a wrist-worn fitness device called Waveband®. Waveband® assesses heart rate and how much it varies over time.
- a hand-cooling device called ClearHeart© which, when used in conjunction with the Caretaker4® monitor, measures changes in blood pressure and heart rate when the hand is cooled.
- a device worn on the head that assesses how the body perceives position and movement of the head called ClearNeck©.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

## 2 What is the purpose of this research?

As an initial treatment for concussion, exercise has been shown to improve the rate of recovery when compared to physical and mental rest. Non-contact forms of aerobic exercise that use oxygen to create energy and that do not worsen concussion symptoms are recommended as a treatment for concussion.

The purpose of this study is to use the ClearPlay© i-Touch application (App) in participants with recently diagnosed concussion to compare the effects and recovery rate of exercise that is gradually increased in intensity against the effects of passive stretching.

The ClearPlay© App collects information regarding heart rate, to recommend the rate at which you should escalate your exercise that should be completed on a daily basis. The information is collected by the Waveband®.

The study also will assess the usefulness of two devices: ClearHeart© and ClearNeck©. ClearHeart© is a hand cooling device, which, when used in conjunction with the Caretaker4® monitor, measures changes in blood pressure and heart rate when the hand is cooled. ClearNeck©, is a device worn on the head that assesses how the body perceives neck position and movement.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Exercise that is gradually increased in intensity is not an approved treatment for initially diagnosed concussion. The ClearPlay© App including Waveband®, the ClearHeart© and the ClearNeck© are experimental devices. This means that they are not approved ways to assess or treat concussion in Australia.

This research is being conducted by ANSwers Neuroscience, Pty Ltd and sponsored in Australia by ANSwers Neuroscience, Pty Ltd.

## 3 What does participation in this research involve?

### Study Design

This is an open-label study which means both the researchers and study participants know which treatment is being given.

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better.

In this study there will be two groups;

1. graded exercise – this is investigational treatment.
2. passive stretching - this is called a control group because the treatment received is considered the current standard of care.

You will have a 50% chance (1-in-2, like flipping a coin) of receiving the graded exercise investigational treatment.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

### Study Activities

You will complete the following assessments in this study. Two study visits are required to the centre. Some activities are completed when you are at home during the 8-week period between the two study visits. Each study visit will take approximately 2 hours.

The following activities will be performed when you attend Alfred Health for study visits:

- Informed consent (Baseline visit only): Before you begin the study, you will be given detailed information about the study treatment, devices and any other relevant information by research staff. If you decide to participate, you will be asked to sign this information sheet and consent form before any procedures are completed.
- Eligibility Criteria Review (Baseline visit only): The study doctor will ask you questions and complete tests to assess if you are eligible for the study.
- Demographic information and medical history (Baseline visit only): The study doctor will ask you about your concussion, other medical conditions that you have, your medical history and demographics.
- Review of previous scans (Baseline visit only): If you have had scans performed previously of your head to help diagnose and treat your concussion, these will be collected and reviewed by the study staff.
- Vital Signs (baseline and 8-week visit): Your vital signs such as heart rate and blood pressure will be measured with a device on your right hand for 6 minutes on two occasions at each study visit. This device is called Caretaker4® and is approved in Australia.
- Medications and treatments (during entire study): You will be asked about the medications and treatments that you have taken in the 7 days prior to the baseline study visit, and between the start of the study until your 8-week study visit. This includes medications such as over-the-counter medicines, vitamins, herbal remedies or other alternative treatments and treatments such as acupuncture, occupational therapy, physical therapy, vestibular therapy, visual therapy, cognitive behavioural therapy, chiropractic therapy, and other therapies.
- Adverse Events (during entire study): You will be asked how you are feeling, if they had to visit a hospital or have been seriously ill.
- Post study survey (8-week visit): you will be asked to complete a survey about your experience on this research study and any leave you have had to take from work or normal duties during your time on the study.
- Sample collection for biomarkers (baseline and 8-week visit): A biomarker is a naturally occurring molecule or substance in your body that allows a specific disease or medical condition to be identified and measured. You can either have a blood test to collect biomarkers, or if you do not want to have a blood test, a sample of your saliva and a cotton tip will be rubbed on the inside of your cheek (a mouth swab) can be collected instead.
- Optional additional blood or saliva samples for genetic testing and biobanking (baseline and 8-week visit): This testing is optional and involves testing your genes, which are the DNA instructions you inherit from your mother and your father. You can nominate your choice to participate in this optional testing at the end of this Participant Information and Consent Form. The results of this optional genetic testing will not be available to you, should you choose to participate in this optional testing because information obtained from these studies will not provide significant information relating to the health of participants, relatives or other family members.
- Questionnaires: You will be asked to complete questionnaires at the Baseline and Follow-up visits, The questionnaires ask about your health, thoughts, feelings, behaviour, exercise habits, and experiences, and take 45- 60 minutes to complete. The questionnaires include;

    - Post-Concussion Symptom Scale (PCSS)
    - Godin Leisure Time Exercise Questionnaire
    - The Beck Anxiety Inventory (BAI)
    - Brief Symptom Inventory
    - Reiss-Epstein-Gursky Anxiety Sensitivity Index
    - Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale (CAARS)
    - Center for Epidemiologic Studies - Depression Scale (CES-D)

You will also be required to complete the Post-Concussion Symptom Scale daily and the Godin Leisure Time Exercise Questionnaire weekly during the study Therapy period. They are available on the ClearPlay© App. It will take approximately 5 minutes each day.

- Assessments that will be administered to you by the study staff (baseline and 8-week visit):
  - Cold Pressor Test: This tests how your heart and blood vessels respond to the cooling of your left hand while placed in ice water for 2 minutes (the ice bucket test) and also when placed in the ClearHeart© hand-cooling device for 2 minutes. You will be asked to remain seated for 5 minutes before and after both of these tests. During this test you will be fitted with the Caretaker4® device on your right hand and finger.
  - Neck range of motion and ClearNeck© testing: The Joint Position Error Test will be performed which assesses your neck's strength, how much it moves, if it is painful or sore and if whiplash is present. Whiplash is when your head extends outside of its normal range of motion. You will also be asked to wear the ClearNeck©, which is a cap that contains a laser. You will be asked to direct the laser onto a target while opening and closing your eyes and moving your head and neck.
  - Buffalo Concussion Bike Test: This test measures the symptoms of concussion during up to 15 minutes of exercise. You will have vital signs collected and will be asked to report your concussion symptom severity and your level of physical exertion for 5 minutes before, during and after riding a stationary bicycle. The intensity of exercise will increase each minute and will be stopped when you are exhausted or want to stop, if you feel unwell, or when you have experienced a significant change in physical exertion compared to before the test.

After the baseline visit, if your study doctor considers you eligible to participate, you will be provided a Waveband® to wear and its charger. This is a wristband that will assess your heart rate and how much it varies over time. You will be asked to return the Waveband® and the charger at your 8-week visit. At your first visit you will also be provided with an Apple i-Touch. You are not required to return the i-Touch at the completion of the study. The ClearPlay© App will be preloaded on your i-Touch. .

You need to complete the exercises the ClearPlay App© recommends for 20 minutes once every day for 8 weeks.

You will be shown how to use the ClearPlay© App. The exercises it recommends will be based on the treatment group you will be randomized to participate in, and the information obtained from your Waveband® and questionnaires.

During the study, you will be contacted by phone each fortnight to check on your progress and how you are feeling.

You will cease your exercise or stretching study intervention once you achieved three daily consecutive PCSS scores that is equalled to or lower than your injury PCSS score. A member of the study team will notify you once you have reached this milestone, advising you to stop your study intervention. You will still be required to complete your 8-week visit, regardless of the date you reach this milestone.

Once you complete the 8-week visit, your involvement in the study will be completed.

The table below outlines the activities performed during the study.

| **Study Activities** | **Baseline Visit** | **Therapy Period (8 weeks)** | **8-week Visit** |
|---|---|---|---|
| Informed consent | X | | |
| Eligibility Criteria Review | X | | |

| Study Activities | Baseline Visit | Therapy Period (8 weeks) | 8-week Visit |
|---|---|---|---|
| Demographic and medical history | X | | |
| Review of medical and medication history | X | | |
| Review of medications and treatments | X | X | X |
| Review of previous scans (if applicable) | X | | |
| Height | X | | |
| Weight | X | | X |
| Vital signs | X | | X |
| Adverse Events | X | X | X |
| Biomarker sample collection | X | | X |
| Optional blood sample for genetic testing and biobanking | X | | X |
| Neuropsychologic Questionnaires | X | | X |
| Ice Bucket and ClearHeart© Tests | X | | X |
| ClearNeck© Testing | X | | X |
| Buffalo Concussion Bike Test | X | | X |
| Neurologic Testing (Eyes, Neck, Balance) | X | | X |
| Download ClearPlay© App | X | | |
| Receive the Waveband® and charger | X | | |
| Use the Waveband® and ClearPlay© App | | X (daily) | |
| Complete activities as instructed by the ClearPlay© App | | X (daily) | |
| Return of Waveband® and charger | | | X |
| Post-study survey | | | X |

## 4 What do I have to do?

If you decide to take part, it is your responsibility to keep your study appointments and complete all study assessments. If you cannot attend an appointment, please tell the study staff (such as the study doctor or research staff) as soon as possible to set a new appointment. Tell the clinical contact person (listed in section 20) about any unusual symptoms you have immediately; do not wait until your next scheduled visit. Also tell them about changes in medications, doctor or nurse appointments, or any hospital admissions.

During the study, you must be willing to exercise or stretch for 20 minutes each day following the directions provided by the ClearPlay© App. Outside of this, you should not engage in any exercise that will cause you to become short of breath during the 8-week study period. You will wear the Waveband® during exercising or stretching for 20 minutes each day. When you achieve three daily consecutive PCSS scores that is equalled to or lower than your injury PCSS score, you may stop your study intervention. If this occurs before the 8-week study visit, then please refer to your doctor to confirm if you can resume exercise or sporting activities at a higher intensity.

During the study, you must upload data from your i-Touch via the ClearPlay© App every day. If you have concerns when using the ClearPlay© App or the Waveband®, please tell the study staff as soon as possible so that they can assist you. You may receive a phone call from the study staff if data is not uploaded.

Once per day, you must complete the Post-Concussion Symptom Scale on the ClearPlay© App. Once per week, you must complete the Godin Leisure Time Exercise questionnaire on the ClearPlay© App.

You also must not smoke, drink alcohol or consume caffeinated or sugary beverages for 1 hour prior to each daily exercise or stretching session.

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking. You should also tell your study doctor about any changes to these during your participation in the research project.

Some medications that affect chemical levels in the brain or impact your mood or behaviour are prohibited during the study. If you do take these medications, please tell your study doctor.

Some medications, current and previous medical conditions and family medical history may prohibit you from participating in the research study. Notify your study doctor if you have any of the following:

- History of prior head injuries in the last 12 months from which you have any associated residual symptoms
- History of prior head injuries in the last 3 months diagnosed as a concussion, or that included amnesia, loss of consciousness, feeling dazed, or "having your bell rung",
- Evidence of small amounts of bleeding found on previously performed scans of your brain,
- Past or present neurological, mental, emotional, or behavioural conditions,
- History of drug or alcohol dependency within the last 2 years,
- Risk factors for cardiac disease, including high blood pressure, high cholesterol in your blood, or a prior diagnosis or indications requiring you to take medication for a cardiac, lung or diabetes related reason.
- Familial history of cardiac disease, heart attacks or sudden death,
- Circulation problems in your arms or legs,
- Swelling from or pooling of lymph fluid in your left arm,
- If you are unable or do not want to exercise,
- Injuries that could make exercise difficult or painful.
- Currently taking beta-blockers, which is a class of high blood pressure medication.

## 5 Other relevant information about the research project

At least 400 participants aged between 14 and 45 years with concussion will be enrolled in this study at up to 5 study centres in Australia. Up to 104 participants will be involved in the study at this treating centre.

The maximum duration for each participant in this study is 8 weeks.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed a maximum of $50AUD per visit for any reasonable travel, parking, meals and other expenses associated with the research project upon presentation of a valid receipt.

If you decide to participate in this research project, the study doctor will inform your local doctor.

## 6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Alfred Health.

## 7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this centre. Other options are available; these include physical and mental rest. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

## 8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. However, your participation in this study may help develop important scientific knowledge that could contribute to the treatment of patients with concussion in the future.

## 9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. If you experience a side effect, contact your study doctor who will discuss the best way to manage the side-effect.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

**Exercise:** The risk caused by undertaking daily exercise that is gradually increased in intensity or passive stretching is minimal.

- When you perform the Buffalo Concussion Treadmill Test, you may experience tiredness, faintness, unsteady on your feet or find it difficult to continue the test, at which point the test will be terminated. You will be assessed and monitored by appropriately trained staff during the test who will ensure that any risks associated with the study including exercise are minimised. Your care will be adjusted if any risks become apparent.

- During your daily home 20 minute exercise sessions you can take breaks while exercising and can stop exercising at any time

- You may experience strained ligaments or joints or other musculoskeletal injuries as a result of exercising. As this is a risk inherent to exercising, by agreeing to participate in this study you agree to assume all the risks of exercising.

- You may experience an adverse cardiac event while exercising. However, such events are extremely rare.

**Blood Tests:** Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to: fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site.

**Mouth swab:** You may experience discomfort when the cotton tip is rubbed on the inside of your cheek.

**Wearing a Waveband® or Caretaker4®:** You may experience discomfort when wearing a Waveband® or Caretaker4®.

**Questionnaire Completion:** You may experience discomfort while completing the questionnaire, because some of the questions are personal questions. You do not have to answer any question that makes you uncomfortable or anxious.

**Ice Bucket and ClearHeart© autonomic testing:** You will experience cold hands, that will resolve in minutes following the test. Very infrequently this testing may cause Peripheral Circulatory Disturbances and/or Lymphedema.

**ClearNeck© whiplash testing:** Infrequently, you may experience mild to moderate neck discomfort during testing for whiplash.

There are no other known risks associated with device deficiencies or serious adverse device effects.

## 10 What will happen to my test samples?

Your samples will be stored in a secure location and will be labelled with your unique study participant number and will not contain any information that can identify you personally.

Your blood or saliva and a mouth swab will be collected to test for biomarkers. This is mandatory testing if you participate in the study. This testing is for research purposes and you will not be notified of the results. The total volume of blood collected is approximately 10 mL (equivalent to 2 teaspoons). Alternatively, if you provide a saliva sample, approximately 1 mL (equivalent to 1/5$^{th}$ teaspoons) of saliva will be collected.

Samples of your blood, saliva and mouth swab obtained for the purpose of this research project will be transferred to Monogram Biosciences, Inc., a division of Labcorp, Inc. The biomarker test will be performed by Monogram Biosciences, Inc. a division of Labcorp, Inc. Your samples will not be sold by Alfred Health, however Alfred Health, may charge study doctors a fee to recover some of the costs of storing and administering these samples.

Once your blood, saliva and mouth swab samples are transferred to Monogram Biosciences, Inc. a division of Labcorp, Inc, Alfred Health, will not be able to control whether Monogram Biosciences, Inc. a division of Labcorp, Inc transfers or sells your samples at some future date, however Alfred Health, will not knowingly transfer your samples to anyone who has expressed intent to sell the samples.

The samples will be retained for future research about concussion for up to 5 years. Samples will then be destroyed by Monogram Biosciences, Inc. a division of Labcorp, Inc. The results maymay be published.

You have the right to request that the sponsor destroy your samples at any time. If you choose to have your samples destroyed, please contact your study doctor. If you decide to have your samples destroyed, any information generated prior to your request will not be destroyed.

**Optional additional blood samples for genetic testing and biobanking**

You may also participate in optional additional blood sample collections. This research will help determine if there are differences in your genetic material that determine your response to exercise, or the severity and recovery from the concussion. The total volume of blood collected for optional biobanking is approximately 10 mL (equivalent to 2 teaspoons). Alternatively, if you provide a saliva sample, approximately 1 mL (equivalent to 1/5$^{th}$ teaspoons) of saliva will be collected. This testing will be performed for research purposes only and the results will not be shared because information obtained from these studies will not provide significant information relating to the health of participants, relatives or other family members. It is hoped that this research may identify differences in genetic material and help determine the best treatment approach following concussion.

Your choice to participate or not in this optional testing will be collected at the end of this Participant Information and Consent Form.

## 11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

## 12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking. This includes medications such as over-the-counter medicines, vitamins, herbal remedies or other alternative treatments and treatments such as acupuncture, occupational therapy, physical therapy, vestibular therapy, visual therapy, cognitive behavioural therapy, chiropractic therapy, and other therapies. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

## 13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team when you withdraw from the research project. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. There are no health risks if you decide to withdraw from this project.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

## 14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment/device being shown not to be effective
- The treatment/device being shown to work and not need further testing
- Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

You may be withdrawn from the study if data is not uploaded via the ClearPlay© App.

## 15 What happens when the research project ends?

At the end of your involvement in the study, you will be required to return your Waveband® ,and charger to the study staff. You should discuss your options for treatment with your doctor.

The results of the study may be published or a summary provided to the study doctor. It is usual for a number of years to elapse before definitive results of this type of study are available. These may be published in medical journals that are available to the public. You will not be

personally identified in any of these publications. Study results can be obtained from your study doctor.

## Part 2 How is the research project being conducted?

### 16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission or in compliance with the law.

Data from your study medical record will be identifiable and stored in secured offices at *Alfred Health.* After the study is completed, your study medical record will be archived at *Alfred Health,* for up to 15 years after the completion of the study.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, ANSwers Neuroscience, Inc. and ANSwers Neuroscience, Pty Ltd and is being funded by ANSwers Neuroscience, Pty Ltd., the institution relevant to this Participant Information Sheet, *Alfred Health,* or in compliance with the law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Your re-identified data may be transferred within Australia or to countries outside Australia such as the USA, where data protection requirements may be different or that are not covered by data protection legislation. Re-identifiable data is information collected about you that is associated with the you by using a code, rather than using identifying information such as your name. It remains possible to re-identify you by using the code. Your name or any other personal identifiers will not appear on any documentation forwarded to the sponsor, nor on any data gathered or published from this study. Although absolute confidentiality cannot be guaranteed, the sponsor will take reasonable measures to keep your personal health information confidential by using a unique study code to label data and not your name or hospital number. By signing this document, you agree to the transfer of your personal health information to such countries.

Data will be stored for 1510 years by ANSwers Neuroscience, Inc. and will be located at Weill Cornell Medicine, 1300 York Ave, New York, NY 10065, United States.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or *Victorian* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 10 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or in compliance with the law.

## 17 What if I get injured in the research?

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. Under Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

Medication required to treat injuries or complications as a result of this research project will be paid by the sponsor.

There are two avenues that may be available to you for seeking compensation if you suffer an injury as a result of your participation in this research project:

• The pharmaceutical industry has set up a compensation process, with which the Sponsor ANSwers Neuroscience, Pty Ltd of this research project has agreed to comply. Details of the process and conditions are set out in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial. In accordance with these Guidelines, the sponsor will determine whether to pay compensation to you, and, if so, how much. The research staff will give you a copy of the Guidelines together with this Participant Information and Consent Form. If you have any questions about the Guidelines, please ask to speak to Brendan Major.

• You may be able to seek compensation through the courts.

## 18 Who is organising and funding the research?

This research project is being conducted by ANSwers Neuroscience, Inc. and sponsored in Australia by ANSwers Neuroscience, Pty Ltd and is being funded by ANSwers Neuroscience, Pty Ltd.

ANSwers Neuroscience, Pty Ltd may benefit financially from this research project if, for example, the project assists ANSwers Neuroscience, Pty Ltd to obtain approval for a new device.

By taking part in this research project you agree that samples of your blood, saliva or mouth swabs (or data generated from analysis of these materials) may be provided to ANSwers Neuroscience, Pty Ltd.

ANSwers Neuroscience, Pty Ltd may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to ANSwers Neuroscience, Pty Ltd.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to ANSwers Neuroscience, Pty Ltd, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Alfred Health will receive a payment from ANSwers Neuroscience, Pty Ltd for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

## 19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Alfred Hospital Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9903 0304 or any of the following people:

**Clinical contact person**

| | |
|---|---|
| Name | *Prof Terence O'Brien* |
| Position | *Department of Neurology* |
| Telephone | *03 9903 0304* |
| Email | *te.obrien@alfred.org.au* |

| | |
|---|---|
| Name | *Brendan Major* |
| Position | *Research Assistant* |
| Telephone | *03 9246 8383* |
| Email | *brendan.major@monash.edu* |

**HREC Office/Complaints contact person**

| | |
|---|---|
| Reviewing HREC name | Alfred Hospital Ethics Committee |
| Position | Complaints Officer, Office of Ethics & Research Governance, Alfred Health |
| Telephone | (03) 9076 3619 |
| Email | research@alfred.org.au |

Please quote the following Project ID number: 60472

# Consent Form - *Adult providing own consent*

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital,*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

## Declaration by Participant

I have read the Participant Information Sheet.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *Alfred Health* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I consent to the storage and use of blood or saliva and mouth swab samples taken from me for biomarker research, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project

**Optional additional blood or saliva sample for genetic testing and biobanking:** By signing this consent section, I agree to the use of my blood or salvia samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

□ **Yes, I agree** to the optional testing
□ **No, I do not agree** to the optional testing

Name of Participant (please print) _____

Signature _____ Date _____

## Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

# Form for Withdrawal of Participation - *Adult providing own consent*

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital,*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Alfred Health*.

Name of Participant (please print) _____

Signature _____ Date _____

*In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.*

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

# Participant Information Sheet/Consent Form – Parent/Guardian

**Interventional Study** - *Parent/Guardian consenting on behalf of participant*

*Alfred Health*

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

## Part 1 What does my child's participation involve?

### 1 Introduction

This is an invitation for the child in your care to take part in this research project because they have mild traumatic brain injury, which is also known as concussion. The research project is testing new ways to assess and treat initially diagnosed concussion. The new treatment is called graded exercise, which is exercise that is gradually increased in intensity. The devices being researched are:

- the i-Touch application called ClearPlay©, the i-Touch application is used with a wristband called the Waveband®. The Waveband® assesses heart rate and how much it varies over time.
- a hand-cooling device called the ClearHeart©, which, when used in conjunction with the Caretaker4® monitor, measures changes in blood pressure and heart rate when the hand is cooled.
- a device worn on the head that assesses how the body perceives position and movement of the head called the ClearNeck©.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your child can take part, you might want to talk about it with a relative, friend or your child's local doctor.

Participation in this research is voluntary. If you do not wish your child to take part, they do not have to. Your child will receive the best possible care whether or not they take part.

If you decide you want your child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to your child taking part in the research project
• Consent for your child to have the tests and treatments that are described
• Consent to the use of your child's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

## 2 What is the purpose of this research?

As an initial treatment for concussion, exercise has been shown to improve the rate of recovery when compared to physical and mental rest. Non-contact forms of aerobic exercise that use oxygen to create energy and that do not worsen concussion symptoms are recommended as a treatment for concussion.

The purpose of this study is to use the ClearPlay© i-Touch application (App) in participants with recently diagnosed concussion to compare the effects and recovery rate of exercise that is gradually increased in intensity against the effects of passive stretching.

The ClearPlay© App collects information, regarding your child's heart rate to recommend the rate at which your child should escalate on a daily basis. The information is collected by the Waveband®.

The study also will assess the usefulness of two devices: ClearHeart© and ClearNeck©. ClearHeart© is a hand cooling device, which, when used in conjunction with the Caretaker4® monitor, measures changes in blood pressure and heart rate when the hand is cooled. ClearNeck©, is a device worn on the head that assesses how the body perceives neck position and movement.

ClearHeart© and ClearNeck© devices are considered safe for use in children.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Exercise that is gradually increased in intensity is not an approved treatment for initially diagnosed concussion. The ClearPlay© App including Waveband®, the ClearHeart© and the ClearNeck© are experimental devices. This means that they are not approved ways to assess or treat concussion in Australia.

This research is being conducted by ANSwers Neuroscience, Pty Ltd and sponsored in Australia by ANSwers Neuroscience, Pty Ltd.

## 3 What does participation in this research involve?

### Study Design

This is an open-label study which means both the researchers and study participants know which treatment is being given.

Your child will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better.
In this study there will be two groups;

1. graded exercise – this is investigational treatment.
2. passive stretching - this is called a control group because the treatment received is considered the current standard of care.

Your child will have a 50% chance (1-in-2, like flipping a coin) of receiving the graded exercise investigational treatment.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

### Study Activities

Your child will complete the following assessments in this study. Two study visits are required to the centre. Some activities are completed when your child is at home during the 8-week period between the two study visits. Each study visit will take approximately 2 hours.

The following activities will be performed when your child attends Alfred Health for study visits:

- Informed consent (Baseline visit only): Before your child begins the study, you will be given detailed information about the study treatment and devices, and any other relevant information by research staff. If you decide that they can participate, you will be asked to sign this information sheet and consent form before any procedures are completed.
- Eligibility Criteria Review (Baseline visit only): The study doctor will ask your child questions and complete tests to assess if they are eligible for the study.
- Demographic information and medical history (Baseline visit only): The study doctor will ask you and your child about their concussion, other medical conditions that they have, their medical history and demographics.
- Review of previous scans (Baseline visit only): If your child has had scans performed previously of their head to help diagnose and treat their concussion, these will be collected and reviewed by the study staff.
- Vital Signs (baseline and 8-week visit): Your child's vital signs such as heart rate and blood pressure will be measured with a device on your right hand for 6 minutes on two occasions at each study visit.
- Medications and treatments (during entire study): You and your child will be asked about the medications and treatments that they have taken in the 7 days prior to the baseline study visit, and between the start of the study, until their 8-week study visit. This includes medications such as over-the-counter medicines, vitamins, herbal remedies or other alternative treatments and treatments such as acupuncture, occupational therapy, physical therapy, vestibular therapy, visual therapy, cognitive behavioural therapy, chiropractic therapy, and other therapies.
- Adverse Events (during entire study): You and your child will be asked how they are feeling, if they had to visit a hospital or have been seriously ill.
- Post study survey (8-week visit): Your child will be asked to complete a survey about their experience on this research study and any leave they have had to take from school, work or normal duties during their time on the study.
- Sample collection for biomarkers (baseline and 8-week visit): A biomarker is a naturally occurring molecule or substance in the body that allows a specific disease or medical condition to be identified and measured. Your child can either have a blood test to collect biomarkers, or if they do not want to have a blood test, a sample of their saliva and a cotton tip will be rubbed on the inside of their cheek (a mouth swab) can be collected instead.
- Optional additional blood samples or saliva for genetic testing and biobanking (baseline and 8-week visit): This testing is optional and involves testing genes, which are the DNA instructions that are inherited from your child's parents. The results of this optional genetic testing will not be available to you, should you choose to participate in this optional testing because information obtained from these studies will not provide significant information relating to the health of participants, relatives or other family members. You can nominate your choice for your child to participate in this optional testing at the end of this Participant Information and Consent Form.
- Questionnaires (during entire study): Your child will be asked to complete questionnaires at the Baseline and Follow-up visits, The questionnaires ask about their health, thoughts, feelings, behaviour, exercise habits, and experiences, and will take 45- 60 minutes to complete. The questionnaires include;
    - Post Concussion Symptom Scale (PCSS)
    - Godin Leisure Time Exercise Questionnaire
    - The Beck Anxiety Inventory (BAI)
    - Brief Symptom Inventory
    - Reiss-Epstein-Gursky Anxiety Sensitivity Index
    - Adult Attention Deficit Hyperactivity Disorder Rating Scale (CAARS)
    - Center for Epidemiologic Studies - Depression Scale (CES-D)

Your child will also be required to complete the Post-Concussion Symptom Scale daily during the study Therapy period and the Godin Leisure Time Exercise Questionnaire weekly during the study Therapy period. They are available on the ClearPlay© App. It will take up to 15 minutes each day.

- Assessments that will be administered to the child by the study staff (baseline and 8-week visit):
  - Cold Pressor Test: This tests how your child's heart and blood vessels respond to the cooling of their left hand while placed in ice water for 2 minutes (the ice bucket test) and also when placed in the ClearHeart© hand-cooling device for 2 minutes. They will be asked to remain seated for 5 minutes before and after both of these tests. During this test your child will be fitted with the Caretaker4® device on their right arm and finger.
  - Neck range of motion and ClearNeck© Testing: The Joint Position Error Test will be performed, which assesses your child's neck strength, how much it moves, if it is painful or sore and if whiplash is present. Whiplash is when the head extends outside of its normal range of motion. Your child will also be asked to wear the ClearNeck©, which is a cap that contains a laser. They will be asked to direct the laser onto a target while opening and closing their eyes and moving their head and neck.
  - Buffalo Concussion Bike Test: This test measures the symptoms of concussion during up to 15 minutes of exercise. Your child will have vital signs collected and will be asked to report their concussion symptom severity and their level of physical exertion for 5 minutes before, during and after riding a stationary bicycle. The intensity of exercise will increase each minute and will be stopped when they are exhausted or want to stop, if they feel unwell, or when they have experienced a significant change in physical exertion compared to before the test.

After the baseline visit, if the study doctor considers that your child is eligible to participate, they will be provided a Waveband® to wear and its charger. This is a wristband that will assess their heart rate and how much it varies over time. They will be asked to return the Waveband® and the charger at the 8-week visit. At your first visit your child will also be provided with an Apple i-Touch. You are not required to return the i-Touch at the completion of the study. The ClearPlay© App will be preloaded on your child's i-Touch.

Your child will need tocomplete the exercises the ClearPlay© App recommends for 20 minutes once every day for 8 weeks. They will be shown how to use the ClearPlay© App. The exercises it recommends will be based on the treatment group your child will be randomized to participate in, and the on the information obtained from the child's Waveband® and questionnaires.

During the study, your child will be contacted by phone each fortnight to check on their progress and how they are feeling.

Your child will cease their exercise or stretching study intervention once they have achieved three daily consecutive PCSS scores that is equalled to or lower than your injury PCSS score. A member of the study team will notify you once your child has reached this milestone, advising your child to stop their study intervention. They will still be required to complete your 8-week visit, regardless of the date they reach this milestone.

Once your child completes the 8-week visit, their involvement in the study will be completed.

The table below outlines the activities performed during the study.

| **Study Activities** | **Baseline Visit** | **Therapy Period (8 weeks)** | **8-week Visit** |
|---|---|---|---|
| Informed consent | X | | |
| Eligibility Criteria Review | X | | |
| Demographic and medical history | X | | |

| Study Activities | Baseline Visit | Therapy Period (8 weeks) | 8-week Visit |
|---|---|---|---|
| Review of medical and medication history | X | | |
| Review of medications and treatments | X | X | X |
| Review of previous scans (if applicable) | X | | |
| Height | X | | |
| Weight | X | | X |
| Vital signs | X | | X |
| Adverse Events | X | X | X |
| Biomarker sample collection | X | | X |
| Optional blood sample for genetic testing and biobanking | X | | X |
| Neuropsychologic Questionnaires | X | | X |
| Ice Bucket and ClearHeart© Tests | X | | X |
| Neck range of motion and ClearNeck© Testing | X | | X |
| Buffalo Concussion Bike Test | X | | X |
| Download ClearPlay© App | X | | |
| Receive the Waveband® and charger | X | | |
| Use the Waveband® and ClearPlay© App | | X (daily) | |
| Complete activities as instructed by the ClearPlay© App | | X (daily) | |
| Return of Waveband® and charger | | | X |
| Post-study survey | | | X |

## 4 What does my child have to do?

If you decide that your child can take part, it is your and their responsibility to keep study appointments and complete all study assessments. If you and your child cannot attend an appointment, please tell the study staff (such as the study doctor or research staff) as soon as possible to set a new appointment. Tell the clinical contact person (listed in section 20) about any unusual symptoms your child has immediately; do not wait until your child's next scheduled visit. Also tell them about changes in medications, doctor or nurse appointments, or any hospital admissions.

During the study, your child must be willing to exercise or stretch for 20 minutes each day following the directions provided by the ClearPlay© App. Outside of this, your child should not engage in any exercise that will cause them to become short of breath during the during the 8-week study period. Your child will wear the Waveband® during exercising or stretching for 20 minutes each day. When your child has achieved three daily consecutive PCSS scores that is equalled to or lower than their injury PCSS score, they may stop their study intervention. If this occurs before the 8-week study visit, then please refer to your child's doctor to confirm if they can resume exercise or sporting activities at a higher intensity.

During the study, you and your child must upload data from their i-Touch via the ClearPlay© App every day. If you or your child have concerns when using the ClearPlay© App or the Waveband®, please tell the study staff as soon as possible so that they can assist you and your child. You or your child may receive a phone call from the study staff if data is not uploaded.

Once per day your child must complete the Post-Concussion Symptom Scale on the ClearPlay© App. Once per week, your child must complete the Godin Leisure Time Exercise questionnaire on the ClearPlay© App.

Your child also must not smoke, drink alcohol or consume caffeinated or sugary beverages for 1 hour prior to each daily exercise or stretching session.

It is important to tell your child's study doctor and the study staff about any treatments or medications that your child may be taking. You should also tell your study doctor about any changes to these during your child's participation in the research project.

Some medications that affect chemical levels in the brain or impact your child's mood or behaviour are prohibited during the study. If your child does take these medications, please tell your child's study doctor.

Some medications, current and previous medical conditions and family medical history may prohibit your child from participating in the research study. Notify your child's study doctor if your child has any of the following:

- History of prior head injuries in the last 12 months from with associated residual symptoms
- History of prior head injuries in the last 3 months diagnosed as a concussion, or that included amnesia, loss of consciousness, feeling dazed, or "having your bell rung",
- Evidence of small amounts of bleeding found on previously performed scans of your childs brain.
- Past or present neurological, mental, emotional, or behavioural conditions,
- History of drug or alcohol dependency within the last 2 years,
- Risk factors for cardiac disease, including high blood pressure, high cholesterol in your blood, or a prior diagnosis or indications requiring you to take medication for a cardiac, lung or diabetes related reason,
- Familial history of cardiac disease, heart attacks or sudden death,
- Circulation problems in your child's arms or legs,
- Swelling from or pooling of lymph fluid in the child's left arm,
- If your child is unable or does not want to exercise, Injuries that could make exercise difficult or painful.
- Currently taking beta-blockers, which is a class of high blood pressure medication.

## 5 Other relevant information about the research project

At least 400 participants aged between 14 and 45 years with concussion will be enrolled in this study at up to 5 study centres in Australia. Up to 104 participants will be involved in the study at this treating centre.

The maximum duration for each participant in this study is 8 weeks.

There are no additional costs associated with participating in this research project, nor will you or your child be paid. All medication, tests and medical care required as part of the research project will be provided to your child free of charge.

You may be reimbursed up to $50AUD per clinic visit for any reasonable travel, parking, meals and other expenses associated with the research project upon presentation of a valid receipt.

If you decide that your child can participate in this research project, the study doctor will inform your child's local doctor.

## 6 Does my child have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your child to take part, they do not have to. If you decide that they can take part and later change your mind, you are free to withdraw your child from the project at any stage.

If you do decide that your child can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision that your child can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with Alfred Health.

## 7 What are the alternatives to participation?

Your child does not have to take part in this research project to receive treatment at this centre. Other options are available; these include physical and mental rest. The study doctor will discuss these options with you before you decide whether or not your child can take part in this research project. You can also discuss the options with your child's local doctor.

## 8 What are the possible benefits of taking part?

We cannot guarantee or promise that your child will receive any benefits from this research. However, your child's participation in this study may help develop important scientific knowledge that could contribute to the treatment of patients with concussion in the future.

## 9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. The participant may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the participant has any of these side effects, or you worried about them, talk with the study doctor. The study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the study doctor immediately about any new or unusual symptoms that the participant gets.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the study doctor may need to stop your child's treatment. Your child's study doctor will discuss the best way of managing any side effects with you.

If your child becomes upset or distressed as a result of participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge

**Exercise:** The risk caused by undertaking daily exercise that is gradually increased in intensity or passive stretching is minimal.

- When your child performs the Buffalo Concussion Treadmill Test, they may experience tiredness, faintness, unsteady on their feet or find it difficult to continue the test, at which point the test will be terminated. Your child will be assessed and monitored by appropriately trained staff during the test who will ensure that any risks associated with the study including exercise are minimised. Your child's care will be adjusted if any risks become apparent.

- During your daily home 20 minute exercise sessions you can take breaks while exercising and can stop exercising at any time.

- Your child may experience strained ligaments or joints or other musculoskeletal injuries as a result of exercising. As this is a risk inherent to exercising, by agreeing that your child can participate in this study you agree to assume all the risks of exercising.

- Your child may experience an adverse cardiac event while exercising. However, such events are extremely rare.

**Blood Tests:** Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to: fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site.

**Mouth swab:** Your child may experience discomfort when the cotton tip is rubbed on the inside of their cheek.

**Wearing a Waveband® or Caretaker4®:** Your child may experience discomfort when wearing a Waveband®, the Caretaker4® device.

**Questionnaire Completion:** Your child may experience discomfort while completing the questionnaire, because some of the questions are personal questions. They do not have to answer any question that makes them uncomfortable or anxious.

**Ice Bucket and ClearHeart© autonomic testing:** Your child will experience cold hands, that will resolve in minutes following the test. Very infrequently this testing may cause Peripheral Circulatory Disturbances and/or Lymphedema.

**ClearNeck© whiplash testing:** Infrequently, your child may experience mild to moderate neck discomfort during testing for whiplash.

There are no other known risks associated with device deficiencies or serious adverse device effects.

## 10 What will happen to my child's test samples?

Your child's samples will be stored in a secure location and will be labelled with a unique study participant number and will not contain any information that can identify them personally.

Their blood or saliva and a mouth swab will be collected to test for biomarkers. This is mandatory testing if they participate in the study. This testing is for research purposes and they will not be notified of the results. The total volume of blood collected is approximately 10 mL (equivalent to 2 teaspoons). Alternatively, if they provide a saliva sample, approximately 1 mL (equivalent to 1/5$^{th}$ teaspoons) of saliva will be collected.
Samples of blood, saliva and mouth swab obtained for the purpose of this research project will be transferred to Monogram Biosciences, Inc. a division of Labcorp, Inc. The biomarker test will be performed by Monogram Biosciences, Inc. a division of Labcorp, Inc. Your child's samples will not be sold by Alfred Health however Alfred Health may charge study doctors a fee to recover some of the costs of storing and administering these samples.

Once your child's blood, saliva and mouth swab samples are transferred to Monogram Biosciences, Inc. a division of Labcorp, Inc, Alfred Health will not be able to control whether Monogram Biosciences, Inc. a division of Labcorp, Inc transfers or sells the samples at some future date, however Alfred Health will not knowingly transfer samples to anyone who has expressed intent to sell the samples.

The samples will be retained for future research about concussion for up to 5 years. Samples will then be destroyed by Monogram Biosciences, Inc. a division of Labcorp, Inc. The results may be published.

You have the right to request that the sponsor destroy your child's samples at any time. If you choose to have your child's samples destroyed, please contact the study doctor. If you decide to have your child's samples destroyed, any information generated prior to your request will not be destroyed.

### Optional additional blood samples for genetic testing and biobanking

You may also agree for your child to participate in optional additional blood sample collections. This research will help determine if there are differences in genetic material that determine a person's response to exercise, or the severity and recovery from concussion. The total volume of blood collected for optional biobanking is approximately 10 mL (equivalent to 2 teaspoons). Alternatively, your child may provide a saliva sample, approximately 1 mL (equivalent to 1/5$^{th}$ teaspoons) of saliva will be collected.

This testing will be performed for research purposes only and the results will not be shared because information obtained from these studies will not provide significant information relating

to the health of participants, relatives or other family members. It is hoped that this research may identify differences in genetic material and help determine the best treatment approach following concussion.
Your choice for the child to participate or not in this optional testing will be collected at the end of this Parent/Guardian Information and Consent Form.

## 11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you and your child about it and discuss with you whether you want the child to continue in the research project. If you decide to withdraw your child, the study doctor will make arrangements for the child's regular health care to continue. If you decide that your child can continue in the research project you and your child will be asked to sign an updated consent form.

Also, on receiving new information, the study doctor might consider it to be in the child's best interests to withdraw them from the research project. If this happens, he/ she will explain the reasons and arrange for your child's regular health care to continue.

## 12 Can my child have other treatments during this research project?

Whilst the child is participating in this research project, they may not be able to take some or all of the medications or treatments that they have been taking for their condition or for other reasons. It is important to tell the study doctor and the study staff about any treatments or medications that they may be taking. This includes medications such as over-the-counter medicines, vitamins, herbal remedies or other alternative treatments and treatments such as acupuncture, occupational therapy, physical therapy, vestibular therapy, visual therapy, cognitive behavioural therapy, chiropractic therapy, and other therapies. You should also tell the study doctor about any changes to these during participation in the research project. The study doctor should also explain to you which treatments or medications need to be stopped for the time that the child is involved in the research project.

## 13 What if I withdraw my child from this research project?

If you decide to withdraw your child from the project, please notify a member of the research when you withdraw from the research project.. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. There are no health risks if your child withdraws from this project.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from your child, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw your child will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

## 14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The treatment/device being shown not to be effective
• The treatment/device being shown to work and not need further testing
• Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

Your child may be withdrawn from the study if data is not uploaded via the ClearPlay© App.

## 15 What happens when the research project ends?

At the end of your child's involvement in the study, they will be required to return the Waveband® and the chargers to the study staff. You should discuss treatment options for your child with their doctor.

The results of the study may be published or a summary provided to the study doctor. It is usual for a number of years to elapse before definitive results of this type of study are available. These may be published in medical journals that are available to the public. Your child will not be personally identified in any of these publications. Study results can be obtained from the study doctor.

## Part 2 How is the research project being conducted?

### 16 What will happen to information about my child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential. Their information will only be used for the purpose of this research project and it will only be disclosed with your permission or in compliance with the law.

Data from your child's study medical record will be identifiable and stored in secured offices at *Alfred Health.* After the study is completed, their study medical record will be archived at *Alfred Health* for up to 15 years from when the child turns 18 years old.

Information about your child may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing your child's health records if they are relevant to their participation in this research project.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, ANSwers Neuroscience, Inc. and ANSwers Neuroscience, Pty Ltd and is being funded by ANSwers Neuroscience, Pty Ltd., the institution relevant to this Participant Information Sheet, *Alfred Health* or in compliance with the law. By signing the Consent Form, you authorise release of, or access to, your child's confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission.

Your child's re-identified data may be transferred within Australia or to countries outside Australia such as the USA, where data protection requirements may be different or that are not covered by data protection legislation. Re-identifiable data is information collected about the child that is associated with the child by using a code, rather than using identifying information such as their name. It remains possible to re-identify your child by using the code. Your child's name or any other personal identifiers will not appear on any documentation forwarded to the sponsor, nor on any data gathered or published from this study. Although absolute confidentiality cannot be guaranteed, the sponsor will take reasonable measures to keep personal health information confidential by using a unique study code to label data and not your child's name or hospital number. By signing this document, you agree to the transfer of your child's personal health information to such countries.

Data will be stored for 15 years from when the child turns 18 years old. by ANSwers Neuroscience, Inc and will be located at Weill Cornell Medicine, 1300 York Ave, New York, NY 10065, United States.

Information about your child's participation in this research project may be recorded in their health records.

In accordance with relevant Australian and/or *Victorian* privacy and other relevant laws, you have the right to request access to your child's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your child's information.

Any information obtained for the purpose of this research project and for the future research described in Section 10 that can identify you or your child will be treated as confidential and securely stored. It will be disclosed only with your permission, or in compliance with the law.

## 17 What if I get injured in the research?

If your child suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment for your child. Under Medicare, your child can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. Medication required to treat injuries or complications as a result of this research project will be paid by the sponsor.

There are two avenues that may be available to you for seeking compensation if your child suffers an injury as a result of their participation in this research project:

• The pharmaceutical industry has set up a compensation process, with which the Sponsor ANSwers Neuroscience, Pty Ltd of this research project has agreed to comply. Details of the process and conditions are set out in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial. In accordance with these Guidelines, the sponsor will determine whether to pay compensation to you, and, if so, how much. The research staff will give you a copy of the Guidelines together with this Participant Information and Consent Form. If you have any questions about the Guidelines, please ask to speak to Brendan Major.

• You may be able to seek compensation through the courts.

## 18 Who is organising and funding the research?

This research project is being conducted by ANSwers Neuroscience, Inc. and sponsored in Australia by ANSwers Neuroscience, Pty Ltd and is being funded by ANSwers Neuroscience, Pty Ltd.

ANSwers Neuroscience, Pty Ltd may benefit financially from this research project if, for example, the project assists ANSwers Neuroscience, Pty Ltd to obtain approval for a new device.

By taking part in this research project you agree that samples of the child's blood, saliva or mouth swabs (or data generated from analysis of these materials) may be provided to ANSwers Neuroscience, Pty Ltd.

ANSwers Neuroscience, Pty Ltd may directly or indirectly benefit financially from the child's samples or from knowledge acquired through analysis of the child's samples.

You will not benefit financially from the child's involvement in this research project even if, for example, the child's samples (or knowledge acquired from analysis of the child's samples) prove to be of commercial value to ANSwers Neuroscience, Pty Ltd.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to ANSwers Neuroscience, Pty Ltd, the study doctors or their institutions, there will be no financial benefit to you, the child, or family from these discoveries.

Alfred Health will receive a payment from ANSwers Neuroscience, Pty Ltd for undertaking this research project.

No member of the research team will receive a personal financial benefit from the child's involvement in this research project (other than their ordinary wages).

## 19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Alfred Hospital Ethics Committee.
This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if your child has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9903 0304 or any of the following people:

**Clinical contact person**

| | |
|---|---|
| Name | Prof Terence O'Brien |
| Position | Department of Neurology |
| Telephone | 03 9903 0304 |
| Email | te.obrien@alfred.org.au |

| | |
|---|---|
| Name | *Brendan Major* |
| Position | *Research Assistant* |
| Telephone | *03 9246 8383* |
| Email | *brendan.major@monash.edu* |

**Reviewing HREC approving this research and HREC Executive Officer details**

| | |
|---|---|
| Reviewing HREC name | Alfred Hospital Ethics Committee |
| Position | Governance Officer, Ethics and Research Governance, Alfred Health |
| Telephone | 03 9076 3619 |
| Email | research@alfred.org.au |

# Consent Form – Parent/Guardian

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital,*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

**Declaration by Parent/Guardian**

I have read the Participant Information Sheet.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *Alfred Health* concerning my child's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my child participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that, if I decide to discontinue my child's study treatment, a request may be made for them to attend follow-up visits to allow collection of information regarding their health status. Alternatively, a member of the research team may request my permission to obtain access to my child's medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from my child for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project

**Optional additional blood/saliva sample for genetic testing and biobanking:** By signing this consent section, I agree to the use of my child's blood samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

☐ **Yes, I agree** to the optional testing

☐ **No, I do not agree** to the optional testing

Name of Child (please print)

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

*Under certain circumstances (see* Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness* to informed consent is required*

Name of Witness* to
Parent/Guardian's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

# Form for Withdrawal of Participation – Parent/Guardian

| | |
|---|---|
| **Title** | Exercise As Concussion Therapy Trial |
| **Protocol Number** | ExACTT-2 |
| **Australian Project Sponsor** | ANSwers Neuroscience, Pty Ltd |
| **Principal Investigator** | *Prof Terence O'Brien* |
| **Location** | *The Alfred Hospital,*<br>*99 Commercial Rd*<br>*Melbourne, VIC 3004* |

**Declaration by Parent/Guardian**

I wish to withdraw my child from participation in the above research project and understand that such withdrawal will not affect their routine treatment, relationships with those treating them or the relationship with *Alfred Health*.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

*In the event that the parent/guardian's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.*

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

# CLINICAL STUDY PROTOCOL

**Protocol Title: A Therapeutic Intervention, Open Label Study to Compare the Efficacy and Safety of Graded Exercise Compared to Passive Stretching in Subjects Who Have Sustained a Mild Traumatic Brain Injury**

**Protocol Short Title: Exercise As Concussion Therapy Trial (ExACTT)**

**Protocol Number: ExACTT-2**

**Sponsor: ANSwers Neuroscience, Pty Ltd**

c/o Prime Accounting & Business Advisory, Pty, Ltd

Level 19, HWT Tower, 40 City Road, Southbank, VIC 3006, Australia

**Version: Final V 4**

**Date: 30 July2020**

## PROTOCOL APPROVAL SIGNATURE

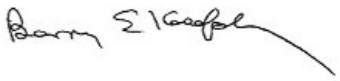
**Protocol Title:** A Therapeutic Intervention, Open Label Study to Compare the Efficacy and Safety of Graded Exercise Compared to Passive Stretching in Subjects Who Have Sustained a Mild Traumatic Brain Injury

**Protocol Number:** ExACTT-2

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice and applicable regulatory requirements.

**Sponsor Signatory** **Signature:**

Barry Kosofsky



President

ANSwers Neuroscience, Pty Ltd **Date:** **July 30, 2020**

## STATEMENT OF COMPLIANCE

The investigator will conduct this study as detailed herein, in compliance with current standards for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice and the applicable regulatory requirements and will make every reasonable effort to complete the study within the time designated.

The investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Human Research Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the study subjects.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by the sponsor or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The investigator agrees that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

**Investigator**:

Print/Type Name: _____

Signed: _____

Date: _____

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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADHD | attention deficit hyperactivity disorder |
| AE | adverse event |
| ASI | Anxiety Sensitivity Index |
| BAI | Beck Anxiety Inventory |
| BCBT | Buffalo Concussion Bicycle Test |
| BCTT | Buffalo Concussion Treadmill Test |
| BESS | Balance Error Scoring System |
| BP | blood pressure |
| BSI | Brief Symptom Inventory |
| CAARS | Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale |
| CES-D | Center for Epidemiologic Studies - Depression Scale |
| CT | computed tomography |
| DNA | deoxyribonucleic acid |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| HR | heart rate |
| HREC | Human Research Ethics Committee |
| HRV | heart rate variability |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| mTBI | mild traumatic brain injury |
| PCSS | Post-Concussion Symptom Scale |
| PICF | patient information and consent form |
| PPCS | persistent post-concussive symptoms |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SNP | single nucleotide polymorphisms |
| SSRI | selective serotonin reuptake inhibitors |
| SUSAR | suspected unexpected serious adverse reactions |
| TBI | traumatic brain injury |
| TCA | tricyclic antidepressants |

| Abbreviation | Definition |
|---|---|
| VOMS | Vestibular-Oculomotor Screening |

# SYNOPSIS

<table>
<tr><td>Protocol Number:</td><td>ExACTT-2</td></tr>
<tr><td>Title:</td><td>A Therapeutic Intervention, Open Label Study to Compare the Efficacy and Safety of Graded Exercise Compared to Passive Stretching in Subjects Who Have Sustained a Mild Traumatic Brain Injury</td></tr>
<tr><td>Therapeutic Intervention:</td><td>The therapeutic intervention (graded exercise) to be used in this study is delivered through the ClearPlay© mobile application. ClearPlay© provides the subject with a graded exercise program or passive stretching program, which is used in conjunction with a wrist-worn heart rate monitoring device (Waveband®).</td></tr>
<tr><td>Study Centre:</td><td>Multiple sites in Australia</td></tr>
<tr><td>Development Phase:</td><td>Phase 2</td></tr>
<tr><td>Objectives and Endpoints:</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
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<tr><td>To compare the effects of graded exercise to passive stretching using ClearPlay© on symptomatic recovery rate following mTBI.</td><td>• Within-subject analysis of change in symptoms over time using the PCSS, comparing short-term ‘survival rates’ between graded exercise and stretching using Kaplan-Meier analyses for days since concussion.</td></tr>
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<tr><td>To compare the safety and tolerability of graded exercise to passive stretching in patients following mTBI.</td><td>• Adverse events reported from Day 1 through Day 56, including those identified during exercise or passive stretching during the 20 minutes of daily therapy.</td></tr>
<tr><td>To compare symptom resolution following graded exercise compared to passive stretching using ClearPlay© following mTBI.</td><td>• Within subject analysis of change in the number of subjects who are symptom free at 8 weeks between the 2 groups. Symptom free is defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion.<br>Note: This objective is similar to the primary one, with the primary endpoint being recovery (binary outcome) vs. symptom resolution (continuous variable).<br>• Determine differences in symptomatic recovery based on gender, baseline scores on the PCSS, baseline athletic fitness (Godin leisure-time exercise questionnaire), the history of injury, a history of migraine, as well as the presence of pre-morbid anxiety.</td></tr>
<tr><td>To compare the effects of graded exercise to passive stretching using ClearPlay© on physiologic recovery rate following mTBI.</td><td>• Within subject analysis of normalization of physiologic measurements obtained during the BCBT comparing data collected on entry to the study on Day 0 vs. follow up on Day 56 including:<br>- Beat to beat BP;<br>• Determine differences in physiologic recovery based on gender, baseline scores on the PCSS, baseline athletic fitness (Godin</td></tr>
</table>
</td></tr>
</table>

| | | |
|---|---|---|
| | | leisure-time exercise questionnaire), the history of injury, a history of migraine, as well as the presence of pre-morbid anxiety (BAI; BSI-18; ASI). |
| | To compare the effects of graded exercise to passive stretching using ClearPlay© on accelerating symptomatic vs. physiologic recovery rate following mTBI. | • Combined analysis of data from the two secondary analyses outlined above to confirm or refute a significant correlation between symptom resolution (defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) and physiologic measurements obtained during the BCBT comparing data obtained on entry to the study on Day 0 vs. follow up on Day 56 including:<br>- Beat to beat BP; |
| | To develop a composite physiologic metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Develop predictive modeling algorithms to establish a composite physiologic metric predictive of subjects becoming symptom free (as defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) using data derived from baseline physiologic testing with:<br>- BCBT<br>- Ice bucket testing<br>- ClearPlay© testing |
| | To develop a composite neuropsychologic metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Develop predictive modeling algorithms to establish a composite neuropsychologic metric predictive of subjects becoming symptom free (as defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) using data derived from baseline neuropsychologic testing with the following instruments:<br>- Attention (CAARS)<br>- Depression (CES-D)<br>- Anxiety (BAI; BSI-18; ASI). |
| | To develop a composite blood-based OR saliva biomarker metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Analysis of biomarkers at baseline testing including:<br>- Structural proteins [t-tau, NF-L, GFAP and UCH-L1]<br>- Inflammatory cytokines [IL-6, IL-10 and TNFα]<br>- SNPs [APO-E4, BDNF, and NFkB] |
| | To validate the performance of ClearHeart© against ice bucket testing. | • Bland-Altman plots will be used to evaluate the agreement between HR measured by ClearHeart© and ice bucket testing.<br>• Bland-Altman plots will be used to evaluate the agreement between BP measured by ClearHeart© and ice bucket testing. |
| | To validate the performance of | • Correlations will be used to assess the association between results obtained through ClearNeck© testing and those obtained |

| | |
|---|---|
| | <table><tr><td>ClearNeck© against examination of the neck</td><td>during the neurologic examination for neck range of motion and tenderness.</td></tr></table><br>Abbreviations: ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BCBT = Buffalo Concussion Bicycle Test, BESS = Balance Error Scoring System,; BP=blood pressure, BSI = Brief Symptom Inventory, CAARS = Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale, CES-D = Center for Epidemiologic Studies - Depression Scale,HRV = Heart Rate Variability, TBI = mild traumatic brain injury; PCSS = Post-Concussive Symptom Scale, SNP = single nucleotide polymorphisms. |
| **Study Design:** | This study is a Phase 2, open label study of a therapeutic intervention (graded exercise) compared to a reference therapy (passive stretching) in patients who have sustained mTBI. Subjects will be randomly assigned with a ratio of 1:1 to complete either graded exercise or passive stretching using a parallel group design. |
| **Recruitment** | The study sites will have well-established concussion research programs and referral populations. |
| **Administration of Therapeutic Intervention:** | The therapeutic intervention is either 20 minutes daily of graded exercise or 20 minutes daily of passive stretching, according to the randomization schedule, from Day 1 to Day 56. |
| **Inclusion Criteria:** | To be eligible for study entry, subjects must satisfy all of the following criteria:<br>1. Male or female subjects aged ≥14 to ≤45, able and willing to provide informed consent (≥18 years), or informed consent is obtained by the parent or legal guardian for minor subjects, with the minor providing age appropriate assent, according to local law and regulations;<br>2. Subject is fluent in English, able to understand and agree to comply with protocol requirements, able to complete all assessments, and able to be;<br>3. Subject has a history of recent concussion as diagnosed by a health care professional within 3 to 14 days of enrolment;<br>*Note: Concussion is defined as a head injury/blow to the head resulting in any of the following 3 signs and/or new symptoms: (1) Amnesia for less than 24 hours; (2) Loss of consciousness for less than 30 minutes; (3) Glasgow Coma Scale score > = 13; (4) Dazed and Confused/bell rung; with at least 1 new symptom or augmentation of a previous symptom on the Post-Concussion Symptom Scale (PCSS) as compared with baseline at the time of enrolment, including: headaches, dizziness, fatigue, irritability, insomnia, difficulty concentrating, and/or memory difficulties; (5) The composite symptom score on the PCSS must be at least 3 points higher post-concussion than pre-concussion.*<br>4. Subject has daily access to the internet. |
| **Exclusion Criteria:** | Subjects will be excluded from the study if any of the following criteria are applicable:<br>1. History of prior head injury as defined by:<br>• An injury/blow to the head within 12 months prior to screening with any associated residual symptoms;<br>• An injury/blow to the head within 3 months prior to screening diagnosed as a concussion;<br>• An injury/blow to the head within 3 months prior to screening with any of the following symptoms: amnesia, loss of consciousness, dazed and confused/bell rung;<br>2. Evidence of blood or micro-hemorrhages on prior or current computed tomography scan or magnetic resonance imaging scan if obtained;<br>3. Diagnosis of a neurological condition including the following: stroke, multiple sclerosis, epilepsy, brain tumor/cancer, encephalitis, dementia, movement disorder, or spontaneous nystagmus; |

| | |
|---|---|
| | 4. Psychiatric history with any of the following:<br>• History of psychiatric hospitalization, history of legal trouble for violence;<br>• Requires psychotropic medication other than (1) stable dose of a selective serotonin reuptake inhibitors (SSRI) medication, or (2) stable dose of a tricyclic antidepressants (TCA) medication;<br>• Prior diagnosis of psychotic disorder, bipolar disorder, eating disorder, substance (incl. alcohol) abuse disorder;<br>5. Current use of beta blockers (an anti-hypertensive medication);<br>6. History of drug or alcohol dependency or abuse within a year before Screening, by self-report;<br>7. Two or more of the following cardiovascular risk factors:<br>• Prior diagnosis of, or currently taking medication for cardiovascular, metabolic or pulmonary conditions;<br>• Family history of myocardial infarction, coronary revascularization or sudden death before 55 years;<br>• Diagnosis of hypertension;<br>• Diagnosis of hyperlipidemia;<br>• Subjects with peripheral circulatory disorders;<br>8. Subjects who are unable or unwilling to exercise for health or personal reasons;<br>9. Subjects who have musculoskeletal injuries which could make exercise difficult or painful. |
| **Sample Size:** | At least 400 subjects aged 14 to 45 will be enrolled in this study at up to 5 study sites. |
| **Analysis:** | No interim analysis is planned for this study.<br>In general, data will be summarized using descriptive statistics (number of non-missing observations, mean, median, standard deviation, minimum and maximum) or frequency counts and percentages, as appropriate to the type of data.<br>Adverse events and medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA, the latest version) and concomitant medications are coded with World Health Organization Drug coding Dictionary (latest version).<br>For all subjects, daily reported PCSS scores collected from ClearPlay© mobile application will be utilized to determine the resolution of symptoms. The resolution of symptoms is defined as a symptom-severity score of less than each subject's pre-injury PCSS score for 3 consecutive days. To assess differences in the probability of symptom resolution between graded exercise and passive stretching during the 8 weeks of therapy, both unadjusted and adjusted logistic regression models will be used. The primary outcome of the study will be to confirm or refute the superiority of sub-threshold aerobic exercise versus passive stretching to result in resolution of symptoms following mTBI. Confounders for the adjusted models will include age, gender, anxiety at baseline, history of migraine, cardiovascular fitness, the presence or absence of neurologic findings, and site of enrolment.<br>The survival probability will be compared using Kaplan-Meier (log rank test) analyses between the 2 treatment arms. Cox proportional hazards regression models will be used to evaluate the differences in time to symptom resolution. Adjusted treatment effects will be estimated in Cox proportional hazards regression models, controlling for the variables listed above. To identify that our randomization strategy was effective, analysis of variance will be used to assess for group-wise differences in age, days since injury to initial visit, initial PCSS score, resting heart rate (HR), and ΔHR during the BCBT and resting BP and ΔBP during the ice bucket test on Day 1. Non-parametric tests of medians will be used to compare the non-normally distributed variable duration of clinical recovery. Chi- |

| | |
|---|---|
| | squared tests will be used to assess group-wise differences in gender, history of concussions, and incidence of persistent post-concussive symptoms.<br>**Safety Analysis**<br>Incidence, severity, relationship of treatment emergent adverse events will be presented by treatment group. All vital signs measurements will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Given the cardiovascular exclusion criteria, ECG data is redundant, and will not be collected.<br>**Efficacy Analysis**<br>Biomarkers will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable.<br>Neuropsychology testing will be assessed using the patient reported outcomes and will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable.<br>Results of the cold pressor test, whiplash test and BCBT will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable. |

# 1 INVESTIGATIONAL TEAM

Refer to the trial specific contact list for details of investigators, sponsor personnel, clinical research organization personnel and facilities used in the study.

# 2 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

## 2.1 Mild Traumatic Brain Injury

Concussion or mild traumatic brain injury (mTBI) is defined as a blow or jolt to the head (i.e., a non- penetrating head injury) that disrupts the normal function of the brain. Concussion can be described as a brain injury defined by a complex pathophysiological process that is induced by biomechanical forces. Mild traumatic brain injury is described as a continuum of brain injury and associated pathophysiology of mild vs. more severe trauma-induced brain injury.[1] Recent years has seen greater emphasis placed on the importance of brainstem systems impaired as a result of diffuse axonal injury resulting from inertial forces imparted by mTBI damaging axonal pathways traversing the interface of the cerebral hemispheres and the brainstem.[2-4] Autonomic function which controls eye movement, balance and neck control appears to be vulnerable to concussive injury. Injury to this pathway may result in impairments in a number of daily functions such as reading or driving [5] which may predispose concussed individuals for more prolonged deficits, and the need for earlier, symptom-targeted therapies.

Traumatic brain injury (TBI) is a major cause of death and disability in all age groups and is responsible for significant healthcare costs. Concussion management consensus statements consistently call for the need for additional research to improve outcomes for this patient population.[6,7]

Accurately identifying the true incidence and duration of ongoing symptoms following concussion has remained elusive, with no reliable way to confirm that symptomatic recovery coincides with brain physiologic recovery.[9] The diagnosis of concussion relies on self-reported symptoms, which are prone to both over-reporting (e.g., in anxious individuals and malingerers[5]); and under-reporting (e.g., in both athletes and members of the military[8]). An estimated 20% of individuals have persistent post-concussive symptoms (PPCS), as defined by symptoms lasting 2 or more weeks in adults, and 4 or more weeks in adolescents.[10] The 2 best validated instruments for assessing symptom persistence are the Post-Concussion Symptom Inventory (validated in youth from age 5 to 18 years of age[11]) and the Post-Concussion Symptom Scale (PCSS) (validated in adults[12] and in 13 to 22 year olds[13]). Four distinct symptom clusters: cognitive-fatigue-migraine, affective, somatic, and sleep have been identified as being affected following a concussion.[13] The presence of pre-existing neuropsychological conditions, especially anxiety, as well as a lack of resilience, have been implicated as contributing to PPCS. Other factors contributing to the severity and duration of post-concussive symptoms have been identified including sex, age, extent of athleticism, history of prior concussions, as well as a history of migraine headaches. Consistent with the objectives of this clinical trial, symptoms of autonomic dysfunction, including exercise-induced headaches, are amongst most prevalent during the first week post-injury, and have also been reported to be the most persistent following mTBI.[5]

Autonomic dysfunction in the form of impaired cerebral autoregulation is commonly seen following mTBI.[15] Standard clinical evaluations are able to assess the integrity of eye movement, balance, and neck function[14], however, there is no easy way to assess autonomic

function in clinical settings. Options for diagnosing autonomic dysfunction following concussion include the Buffalo Concussion Treadmill Test (BCTT);[16] a test performed within a week of injury that has the ability to predict prolonged recovery in concussed adolescents with a sensitivity of 73% and a specificity of 78%.[17] and the "ice bucket test" (also known as the cold pressor test);[18] a simpler and faster way to diagnose autonomic dysfunction following mTBI[19].

The current standard of care for patients with mTBI is cognitive and physical rest. However, a recently conducted randomized control trial suggests that the implementation of exercise activity as opposed to physical and cognitive rest during the initial period of injury accelerates recovery.[20] Sub-symptom threshold aerobic exercise, has been shown to improve autonomic function as reflected by non-invasive measures such as heart rate variability (HRV),[21] and to accelerate recovery following concussion.

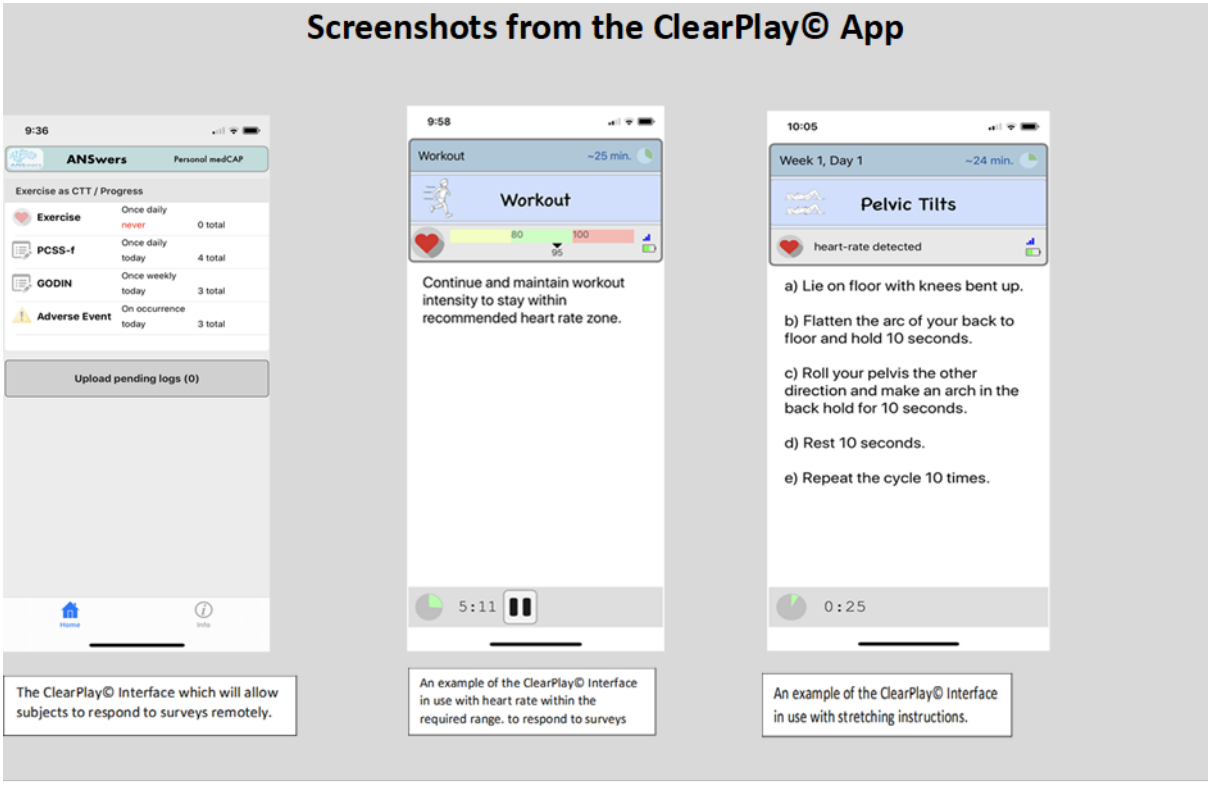
It is anticipated that results from our study, in combination with those evolving from similar research studies now underway in Australia as well as the US, will provide support for decision making by physicians, trainers, and other clinicians during the days/weeks following concussion, including what activities should be avoided, what therapies can accelerate recovery, and when the brain has recovered so that it is safe to resume sport or work.

### 2.2 Therapeutic Intervention

A number of governing bodies now endorse an active rehabilitation program of progressive reintroduction of noncontact aerobic activity that does not exacerbate symptoms along with close monitoring of symptom expression.[22]

In order to promote this, ANSwers Neuroscience Pty Ltd has developed a novel therapeutic intervention, downloadable to an Apple i-touch or i-phone device, that provides a telemetry-based graded exercise program which enables remote monitoring of symptoms. The sponsor will provide an i-touch or i-phone to each eligible subject during the Baseline Visit, which they will use daily during the 8 weeks of clinical study. Subjects keep the i-touch or i-phone on completion of study participation. The digital therapeutic application permits the 'dosing of heart rate (HR)' approach[23] while monitoring symptomatic and physiologic recovery on a daily basis. It is hypothesized that the mobile application, ClearPlay©, will accelerate recovery time following concussion by improving activity-induced blood flow to the brain and aid in the rehabilitation process. ClearPlay© is intended to be used in a professional setting following point of injury or onset of the condition and can also be used by patients at home. Refer to Figure 1 for an image of the ClearPlay© interface.

**Figure 1: Sample of ClearPlay© Interface**




To support the use of ClearPlay©, ANSwers Neuroscience Pty Ltd has developed 2 devices:

- ClearHeart©, a Cooling Glove System as an alternative to ice bucket testing, to enable providers to perform a quick, real-time diagnosis of autonomic nervous system disorders, including mTBI. The results are available immediately through a computer interface, permitting healthcare providers to make immediate diagnostic assessments and therapeutic recommendations.

- ClearNeck© a prototype device for cervico-genic proprioception measurement. This test is based on the joint position error test to assess “whiplash”.

## 2.3 Clinical Studies

Historically, concussion has been described as a cognitive injury and patients have been advised not to engage in any cognitive or physical exertion while symptomatic. More recently, however, concussion has been described as a physiological injury affecting both the heart and autonomic nervous system, and patients suffering from prolonged concussion-related symptoms and deficits have been encouraged to begin aerobic exercise as part of their concussion care. While intensive exercise too soon after concussion has been associated with delayed recovery and used to justify prolonged periods of rest, recent studies have shown that controlled, sub-symptom threshold aerobic exercise may aid recovery by improving autonomic balance and cerebral blood flow auto-regulation after concussion.

## 2.4 Known and Potential Risks

Potential risks exist to the following groups of patients:

- Subjects with musculoskeletal or cardiac or pulmonary conditions that preclude participation in exercise;
- Subjects using anti-hypertensive medications;
- Subjects with peripheral circulatory disorders due to conditions such as, but not limited to, Raynaud's syndrome, scleroderma, or diabetes. These subjects may experience hand discomfort when exposed to the ClearHeart© cooling;
- Subjects with lymphedema in the left arm, as they may experience arm discomfort when using the ClearHeart© device.

## 2.5 Study Rationale

This study has been designed as a multicenter, open-label clinical intervention trial to compare 8 weeks of graded exercise to passive stretching to accelerate recovery following mTBI. The study aims to demonstrate the superiority of graded exercise to passive stretching to accelerate subjective symptoms following mTBI. The primary endpoint is resolution of self-reported symptoms (therapeutic). Symptom resolution will be defined as a symptom-severity score less than pre-mTBI values on the PCSS for 3 consecutive days. The secondary endpoint is physiologic normalization of autonomic function (diagnostic/prognostic). Change in physiologic measures (e.g. HRV) over time will be disturbed using the Buffalo Concussion Bike Test (BCBT) and ice bucket test.

Mild TBI is one of the most common neurological conditions that occurs during childhood and, depending on the age of the individual, typical causes of mTBI vary greatly. Children aged 5 to 14 years are most likely to be seen in the emergency department with TBI resulting from falls (approximately 35%) and from being struck by or against an object (35%) occurring during athletic and recreational activities. Motor vehicle accidents, assaults, falls, and being struck by or against an object, each account for approximately 20% of emergency department visits for TBI in adolescents and young adults (15-24 years), with an increased incidence of sport-related injuries in that age range.[4] Females tend to report a greater number, more severe, and a longer duration of symptoms compared to men, both before as well as after puberty.[24] Most publications in middle aged adults have studied sport-induced concussion in athletes, a population who may recover more quickly as a result of cardiovascular conditioning.[25] By broadening the enrolment criteria in this study to include athletic and non-athletic men and women aged 14-45, and by including individuals with known co-morbidities (such as migraine,[26] anxiety,[27] and other psychologic factors[28]) this study aims to yield results that are relevant to the general population who may experience mTBI.

## 2.6 Risk Assessment

As this is a therapeutic intervention study, there are minimal risks associated with taking part in this investigational study. The current standard of care for subjects with mTBI is cognitive and physical rest. However, a number of governing bodies now endorse an active rehabilitation program following concussion and clinical trials have also been completed to assess the safety of graded exercise following mTBI.

During the study, appropriately trained staff will ensure that any risks associated with the study, including exercise testing, are closely monitored. Real time review of safety data will

be performed, with safety monitoring to be adjusted as required if any risks become apparent. Enrolment of subjects will only occur at study sites that have appropriately trained staff to ensure subjects receive the best standard of care.

# 3 STUDY OBJECTIVES

## 3.1 Primary Objective

The primary objective of the study is to compare the effects of graded exercise and passive stretching using ClearPlay© (ANSwers Neuroscience Pty Ltd commercial mobile application) on recovery following mTBI in the Australian setting.

## 3.2 Secondary Objectives

The secondary objectives of the study are to:

- Compare the safety and tolerability of graded exercise compared to passive stretching following mTBI;
- Develop a composite physiologic scale to predict the magnitude and duration of ongoing post-concussive symptoms;
- Validate the performance of ClearHeart©, ANSwers Neuroscience Pty Ltd commercial prototype for cold pressure testing, compared to ice bucket testing.

## 3.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Validate the performance of ClearNeck©, ANSwers Neuroscience Pty Ltd commercial prototype based on the joint position error test to assess “whiplash”.

# 4 STUDY DESIGN AND ENDPOINTS

## 4.1 Description of the Study Design

This study is designed as an open label study of a therapeutic intervention in subjects who have sustained mTBI. At least 400 subjects aged 14 to 45 inclusive will be enrolled in this study at up to 5 study sites. Subjects will be randomly assigned with a ratio of 1:1 to complete either graded exercise or passive stretching. The study sites will have well-established concussion research programs and referral populations.

The therapeutic intervention is either 20 minutes daily of graded exercise or 20 minutes daily of passive stretching delivered through the ClearPlay© mobile application, downloaded to an Apple i-touch or i-phone device, used in conjunction with a wrist-worn heart rate monitoring device (Waveband®). The sponsor will provide one i-touch or i-phone to each subject to provide them with access to ClearPlay App. This device will also allow subjects to access music for use during exercise or stretching.

Randomization of each subject will occur when the subject has completed all of their Baseline physiologic testing (Ice Bucket Test, ClearHeart© and BCBT) on Day 0.

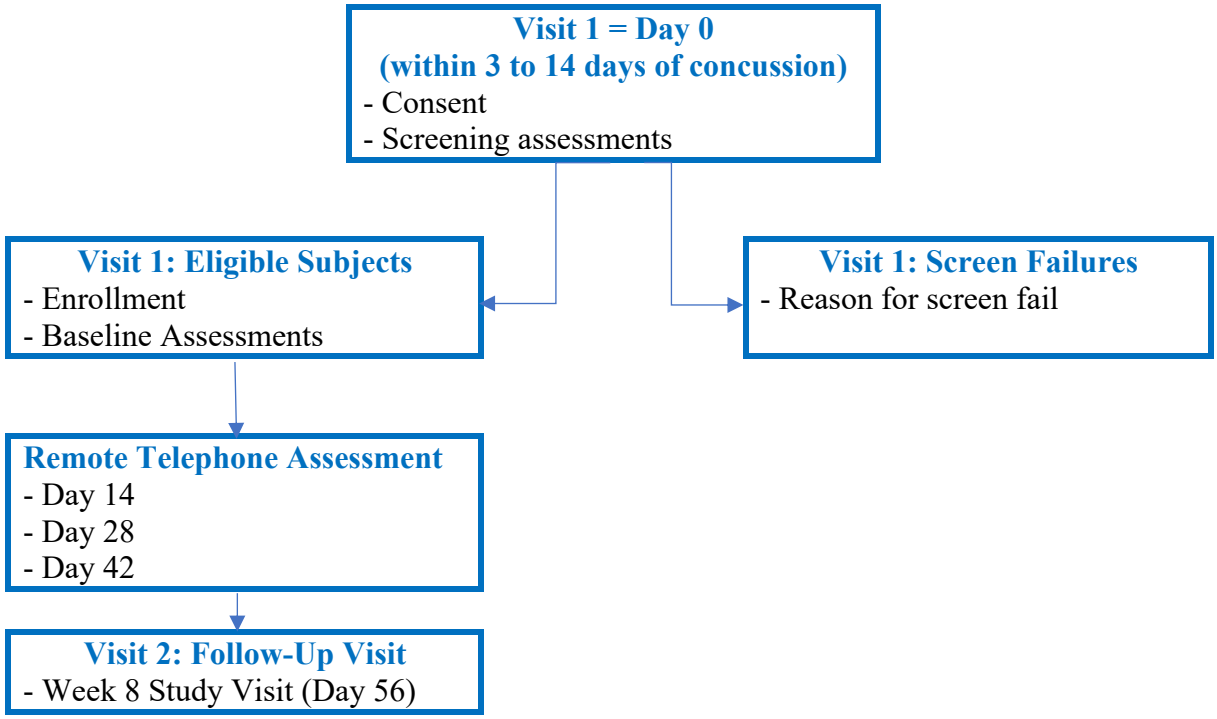
Both the site staff treating subjects and the subjects themselves will be aware of the assigned exercise regimen. Subjects will be stratified based on baseline scores on the PCSS (threshold ≥30).

The study consists of 2 study visits and 3 remote telephone visits between the 2 study visits:

- Study Visit 1 (Day 0) – Screening/Baseline visit: within 3 to 14 days of concussion. This visit will serve as a screening visit, to determine eligibility to participate in the study. Eligible subjects will be enrolled, and baseline assessments performed;
- Remote telephone safety assessments – Day 14, Day 28 and Day 42 for safety follow up;
- Study Visit 2 – Follow-up visit: 8 weeks following enrolment (Day 56).

A schematic diagram of the study design is presented in Figure 2.

**Figure 2: Study Design**



## 4.2 Study Objectives and Endpoints

The study objectives and endpoints to be evaluated in this study are presented in Table 1.

**Table 1: Study Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary Objectives** | **Primary Endpoints** |
| To compare the effects of graded exercise to passive stretching using ClearPlay© on symptomatic recovery rate following mTBI. | • Within-subject analysis of change in symptoms over time using the PCSS, comparing short-term 'survival rates' between graded exercise and stretching using Kaplan-Meier analyses for days since concussion. |
| **Secondary Objectives** | **Secondary Endpoints** |
| To compare the safety and tolerability of graded exercise to passive stretching in patients following mTBI. | • Adverse events reported from Day 1 through Day 56, including those identified during exercise or passive stretching during the 20 minutes of daily therapy. |
| To compare symptom resolution following graded exercise compared to passive stretching using ClearPlay© following mTBI. | • Within subject analysis of change in the number of subjects who are symptom free at 8 weeks between the 2 groups. Symptom free is defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion.<br>*Note: This objective is similar to the primary one, with the primary endpoint being recovery (binary outcome) vs. symptom resolution (continuous variable).*<br>• Determine differences in symptomatic recovery based on gender, baseline scores on the PCSS, baseline athletic fitness (Godin leisure-time exercise questionnaire), the history of injury, a history of migraine, as well as the presence of pre-morbid anxiety. |
| To compare the effects of graded exercise to passive stretching using ClearPlay© on physiologic recovery rate following mTBI. | • Within subject analysis of normalization of physiologic measurements obtained during the BCBT comparing data collected on entry to the study on Day 0 vs. follow up on Day 56 including:<br>- Beat to beat BP;<br>• Determine differences in physiologic recovery based on gender, baseline scores on the PCSS, baseline athletic fitness (Godin leisure-time exercise questionnaire), the history of injury, a history of migraine, as well as the presence of pre-morbid anxiety (BAI; BSI-18; ASI). |
| To compare the effects of graded exercise to passive stretching using ClearPlay© on accelerating symptomatic vs. physiologic recovery rate following mTBI. | • Combined analysis of data from the two secondary analyses outlined above to confirm or refute a significant correlation between symptom resolution (defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) and physiologic measurements obtained during the BCBT comparing data obtained on entry to the study on Day 0 vs. follow up on Day 56 including:<br>- Beat to beat BP; |

| Objectives | Endpoints |
|---|---|
| To develop a composite physiologic metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Develop predictive modeling algorithms to establish a composite physiologic metric predictive of subjects becoming symptom free (as defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) using data derived from baseline physiologic testing with:<br>- BCBT<br>- Ice bucket testing<br>- ClearPlay© testing |
| To develop a composite neuropsychologic metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Develop predictive modeling algorithms to establish a composite neuropsychologic metric predictive of subjects becoming symptom free (as defined by subjects having 3 consecutive days of PCSS scores lower than pre-concussion) using data derived from baseline neuropsychologic testing with the following instruments:<br>Attention (CAARS)<br>- Depression (CES-D)<br>- Anxiety (BAI; BSI-18; ASI). |
| To develop a composite blood-based or saliva biomarker metric to predict the magnitude and duration of ongoing post-concussive symptoms. | • Analysis of biomarkers at baseline testing including:<br>- Structural proteins [t-tau, NF-L, GFAP and UCH-L1]<br>- Inflammatory cytokines [IL-6, IL-10 and TNFα]<br>- SNPs [APO-E4, BDNF, and NFkB] |
| To validate the performance of ClearHeart© against ice bucket testing. | • Bland-Altman plots will be used to evaluate the agreement between HR measured by ClearHeart© and ice bucket testing.<br>• Bland-Altman plots will be used to evaluate the agreement between BP measured by ClearHeart© and ice bucket testing. |
| To validate the performance of ClearNeck© against examination of the neck | • Correlations will be used to assess the association between results obtained through ClearNeck© testing and those obtained during the neurologic examination for neck range of motion and tenderness. |

Abbreviations: ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BCBT = Buffalo Concussion Bicycle Test, BESS = Balance Error Scoring System,; BP=blood pressure, BSI = Brief Symptom Inventory, CAARS = Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale, CES-D = Center for Epidemiologic Studies - Depression Scale,; HRV = heart rate variability; mTBI = mild traumatic brain injury; PCSS = Post-Concussive Symptom Scale, SNP = single nucleotide polymorphisms

### 4.3 Appropriateness of Measures

Multiple study sites are required to ensure efficient recruitment of subjects. Medical centers with well-established concussion research programs and referral populations have been selected to ensure subjects have access to appropriately trained and qualified healthcare providers.

The study is randomized to avoid the bias of subject selection for factors known and unknown between the treatment groups.

Randomization will be stratified by site and baseline symptom severity score on the PCSS (threshold < or ≥30).

All assessments proposed in this study are considered by ANSwers Neuroscience Pty Ltd and the Investigators to be appropriate and necessary to compare graded exercise to passive stretching in post-mTBI recovery.

The PCSS is a well validated 21-item self-report measure that records symptom severity using a 7-point Likert scale of severity. This widely used symptom checklist ranks concussion symptoms by their severity and persistence.

Assessments used in this study to assess autonomic function include the BCBT, which measures the exacerbation of post-concussive symptoms during 15 minutes of step-wise escalation of cardio-vascular function and the cold pressor test (known as the "ice bucket test"), which has been shown to be diagnostic of mTBI. The BCBT has been validated against the BCTT, which has been shown to be diagnostic of mTBI, and to be predictive of PPCS.

The safety assessments used in this study such as adverse events (AEs) identified during graded exercise or passive stretching during the 20 minutes of daily therapy from Day 1 through Day 56, remote monitoring of vital signs including beat to beat blood pressure (BP), and daily self-reporting of symptoms on the PCSS are considered appropriate for monitoring subject health and well-being in this type of study.

In collaboration with a private diagnostic laboratory (Monogram Biosciences, a Division of Labcorp) who have validated a set of biomarkers reflective of the severity of mTBI assay structural proteins [t-tau, NF-L, GFAP and UCH-L1] and inflammatory cytokines [IL-6, IL-10 and TNFα]) will be analyzed. Blood and saliva samples will be collected at the time of enrollment and at the end of the study.

In addition, a set of single nucleotide polymorphisms (SNP) and micro ribonucleic acids (RNA) that have been implicated in contributing to the biologic vulnerability to PPCS will be analyzed. Deoxyribonucleic acid (DNA) and RNA will be isolated for bio-banking and subsequent analysis. Sample collection will be either blood collection or buccal swab and collection of saliva.

New tests, ClearHeart© and ClearNeck© will be validated as part of the study objectives by comparing against the equivalent validated methods, Ice Bucket Testing and neurological examination respectively, which will be also be performed as part of the study.

# 5 STUDY ENROLMENT AND WITHDRAWAL

## 5.1 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria:

1. Male or female subjects aged ≥14 to ≤45, able and willing to provide informed consent (≥18 years), or informed consent is obtained by the parent or legal guardian for minor subjects, with the minor providing age appropriate assent, according to local law and regulations;

2. Subject is fluent in English, able to understand and agree to comply with protocol requirements, and complete all assessments;

3. Subject has a history of recent concussion as diagnosed by a health care professional within 3 to 14 days of enrolment;

   Note: Concussion is defined as a head injury/blow to the head resulting in any of the following 3 signs and/or new symptoms: (1) amnesia for less than 24 hours; (2) Loss of consciousness for less than 30 minutes; (3) Glasgow Coma Scale score > = 13; (4) Dazed and Confused/bell rung; with at least 1 new symptom or augmentation of a previous symptom on the PCSS as compared with baseline at the time of enrolment, including: headaches, dizziness, fatigue, irritability, insomnia, difficulty concentrating, and/or memory difficulties; (5) The composite symptom score on the PCSS must be at least 3 points higher post-concussion than pre-concussion.

4. Subject has daily access to the internet.

### 5.2 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criteria are applicable:

1. History of prior head injury as defined by:

   - An injury/blow to the head within 12 months prior to screening with any associated residual symptoms;

   - An injury/blow to the head within 3 months prior to screening diagnosed as a concussion;

   - An injury/blow to the head within 3 months prior to screening with any of the following symptoms: amnesia, loss of consciousness, dazed and confused/bell rung;

2. Evidence of blood or micro-hemorrhages on prior or current computed tomography scan or magnetic resonance imaging scan if obtained;

3. Diagnosis of a neurological condition including the following: stroke, multiple sclerosis, epilepsy, brain tumor/cancer, encephalitis, dementia, movement disorder, or spontaneous nystagmus;

4. Psychiatric history with any of the following:

   - History of psychiatric hospitalization, history of legal trouble for violence;

   - Requires psychotropic medication other than (1) stable dose of a selective serotonin reuptake inhibitors (SSRI) medication, or (2) stable dose of a tricyclic antidepressants (TCA) medication;

   - Prior diagnosis of psychotic disorder, bipolar disorder, eating disorder, substance abuse disorder;

5. Current use of a beta blocker;

6. History of drug or alcohol dependency or abuse within a year before Screening, by self-report;

7. Two or more of the following cardiovascular risk factors:

    - Prior diagnosis of, or currently taking medication for cardiovascular, metabolic or pulmonary conditions;

    - Family history of myocardial infarction, coronary revascularization or sudden death before 55 years;

    - Diagnosis of hypertension;

    - Diagnosis of hyperlipidemia;

    - Subjects with peripheral circulatory disorders;

8. Subjects who are unable or unwilling to exercise for health or personal reasons;

9. Subjects who have musculoskeletal injuries which could make exercise difficult or painful.

## 5.3 Withdrawal and Replacement of Subjects

### 5.3.1 Reasons for Withdrawal of Subjects

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Subject non-adherence to therapeutic intervention or protocol requirements. Please refer to Section 6.5 for lifestyle and dietary study restrictions. Subjects must also be able to upload data via the ClearPlay© mobile application daily. Failure to do so for 3 consecutive days will trigger a call from the site. Subjects who do not upload data for 5 consecutive days are to be contacted by the site again. Subjects who do not upload for 7 consecutive days are to be withdrawn from the study for poor compliance;

- Subjects from either group who exercise at a rate that exceeds that which is prescribed, as identified by either self-report (the Godin Leisure Time Exercise questionnaire) or by autonomic monitoring (using ClearPlay©) will be withdrawn from the study and coded as “lost to follow up”.

- Subject unwillingness to continue in the study;

- Any other reason based upon the medical judgment of the investigator.

The reason for study withdrawal is to be documented in the subject’s source documents and electronic case report form (eCRF).

At the time of discontinuation from the study, subjects are to have all the assessments planned for the follow-up visits performed after the last study drug dose, if feasible.

### 5.3.2 Handling of Withdrawals or Early Termination of Subjects

Withdrawals or early termination: If a subject is withdrawn from the study for any reason, whether related to the study drug or not, or if a subject voluntarily withdraws, such subject will be considered an early termination subject. The investigator will make every effort to ensure that early-termination subjects complete an Early Termination visit.

Lost to follow-up: Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

## 5.4 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, and regulatory authorities.

If the study is prematurely terminated or suspended, the investigator will promptly inform the Human Research Ethics Committee (HREC) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Sponsor terminates the study for administrative, financial or other reasons.

# 6 THERAPEUTIC INTERVENTION

## 6.1 Therapeutic Interventions Administered

The therapeutic intervention (graded exercise) to be used in this study is delivered through the ClearPlay© application. This application will be preloaded on the i-touch or i-phone device, which will be supplied to each eligible subject during the Baseline Visit. ClearPlay© provides the subject with a graded exercise program or passive stretching, which is used in conjunction with a wrist-worn HR monitoring device (Waveband®).[29]

Each subject will cease their assigned Therapeutic Intervention when they have reach three consecutive days of PCSS score that is less than or equalled to the subject's pre-mTBI PCSS score. All subjects will be required to complete the Follow Up, Day 56 Visit, regardless of the date they cease Therapeutic Intervention.

**Table 2: Therapeutic Interventions**

| Therapeutic Intervention | Description | Duration | Frequency |
|---|---|---|---|
| Telemetry-based graded exercise | Sub-symptom threshold aerobic exercise | 20 minutes | Daily for 8 weeks |
| Passive stretching | Passive stretching | 20 minutes | Daily for 8 weeks |

## 6.2 Therapeutic Intervention Components

ClearPlay© Application: The downloadable app will be available from the app store. The app has 4 components: connectivity with the Waveband® to transmit physiologic (HRV) data remotely; a fillable version of the PCSS; and a fillable version of the Godin leisure-time exercise questionnaire; an instrument for communication of AEs.

Waveband®: Each subject will be fitted with a Waveband® (fit-bit like device to remotely detect HR and HRV). This is to be worn while the subject completes the graded exercise program or passive stretching program.

## 6.3 Blinding and Randomization

### 6.3.1 Blinding

This study is an open-label study and thus the investigator, site staff, sponsor, sponsors delegates (if applicable) and subjects will not be blinded to treatment allocation.

### 6.3.2 Randomization

A computer-generated randomization schedule will be prepared by a statistician prior to the start of the study. Treatment allocation will be made per the randomization list.

After signing the informed consent form/providing assent, subjects will be administered the screening instruments via REDCap Cloud, along with generation of unique subject ID.

Once eligibility has been established, subjects must proceed to complete all Baseline assessments. The Order of Assessment is listed in Section 8.1, Table 4. Randomization of each subject will occur when the subject has completed all of their Baseline physiologic testing on Day 0.

The subject will be assigned a unique randomization number, which will be allocated sequentially based on the pre-determined randomization schedule, and according to their chronological order of inclusion in the study.

Both the unique subject ID and randomization numbers will be used to identify the subject throughout the study period and on all study-related documentation.

Stratification: randomization will be stratified at each enrolment site by the baseline symptom severity score on the PCSS (threshold < or ≥30). The baseline PCSS score is reflective of multiple pre-morbid, neurologic, psychologic, and other factors that collectively are likely to significantly impact the presence of PCSS. Rather that stratify the population based on

individual factors, the single composite measure should provide the most efficient and effective starting point for this clinical trial.

## 6.4 Accountability Procedures

The investigator is responsible for the accountability of study materials. The investigator or designated site staff must maintain product accountability records throughout the course of the study. The amount of product received from the sponsor, the amount supplied and/or administered to and returned by subjects, if applicable, will be documented.

### 6.4.1 Storage of Supplies

Study materials will be stored by the study personnel according to the documentation provided with the study materials. The sponsor reserves the right to inspect the storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator File.

### 6.4.2 Control of Supplies

Dispensing of the study materials will be carefully recorded on appropriate forms.

The accountability logs should include dates, quantities, material identification number assigned to the study materials and/or subject. The accountability logs will also include general details related to the study including the protocol/amendment number, sponsor name, indication and the investigator.

### 6.4.3 Return of Supplies

The study monitor will review the study materials accountability logs and check all product returns prior to authorizing the return of the product to the sponsor.

### 6.4.4 Compliance to Therapeutic Intervention

The study site will be able to monitor subject use of the ClearPlay mobile application in conjunction with the Waveband® for compliance and to monitor AEs and symptom escalation. Subjects who do not upload data for 3 consecutive days are to be contacted and reminded of the study requirements. Subjects who do not upload data for 5 consecutive days are to be contacted again. Subjects who do not upload for 7 consecutive days are to be withdrawn from the study for poor compliance.

## 6.5 Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrolment (within 14 days before the time of randomization) or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency;

If the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF. The medical monitor must be notified of all prohibited medications administered to any subject, in order to assess the subject's eligibility to continue in the study.

### 6.5.1 Prohibited Medications

The following medications are prohibited during the study:

- Psychotropic medications other than stable dose of an SSRI medication, or stable dose of a TCA medication;
- Subjects using beta-blockers.

Use of prohibited medications during the study will be captured as protocol deviations and discussed with the sponsor.

### 6.5.2 Allowed Medications

All medications are permitted, with the exception of those listed in Section 6.5.1.

## 6.6 Concomitant Therapies

Any concomitant therapy (occupational therapy, physical therapy, vestibular therapy, visual therapy, cognitive behavioral therapy, acupuncture, chiropractor, and/or other therapies) that the subject is receiving or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of therapy including start and end dates.

## 6.7 Lifestyle and Dietary Study Restrictions

The following lifestyle and dietary restrictions should be followed during the study:

- Physical Exercise: Subjects must be willing to exercise or stretch for 20 minutes each day, while wearing the wrist-worn HR monitoring device (Waveband®), by following the directions provided by the ClearPlay© mobile application. Outside of this, subjects should not engage in any exercise during the 8-week study period that will make them short of breath.
- Smoking: Subjects must be willing to refrain from smoking for 1 hour prior to their daily exercise or stretching sessions.
- Alcohol: Subjects must be willing to refrain from drinking alcohol for 1 hour prior to their daily exercise or stretching sessions.
- Dietary: Subjects must be willing to refrain from consuming caffeinated or sugary beverages that may impact HR for 1 hour prior to their daily exercise or stretching sessions.

# 7 STUDY ASSESSMENTS AND SCHEDULES

## 7.1 Safety Assessments

Refer to the Schedule of Events (Table 5) for the timing of all safety assessments.

### 7.1.1 Baseline Demographics

Subject demographics will be recorded, including date of birth, gender, race, ethnicity, alcohol history, drug/tobacco history.

### 7.1.2 Medical and Medication History

A detailed history of the head injury will be taken.

A complete medical history will be collected, not limited to but including evaluation for past or present neurological, cardiovascular, metabolic or pulmonary conditions, history of migraines, psychiatric history.

A detailed record of the head injury will be collected. Review of computed tomography (CT) scans or magnetic resonance imaging (MRI)s to be performed if applicable.

A review of prior medications will be completed. Prior medications are those used within 7 days of Screening.

### 7.1.3 Body Weight and Height

Body weight (in kg) (wearing light clothes, no shoes) and height (in cm) will be measured to allow the calculation of body mass index (rounded to 1 decimal place). *Note: Height will only be captured at the screening visit.*

### 7.1.4 Vital Signs including Beat to Beat Blood Pressure

Vital signs will be collected via a third-party FDA approved device (Caretaker4®).[30] The subject will be fitted with the Caretaker4® device which attaches to right arm and right finger and measures continuous beat to beat HR and BP. Once connected, 2 minutes of baseline data collection will occur, followed by 2 minutes of ice bucket (or ClearHeart©) data collection, and a further 2 minutes post-ice bucket data collection.

The investigator (or a qualified observer at the investigational site) will interpret the vital signs using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant (reported with corresponding AE).

### 7.1.5 Adverse Events

The categorization of AEs by seriousness, relationship and expectedness is summarized in Table 3, and forms the basis for understanding the reporting requirements of events.

**Table 3: Categories of Adverse Events**

| Event Seriousness | Event Relationship and Expectedness | | |
|---|---|---|---|
| | **Not Related** | **Related** | |
| Non-serious | Adverse event | Adverse event | |
| Serious | Serious adverse event | Serious Adverse Event | |
| | | **Expected** Serious Adverse Event | **Unexpected** Suspected Unexpected Serious Adverse Reaction) |

Unanticipated problems relating to the therapeutic intervention, involving risks to subjects and others will be monitored throughout the study.

#### 7.1.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be reported on the appropriate page of the eCRF.

#### 7.1.5.2 Adverse Device Effect

An ADE is an AE related to the use of an investigational medical device.
This definition includes:

- Adverse events with a relationship to the use of the investigational medical device;
- Adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device;
- Any event resulting from use error or from intentional misuse of the investigational medical device.

#### 7.1.5.3 Definition of Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (ie, the subject is at immediate risk of death at the time the event occurred; it does not refer to an event which might hypothetically have caused death had it been more severe);

- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse.

The following hospitalizations/admissions do not need to be reported as SAEs:

- Hospitalization for social reason (e.g. caregiver relief);
- Hospitalization for surgery/procedure planned prior to study entry;
- Hospital visit less than 24 hours e.g. held for observation or treatment, but duration of stay less than 24 hours;
- Treatment at hospital or center for minor procedures (e.g. laser eye surgery).

#### 7.1.5.4 Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a related SAE that is both serious and unexpected as assessed using the current Investigator's Brochure or Product Information.

#### 7.1.5.5 Anticipated Serious Adverse Device Effect

An anticipated SADE is a SADE which by its nature, incidence, severity or outcome has been identified in the current version of the Investigator's Brochure or Product Information.

#### 7.1.5.6 Unanticipated Serious Adverse Device Effect

An unanticipated SADE is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator's Brochure or Product Information.

#### 7.1.5.7 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.

#### 7.1.5.8 Severity of Adverse Events

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The severity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

| | |
|---|---|
| Mild: | An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities. |
| Moderate: | An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed. |
| Severe: | An AE that prevents normal everyday activities; treatment or other intervention usually needed |

#### 7.1.5.9 Relationship of Adverse Events

The investigator is obligated to assess the relationship between graded exercise and passive stretching and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the therapeutic intervention will be considered and investigated.

The causal relationship of the AE to the therapeutic intervention or study procedures should be assessed by the investigator (or medically qualified delegate) using the following classifications:

| | |
|---|---|
| Not Related: | In the investigator's opinion, there is not a causal relationship between the therapeutic intervention and the AE. |
| Unlikely: | The temporal association between the AE and therapeutic intervention is such that the study product is not likely to have any reasonable association with the AE. |
| Possible: | The AE follows a reasonable temporal sequence from the time of therapeutic intervention but could have been caused by the study subject's clinical state or other modes of therapy administered to the subject. |
| Probable: | The AE follows a reasonable temporal sequence from the time of therapeutic intervention, abates upon discontinuation of the therapeutic intervention and cannot be reasonably explained by the known characteristics of the study subject's clinical state. |
| Highly Probable: | The AE follows a reasonable temporal sequence from the time of therapeutic intervention, abates upon discontinuation of the therapeutic intervention and reappears when the therapeutic intervention is reintroduced. |

### 7.1.5.10 Relationship of Adverse Events to Investigational Device

The investigator is obligated to assess the relationship between the investigational device and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the device use will be considered and investigated.
The causal relationship of the AE to the investigational device or study procedures should be assessed by the investigator (or medically qualified delegate) using the following classifications:

| | |
|---|---|
| Not Related: | In the investigator's opinion, there is not a causal relationship between the investigational device and the AE. |
| Unlikely: | The temporal association between the AE and investigational device is such that the investigational device is not likely to have any reasonable association with the AE. |
| Possible: | The AE follows a reasonable temporal sequence from the time of use of the investigational device but could have been caused by the study subject's clinical state or other modes of therapy administered to the subject. |
| Probable: | The AE follows a reasonable temporal sequence from the time of use of the investigational device, and cannot be reasonably explained by the known characteristics of the study subject's clinical state. |

Adverse events that have a relationship (possible or probable) to the investigational device, are termed ADEs.

### 7.1.5.11 Recording of Adverse Events

Adverse events will be recorded and reported from Day 1 to Day 56. Adverse events will be captured at clinic visits on Day 1 and Day 56, and at telephone safety visits on Day 14, Day 28 and Day 42.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in to the eCRF. All details of any treatments initiated due to the AE should also be recorded in the subjects' notes and the eCRF.

Each AE will be documented in the subject's eCRF. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the eCRF.

In the event where the principal investigator is not a clinician, then the principal investigator must delegate the safety review duty to a clinician.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event;
- Classification of 'serious' or 'not serious';
- Severity;
- Date of first occurrence and date of resolution (if applicable);
- Action taken;
- Causal relationship;
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported].

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subjects' condition.

All AEs are required to be assessed by a medical practitioner. All AEs or SAEs documented at a previous visit/contact that are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs or SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

#### 7.1.5.12 Reporting of Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the study. Device deficiencies will be further classified as those that potentially could lead to SADE (device deficiency with SADE potential), and those that could not (device deficiency without SADE potential).

To determine SADE potential, the investigator may consider whether the device deficiency might have led to an important medical occurrence in any of the following situations:

a) if either suitable action had not been taken;
b) if intervention had not been made, or;
c) if circumstances had been less fortunate.

#### 7.1.5.13 Reporting of Serious Adverse Events

As the sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of a new therapeutic intervention, prompt notification by the investigator, or nominee, of any SAEs, SADEs or device deficiencies with SADE potential, to the sponsor is required.

All SAEs, SADEs or device deficiencies with SADE potential, whether related or unrelated, and regardless of expectedness, should be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness via email as follows:

- Email to: pharmacovigilance@answersneuro.com

If the investigator learns of any SAE/SADEs/device deficiency with SADE potential, including death, at any other time after a subject completes the study, and he/she considers the event reasonably related to the therapeutic intervention, the investigator will promptly notify the sponsor.

In addition to reporting the SAE/SADEs/device deficiency with SADE potential to sponsor, the investigator must also notify the HREC which approved the study according to their requirements.

Copies of all correspondence relating to reporting of any SAEs/SADEs/device deficiency with SADE potential should be maintained in the site's study files and will be checked routinely by the Study Monitor.

If the sponsor and the investigator consider that the SAE/SADEs/device deficiency with SADE potential is related to the therapeutic intervention (ie, an adverse reaction) and unexpected it will be reported to the appropriate regulatory authorities by the sponsor (or designee) within the pre-defined timelines.

In the event where the principal investigator is not a clinician, then the principal investigator must delegate the safety review duty to a clinician.

Non-serious or expected adverse reactions, or events (without causal relationship to the therapeutic intervention), should be recorded in the eCRF by the investigator as part of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and will be reported to the appropriate regulatory authorities by the sponsor (or designee) as required.

### 7.2 Biomarkers

Samples will be collected at Baseline and Week 8. The following biomarkers will be assessed:

- Structural proteins [t-tau, NF-L, GFAP and UCH-L1]
- Inflammatory cytokines [IL-6, IL-10 and TNFα]
- Single nucleotide polymorphisms [APO-E4, BDNF, and NFkB]

Analyses will be performed by Monogram Biosciences/ LabCorp for structural proteins (t-tau, NF-L, GFAP, and UCH-L1) and inflammatory cytokines (IL-6, IL-10, and TNF-alpha).

Samples may be collected as follows:

- Blood collection by direct venipuncture is the preferred option;
- Buccal swab and collection of saliva if subject is needle phobic.

A detailed description of sample handling and processing of samples will be provided in the Study Procedures Manual.

## 7.3 BioBank

Genetics will be evaluated at a future date as a supplemental component of this study.

A blood or saliva sample for DNA and RNA isolation will be collected at baseline and a blood or saliva sample for RNA isolation will be collected at Week 8 from subjects who have consented to participate in the BioBank project. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study. Separate consent will be obtained for this sample collection.

Genetic variation may impact a subject's response to study intervention, susceptibility to, and severity and recovery from mTBI. Research will be limited to genetic, epigenetic and transcriptomic factors that will inform prognosis and aid in evaluation of clinical outcomes in mTBI. Therefore, where local regulations and IRB/IEC allow, a blood OR saliva sample will be collected for DNA and RNA analysis from consenting subjects. A blood sample is the preferred option, if agreeable to the subject.

Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for single nucleotide polymorphisms and RNA for RNAseq analyses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples will be analyzed as part of a multi-study assessment of genetic factors involved in the clinical outcomes of mTBI.

The results of genetic analyses will not be reported in the clinical study report or provided to subjects.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on mTBI continues but no longer than 5 years or other period as per local requirements.

Details on processes for collection and shipment and destruction of these samples can be found in the Study Manual.

## 7.4 Neuropsychology Testing

### 7.4.1 Post-Concussion Symptom Scale

The PCSS is a well validated 21-item self-report measure that records symptom severity using a 7-point Likert scale of severity. It ranks possible concussion symptoms by their severity to determine if a concussion has occurred, and whether further evaluation is required.

For all subjects, daily reported PCSS scores collected from ClearPlay© mobile application will be utilized to determine the resolution of symptoms.

This scale will be used to identify post-concussion symptom burden of each subject daily.

### 7.4.2 Godin Leisure Time Exercise Questionnaire

The Godin leisure-time exercise questionnaire is a well validated activity scale. It asks subjects to rate their exercise as either mild, moderate or strenuous, and will provide an indication for how each subject perceived the exercise allocated to them.

This scale will be used to identify the degree of self-reported athletic exertion of each subject weekly.

### 7.4.3 Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) enables clinicians to measure the severity of anxiety in adolescents and adults. The BAI has been found to discriminate well between anxious and non-anxious diagnostic groups in a variety of clinical populations.

Subjects respond to 21 items rated on a scale from 0 to 3, each item is descriptive of subjective, somatic, or panic-related symptoms of anxiety.

This scale will be used as a predictor of anxiety-induced prolongation of PPCS.

### 7.4.4 Brief Symptom Inventory-18

The Brief Symptom Inventory (BSI)-18 is an instrument that evaluates psychological distress and psychiatric disorders in people. The test can be used for areas such as subject progress, treatment measurements, and psychological assessment.

The BSI-18 is a 53-item self-report scale that uses the 5 point Likert scale.

This scale will be used as a predictor of anxiety-induced prolongation of PPCS.

### 7.4.5 Reiss-Epstein-Gursky Anxiety Sensitivity Index

The Reiss-Epstein-Gursky Anxiety Sensitivity Index (ASI) is a 16-item scale that focuses on apprehension about the symptoms of anxiety itself.

The ASI is a good predictor of anticipatory and situational anxiety-induced prolongation of PPCS.

### 7.4.6 Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale

The Conners’ adult attention deficit hyperactivity disorder (ADHD) Rating Scale (CAARS) provides a multimodal assessment of symptoms and behaviors associated with ADHD in patients.

The CAARS is a well validated diagnostic instrument to identify ADHD, which is a predictor of PPCS.

### 7.4.7 Center for Epidemiologic Studies - Depression Scale

The Center for Epidemiologic Studies - Depression Scale (CES-D) is a brief self-report scale designed to measure self-reported symptoms associated with depression. The items of the

scale are symptoms associated with depression which have been used in previously validated longer scales.

The CES-D is a well validated diagnostic instrument to identify depression, which is a predictor of PPCS.

## 7.5 Autonomic Tests

### 7.5.1 Cold Pressor Test (Ice Bucket and ClearHeart© Testing)

The cold pressor test measures the cardiovascular response to acute cooling of the hand. The cold pressor test will be performed using 2 different tests, with a break in-between each test (refer to Section 8.1 for details of the order of assessments to achieve this).

Ice Bucket Testing: The subject will rest in the supine position for at least 3 minutes. The subject will be fitted with the Caretaker4® device which attaches to right arm and right finger and measures continuous beat to beat HR and BP. Once connected, 5 minutes of baseline data collection will occur, followed by 2 minutes data collection while the subjects' left hand will be submerged in ice water for 120 seconds (ice bucket testing), and a further 2 minutes post-ice bucket data collection.

Testing with ClearHeart©: ClearHeart© is ANSwers Neuroscience Pty Ltd commercial prototype for cold pressure testing. The subject will rest in the supine position for at least 3 minutes. The subject will be fitted with the Caretaker4® device which attaches to right arm and right finger and measures continuous beat to beat HR and BP. Once connected, 5 minutes of baseline data collection will occur, followed by 2 minutes data collection while the subjects' left hand will be placed in the hand cooling device (ClearHeart©) for 120 seconds, and a further 2 minutes ClearHeart© data collection.

### 7.5.2 Buffalo Concussion Bicycle Test

The BCBT measures the exacerbation of post-concussive symptoms during 15 minutes of graded exercise.

The subject will be fitted with the Caretaker4® device which attaches to right arm and right finger and measures continuous beat to beat HR and BP. Once connected, 5 minutes of baseline data collection will occur, during this time, the subject will record their rating of perceived exertion (RPE) on a scale of 6 to 20, and symptom severity using a 10--point visual analog scale.

Exercise will be initiated, and at each minute RPE and symptom severity will be recorded and the bike grade increased to next stage. This will be repeated every minute until termination by:

- Maximum exertion (i.e., exhaustion);
- Three-point increase in symptom severity compared to pre-test, addition of new symptom, or increase in severity resulting in difficulty continuing test;
- Rapid progression of complaints, subject appears faint or unsteady or staff determines inability to continue test safely.

On completion of the exercise, subjects will complete a 5-minute cool down (if safe to do so), during which RPE and symptom severity assessment will continue at 1-minute intervals.

## 7.6 Evaluation of Neck Range and Motion

The evaluation of neck range and motion will be performed using 2 different tests. The neurologic examination will be completed first followed by the ClearNeck© assessment.

### 7.6.1 Whiplash Test (Whiplash Testing (ClearNeck©)

The ClearNeck© is ANSwers Neuroscience Pty Ltd commercial prototype for cervico-genic proprioception measurement. The subject will be seated 40 to 50 cm from a bullseye target, and the ClearNeck© (cap with inbuilt laser) will be placed on the subject's head. During testing, the subject will direct the laser onto the target from zero angle (by looking straight ahead with eyes open), and 8 trials (4 left and 4 right) of proprioception (eyes closed, rotate head 90 degrees to the left or right, then back to starting point).

### 7.6.2 Neurologic Examination

The neurologic examination, by an allied health professional, will include performing the following neurological tests:

- Orthostatic Vital signs: Blood pressure, Heart Rate and Symptoms are measured Supine after 2 minutes rest and Standing after 1 minute rest. Test results are deemed clinically significant if they include at least one of the following AND symptomatic: (1) systolic BP drop of ≥ 20mmHg or (2) diastolic BP drop of ≥10mmHg.

- Neck and Sub-Occipital Region Exam: Evaluation of neck muscle spasm, tenderness, and range of motion, to evaluate for any signs or symptoms of whiplash

- Oculomotor/Ophthalmologic Evaluation: Evaluations of visual tracking, smooth pursuits, repetitive saccades, gaze stability, and near point of convergence (NPC) and accommodation.

- Postural Control and Motor Coordination: Evaluation of tandem gait with eyes open and closed, and tandem stance.

## 7.7 Post Study Survey

On completion of the study only, subjects will be invited to comment on study participation and provide suggestions for improvement. Subjects will also be asked to provide a summary of school or work absence during study.

# 8 STUDY SCHEDULE OF EVENTS

## 8.1 Order of Assessments

The order of assessment for each subject is dependent on their assigned subject identification numbers. Refer Table 4 for detail.

**Table 4: Order of Assessments :**

| **Subjects Assigned to ODD numbered subject identification numbers** | **Subjects Assigned to EVEN numbered subject identification numbers** |
|---|---|
| Biomarker sample collection | Biomarker sample collection |
| Ice Bucket Test | ClearHeart© |
| Neuropsychology Testing (CAARS, CES-D, BAI, ASI [Pre/Post mTBI], BSI-18 [Pre/Post mTBI]. | Neuropsychology Testing (CAARS, CES-D, BAI, ASI [Pre/Post mTBI], BSI-18 [Pre/Post mTBI]. |
| Neurologic Evaluation | Neurologic Evaluation |
| ClearNeck© | ClearNeck© |
| ClearHeart© | Ice Bucket Test |
| Buffalo Concussion Bike Test | Buffalo Concussion Bike Test |
| **Randomize subject to Exercise or Stretching Group** | |
| Dispense i-touch or i-phone with appropriate software loaded (whether randomized to graded exercise vs. passive stretching).<br>Subject to enter test PCSS and Godin score via ClearPlay App©; to ensure subject is able to use this App. | Dispense i-touch or i-phone with appropriate software loaded (whether randomized to graded exercise vs. passive stretching).<br>Subject to enter test PCSS and Godin score via ClearPlay App©; to ensure subject is able to use this App. |
| Adverse Events | Adverse Events |

Post-study survey to be completed at Day 56 only
Abbreviations: ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BESS = Balance Error Scoring System, BSI = Brief Symptom Inventory, CAARS = Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale, CES-D = Center for Epidemiologic Studies - Depression Scale, DNA = deoxyribonucleic acid, PCSS = Post-Concussion Symptom Scale, RNA = ribonucleic acid, VOMS = Vestibular-Oculomotor Screening

**Table 5: Schedule of Events**

| Study Assessments | Baseline Visit | | Therapy Period | Telephone Safety Visit | Follow-Up/ET |
|---|---|---|---|---|---|
| | Day 0 (within 3 to 14 days of concussion) | | Day 1 to Day 55 | Day 14, Day 28, Day 42 (±2 days) | Day 56 (±3 days) |
| | Screening Evaluation | Study Evaluation | | | |
| Study Assessments | | | | | |
| Informed consent | X | | | | |
| Allocate unique subject study identification | X | | | | |
| Inclusion/exclusion criteria review | X | | | | |
| Demographic data | X | | | | |
| Medical and medication history | X | | | | |
| Review of CT or MRI (if obtained) | X | | | | |
| Height and weight[a] | X | | | | X |
| Subject Completed Questionnaires | | | | | |
| Post-Concussion Symptom Scale (pre- and post-mTBI) | | X | X | | |
| Godin leisure time exercise questionnaire[b] | | X | X | | X |
| Brief Symptom Inventory (pre- and post-mTBI) | | X | | | X[f] |
| Anxiety Symptom Index (pre- and post-mTBI) | | X | | | X[f] |
| Beck Anxiety Inventory | | X | | | X |
| CAARS (Attention) | | X | | | |
| CES-D (Depression) | | X | | | |

| Study Assessments | Baseline Visit | | Therapy Period | Telephone Safety Visit | Follow-Up/ET |
|---|---|---|---|---|---|
| | Day 0 (within 3 to 14 days of concussion) | | Day 1 to Day 55 | Day 14, Day 28, Day 42 (±2 days) | Day 56 (±3 days) |
| | Screening Evaluation | Study Evaluation | | | |
| Post-study survey | | | | | X |
| Autonomic Tests | | | | | |
| Ice Bucket Testing | | X | | | X |
| ClearHeart© Testing | | X | | | X |
| Buffalo Concussion Bike Test | | X | | | X |
| Other Physical Tests | | | | | |
| ClearNeck© Testing | | X | | | X |
| Neurologic Testing | | X | | | X |
| Biomarkers/BioBank | | | | | |
| Biomarker sample collection | | X | | | X |
| DNA and RNA sample collection | | X | | | X[d] |
| Therapeutic Intervention | | | | | |
| Dispense i-touch or i-phone. | | X | | | |
| Waveband® – dispense and instruct | | X | | | |
| ClearPlay© - dispense and instruct via initial entry of PCSS and Godin data on i-touch or i-phone | | X | | | |
| Enter/Review ClearPlay© mobile application entries | | | X[e] | | |
| Return of Waveband® | | | | | X |

| Study Assessments | Baseline Visit | | Therapy Period | Telephone Safety Visit | Follow-Up/ET |
|---|---|---|---|---|---|
| | Day 0 (within 3 to 14 days of concussion) | | Day 1 to Day 55 | Day 14, Day 28, Day 42 (±2 days) | Day 56 (±3 days) |
| | Screening Evaluation | Study Evaluation | | | |
| Safety Assessments | | | | | |
| Vital signs including beat to beat BP | | X | | | X |
| Adverse event monitoring | | X | X | X | X |
| Concomitant medications | | X | X | X | X |
| Concomitant therapies | | X | X | X | X |

Abbreviations: AE = Adverse Event, ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BESS = Balance Error Scoring System, BP = blood pressure; BSI = Brief Symptom Inventory, CAARS = Conners' Adult Attention Deficit Hyperactivity Disorder Rating Scale, CES-D = Center for Epidemiologic Studies - Depression Scale, CT = DNA = deoxyribonucleic acid, , ET = early termination, MRI = magnetic resonance imaging, mTBI = mild traumatic brain injury, PCSS = Post-Concussion Symptom Scale, RNA = ribonucleic acid, VOMS = Vestibular-Oculomotor Screening

**Footnotes for Table 5**

a) Height will only be captured at the Screening Visit;
b) Godin leisure time exercise questionnaire to be administered weekly;
c) Optional consent required;
d) RNA collection only;
e) Site to monitor AEs and symptom escalation. Subjects who do not upload data for 3 consecutive days are to be contacted. Subjects who do not upload data for 5 consecutive days are to be contacted again. Subjects who do not upload for 7 consecutive days are to be withdrawn from the study for poor compliance.
f) Questionnaires to be completed at Day 56, based on subject's current condition.

# 9 STATISTICAL METHODS

## 9.1 Determination of Sample Size

The sample size for this study is 400 subjects: 200 to be randomized to graded exercise, and 200 to be randomized to passive stretching. A power calculation was conducted with the minimum difference in probability of symptom recovery of 13%. Specifically, the probability of symptom resolution of passive stretching and graded exercise groups were set to be 80% and 93%, respectively. In order to achieve power of 90% with $\alpha$=0.05, a sample of 316 subjects is required. Allowing the attrition rate of 15%, a total of 363 subjects is required. To be conservative we plan to enroll 400 subjects to appropriately power this study.

## 9.2 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) will be written after finalizing the protocol and prior to database lock. The SAP will detail the implementation of all the planned statistical analysis in accordance with the principal features stated in the protocol. Any deviations from the SAP will be presented in the final clinical study report.

In general, data will be summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum) or frequency counts and percentages, as appropriate to the type of data. Baseline will be defined as the last available, valid, non-missing assessment prior to dosing.

Only data from protocol scheduled visits/time points will be included in the summary tables. Data from unscheduled visits/time points will not be included in the summary tables but will be included in the figures and listings.

All analyses will be performed using Statistical Analysis Software 9.4 (SAS Institute, Cary, NC) and R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

## 9.3 Analysis Populations

### 9.3.1 All Subjects Population

The all subject's population will include all enrolled subjects and will be based on the randomized intervention regardless of which intervention the subject actually completed. The all subject's population will be used for all summaries of baseline and demographic data.

### 9.3.2 Safety Population

The safety population will include all randomized subjects who completed at least Day 1 of therapeutic intervention and will be based on the actual therapy received, if this differs from that to which the subject was randomized to. The safety population will be used for the summaries of all safety data.

### 9.3.3 Efficacy Population

The efficacy population will include all randomized subjects who completed, at least Day 1 of therapeutic intervention, who had PCSS data at baseline and at least 1 post-baseline assessment and will be based on the actual therapy received. The efficacy population will be

used for the summaries of all neuropsychology and autonomic data, and for the validation of ClearHeart© and ClearNeck© performance.

## 9.4 Demographic and Other Baseline Characteristics

Subject enrolment and disposition will be summarized by randomized treatment group and will include the total number of subjects randomized into the study and in each analysis population. The number of subjects prematurely discontinuing from the study, along with the reason for early discontinuation will also be summarized.

Demographic and baseline data recorded at screening and prior to dosing will be summarized, by randomized treatment group.

## 9.5 Safety Analysis

### 9.5.1 Adverse Event Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be grouped by system organ class and preferred term and summarized, by treatment group at the time of onset of the AE (ie, the therapeutic intervention most recently prior to the onset of the AE). The summary tables will present the number and percentage of total subjects and number of events, by system organ class and by preferred term.

All AE summaries will be restricted to treatment emergent AEs only. Treatment emergent AEs are defined as AEs which commence on or after the time of start of therapeutic intervention.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once for that event in the number of subjects but all occurrences of the same event will be counted in the number of events.

Separate summaries will be provided for AEs by severity and relationship to study intervention.

Serious adverse events will be summarized and listed separately.

### 9.5.2 Vital Signs Analysis

Vital signs will be summarized at each protocol scheduled time point, by treatment group at each time point. Where vital signs were captured as continual measures, mean values for that time interval will be recorded. Actual values and actual changes from baseline will be presented.

### 9.5.3 Prior and Concomitant Medication Analysis

Prior and concomitant medications will be coded using the World Health Organization Drug coding dictionary. Prior and concomitant medications will be grouped by preferred term.

Prior medications are those medications that were stopped prior to commencing the therapeutic intervention. Concomitant medications are medications that are taken at least

once after commencing the therapeutic intervention. Medications stopping on the same day as commencing therapeutic intervention will be considered as concomitant medications.

## 9.6 Efficacy Analysis

The full presentation of the analysis of efficacy data will be presented in the SAP.

For all subjects, daily reported PCSS scores collected from ClearPlay© mobile application will be utilized to determine the resolution of symptoms. The resolution of symptoms is defined as a symptom-severity score of less than each subject's pre-injury PCSS score for 3 consecutive days. To assess differences in the probability of symptom resolution between graded exercise and passive stretching during the 8 weeks of therapy, both unadjusted and adjusted logistic regression models will be used. The primary outcome of the study will be to confirm or refute the superiority of sub-threshold aerobic exercise versus passive stretching to result in resolution of symptoms following mTBI. Confounders for the adjusted models will include age, gender, anxiety at baseline, history of migraine, cardiovascular fitness, the presence or absence of neurologic findings, and site of enrollment.

The survival probability will be compared using Kaplan-Meier (log rank test) analyses between the 2 treatment arms. Cox proportional hazards regression models will be used to evaluate the differences in time to symptom resolution. Adjusted treatment effects will be estimated in Cox proportional hazards regression models, controlling for the variables listed above. To identify that our randomization strategy was effective, analysis of variance will be used to assess for group-wise differences in age, days since injury to initial visit, initial PCSS score, resting HR, and ΔHR during the BCBT and resting BP and ΔBP during the ice bucket test on Day 1. Non-parametric tests of medians will be used to compare the non-normally distributed variable duration of clinical recovery. Chi-squared tests will be used to assess group-wise differences in gender, history of concussions, and incidence of PPCS.

### 9.6.1 Biomarker Data Analysis

Biomarkers will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable.

### 9.6.2 Neuropsychology Testing Analysis

Neuropsychology testing will be assessed using the patient reported outcomes and will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable.

Results of the cold pressor test, whiplash test and BCBT will be summarized at each protocol scheduled time point by treatment group, using either summary statistics or frequency tabulations, as applicable to the type of data. Changes from baseline will also be presented where applicable.

## 9.7 Interim Analyses

There are no formal interim analyses planned for this study.

### 9.8 Handling of Missing Data

For subjects who are withdrawn from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

Subjects who are withdrawn prematurely from study intervention will be included in all analyses regardless of the duration of intervention.

There will be no imputation for missing data, unless otherwise stated.

## 10 STUDY DOCUMENTATION

### 10.1 Data Management

A comprehensive data management plan will be prepared to support the study.

### 10.2 Access to Source Documents

In compliance with local regulations and ICH GCP guidelines, it is required that the investigator and institution permit authorized representatives of the sponsor, the regulatory agency(s), and the HREC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the subject and obtain their consent to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

### 10.3 Protocol Amendments

No changes (amendments) to the protocol may be implemented without prior approval from the sponsor and the appropriate HREC, except where necessary to eliminate an immediate hazard to subjects, or when the change involves only logistical or administrative aspects of the study. If a protocol amendment requires changes to the Patient Information and Consent Form (PICF), the revised PICF, prepared by the investigator, must be approved by the HREC.

### 10.4 Protocol Deviations

If any issue relating to the safety of study subject arises which requires a deviation from the protocol, the study unit through the investigator may immediately make such a deviation. If there is a need for such a deviation the study unit must notify the sponsor and the responsible IEC of the facts and circumstance causing the deviation as soon as is reasonably practical, but in any event no later than 5 working days after the change is implemented. The nature and reasons for the protocol deviations will be recorded in the subject's eCRF.

The sponsor may not reimburse the investigator for cases in which the study procedures and evaluations are conducted such that they result in major protocol violations.

# 11 QUALITY ASSURANCE AND QUALITY CONTROL

## 11.1 Audit and Inspection

Study sites and study documentation may be subject to quality assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

## 11.2 Monitoring

Data for each subject will be recorded on a eCRF. Data collection must be completed for each subject who signs a PICF and is commences therapeutic intervention.

In accordance with the ICH GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the HREC, the sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

# 12 ETHICS

## 12.1 Human Research Ethics Committee Approval

The protocol will be submitted for approval to the appropriate HREC. Prior to initiation of the study, the investigator must provide the sponsor with a copy of the written HREC approval of the protocol and study PICF. This approval letter will identify the study PICF by date and the study protocol by protocol number, title and date. The investigators will receive all the documentation needed for submitting the present protocol to the HREC. The composition of the HREC will also be provided to the sponsor. If approval is suspended or terminated by the HREC, the investigator will notify the sponsor immediately.

It is the responsibility of the investigator to report study progress to the HREC as required or at intervals not greater than 1 year.

The investigator at the study site or his/her nominee, will be responsible for reporting any SAEs to the HREC as soon as possible, and in accordance with the guidelines of the HREC.

## 12.2 Regulatory Approval

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended

The investigator will ensure that this study is conducted in full compliance with the protocol, the Declaration of Helsinki, the ICH GCP guidelines, Therapeutic Goods Administration regulations, and all other applicable local laws and regulations. Compliance with these standards provides assurance that the rights, safety, and well-being of subjects are protected.

In agreeing to the provisions of the protocol, these responsibilities are accepted by the investigator.

### 12.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, ICH GCP guidelines, and the applicable local laws and regulatory requirements.

### 12.4 Subject Information and Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP guidelines.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the PICF. After signatures are obtained, the PICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject PICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new PICF will be approved by the HREC (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

## 13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the therapeutic intervention. It is the responsibility of the sponsor to inform the study site when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study sites in multicenter studies must not be published separately.

## 14 FINANCING AND INSURANCE

Financing of this study will be outlined in a separate agreement.

Subjects may be compensated for the costs associated with travel to and from and parking at the study site for the 2 study visits.

Insurance will be provided in conformity with the Medicines Australia Guidelines for all subjects involved in the study. The subject should not take part in any other clinical study whilst enrolled in this study. The subject should report any health injury that could have occurred as a result of the clinical study to the investigator without delay.

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# 16 APPENDICES

## 16.1 Post-Concussion Symptom Scale

## 16.2 Godin Leisure Time Exercise Questionnaire

## 16.3 Beck Anxiety Inventory

## 16.4 Brief Symptom Inventory

## 16.5 Reiss-Epstein-Gursky Anxiety Sensitivity Index

## 16.6 CAARS (Attention)

## 16.7 CES-D (Depression)

## 16.8 Post-study survey