PROTOCOL TITLE: *A Randomized Controlled Trial of Exercise Treatment for Concussion*

PROTOCOL TITLE:

Include the full protocol title.

Response: A Randomized Controlled Trial of Exercise Treatment for Concussion

PRINCIPAL INVESTIGATOR:

Name
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Telephone Number
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Response: John Leddy MD. Orthopaedics. 716-829-5501. leddy@buffalo.edu

VERSION NUMBER:

Include the version number of this protocol.

Response: 1

DATE:

Include the date of submission or revision.

Response: June 9, 2015

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Table of Contents

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

Response: To determine the efficacy of early exercise treatment in patients with concussion.

1.2 State the hypotheses to be tested.

Response: We hypothesize that sub-threshold aerobic exercise as opposed to placebo stretching will speed recovery in patients acutely after concussion.

2.0 Background

2.1 Describe the relevant prior experience and gaps in current knowledge.

Response: We are the first group in the world to use exercise safely for treatment of humans with post-concussion syndrome. There are no data on the use of exercise treatment in the acute phase of concussion recovery. We recently completed an RCT that evaluated whether it was safe to test exercise tolerance in adolescents. We found that it was perfectly safe to do so and that the heart rate achieved on the early treadmill test predicted who would recover in two weeks vs. those who would not.

2.2 Describe any relevant preliminary data.

Response:

We have published on the safety, efficacy and long-term prognosis of sub-threshold exercise treatment in patients with physiological post-concussion disorder.

In a recent study, 41 adolescents (mean age 15.8, range 14-19 years) with recent SRC (mean 5.2 days since injury, range 1-10 days) were randomly assigned to treadmill testing or not when first seen in clinic (Day 1). Participants had ImPACT testing, completed a symptom checklist, and reported symptoms daily on a dedicated website. All participants had treadmill testing on follow up (2 weeks after Day 1). Heart rate (HR) and perceived exertion (RPE) at symptom exacerbation threshold on the treadmill determined level of exercise tolerance. Linear regression analysis determined which variables predicted recovery, defined as being asymptomatic, exercise tolerant (i.e., 17 or above on the Borg RPE scale), and receiving a positive evaluation after a blinded physician assessment.

Results: On follow up, 14/19 participants randomized to treadmill and 18/22 participants randomized to no treadmill had normal exercise tolerance and were assessed as recovered by the physician. There was no significant difference in the daily symptom reports between the two

groups. Gender, age, number of prior concussions, symptom severity and ImPACT scores on Day 1 did not predict recovery at two weeks. In the Day 1 treadmill group, HR at threshold was the only variable that predicted recovery by Day 14 ($R^2 = 0.514$; p=.001). All participants whose Day 1 threshold HR exceeded 130 bpm recovered by 14 days.

Conclusions: Early systematic evaluation of exercise tolerance in adolescents with SRC did not delay recovery. The degree of exercise intolerance early after SRC strongly predicted recovery at follow up.

Significance: Exercise tolerance can safely be assessed early after SRC to establish short-term prognosis for recovery. The logical next step is to use sub-threshold exercise in those with exercise intolerance to see if it speeds recovery versus traditional therapy (rest).

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Response: We have developed a standard treadmill test that is the only functional test thus far shown to safely[1] and reliably[2] diagnose physiologic dysfunction in concussion, differentiate it from other diagnoses (e.g., cervical/vestibular injury, depression, migraines)[3], and quantify the clinical severity and exercise capacity of concussed patients.[1,2] Animal research shows that exercise is beneficial to cognitive recovery if administered three or more weeks after concussion.[4,5] We were the first group to treat human PCS patients with individualized aerobic exercise and to demonstrate that the program could safely speed recovery and restore function (sport and work).[1,3] There is evidence of altered autonomic nervous system (ANS) balance and control of cerebral blood flow (CBF) in concussion.[6] In a recent controlled study, we showed that exercise treatment restored normal local CBF regulation, as indicated by functional MRI (fMRI) activation, versus a placebo stretching intervention, in association with improved aerobic capacity and resolution of symptoms.[7] Some concussion symptoms may therefore be related to abnormal CBF regulation that is amenable to individualized aerobic exercise treatment. The traditional therapy for concussion is rest. Physical deconditoning as a result of rest reduces control of CBF[8] whereas exercise training has beneficial effects on CBF control[9] and restores ANS balance.[10] The ability to exercise to exhaustion on a treadmill test without symptom exacerbation defines physiologic recovery from concussion, which conforms to expert consensus opinion.[11] Individualized exercise treatment for concussion patients results in greater than 50% improvement versus controls and is well accepted as < 10% of subjects refuse exercise treatment.[3]

Concomitant injury to the cervical spine resembling whiplash may occur as a result of the acceleration-deceleration forces sustained in concussive trauma.[12] Structural and functional injury to the cervical spine can be

associated with prolonged symptoms such as headache, dizziness, blurred vision and vertigo.[13,14] Cognitive complaints, including poor concentration and memory deficits have also been reported following whiplash injury.[15] Symptoms such as headache, dizziness, poor memory, and vertigo may therefore result either from a brain injury, from injury to the cervical spine, or from both. Accurate and early detection of concomitant neck injury and/or vestibular/ocular abnormalities in concussed patients could allow for the appropriate direction of cervical spine and vestibular therapy, which has the potential to reduce symptoms and speed recovery.[16]

The therapeutic promise of aerobic and vestibular exercise for concussion recovery should be tested in a randomized controlled trial (RCT).

2.3 Include complete specific citations/references.

Response:

1. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clinical Journal of Sport Medicine.* 2010;20(1):21-27.
2. Leddy JJ, Baker JG, Kozlowski K, Bisson L, Willer B. Reliability of a graded exercise test for assessing recovery from concussion. *Clin J Sport Med.* 2011;21(2):89-94.
3. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. *Rehabilitation research and practice.* 2012;2012:705309.
4. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res.* 2004;1016(2):154-162.
5. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience.* 2004;125(1):129-139.
6. Leddy JJ, Kozlowski K, Fung M, Pendergast DR, Willer B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. *NeuroRehabilitation.* 2007;22(3):199-205.
7. Leddy JJ, Cox JL, Baker JG, et al. Exercise Treatment for Postconcussion Syndrome: A Pilot Study of Changes in Functional Magnetic Resonance Imaging Activation, Physiology, and Symptoms. *J Head Trauma Rehabil.* 2012.
8. Zhang R, Zuckerman JH, Pawelczyk JA, Levine BD. Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress. *J Appl Physiol.* 1997;83(6):2139-2145.
9. Alderman BL, Arent SM, Landers DM, Rogers TJ. Aerobic exercise intensity and time of stressor administration influence cardiovascular responses to psychological stress. *Psychophysiology.* 2007;44(5):759-766.
10. Kozlowski KF, Graham J, Leddy JJ, Devinney-Boymel L, Willer BS. Exercise Intolerance in Individuals With Postconcussion Syndrome. *J Athl Train.* 2013.

11. McCrory P, Meeuwisse W, Johnston K, et al. Consensus statement on Concussion in Sport 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *Clinical Journal of Sport Medicine.* 2009;19(3):185-200.
12. Barth JT, Freeman JR, Broshek DK, Varney RN. Acceleration-Deceleration Sport-Related Concussion: The Gravity of It All. *J Athl Train.* 2001;36(3):253-256.
13. Endo K, Ichimaru K, Komagata M, Yamamoto K. Cervical vertigo and dizziness after whiplash injury. *Eur Spine J.* 2006;15(6):886-890.
14. Treleaven J. Dizziness, unsteadiness, visual disturbances, and postural control: implications for the transition to chronic symptoms after a whiplash trauma. *Spine (Phila Pa 1976).* 2011;36(25 Suppl):S211-217.
15. Sturzenegger M, Radanov BP, Winter P, Simko M, Farra AD, Di Stefano G. MRI-based brain volumetry in chronic whiplash patients: no evidence for traumatic brain injury. *Acta Neurol Scand.* 2008;117(1):49-54.
16. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med.* 2013;47(5):304-307.
17. Lovell MR, Iverson GL, Collins MW, et al. Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. *Appl Neuropsychol.* 2006;13(3):166-174.
18. *ACSM's Guidelines for Exercise Testing and Prescription* 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
19. Leddy JJ, Cox JL, Baker JG, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *J Head Trauma Rehabil.* 2013;28(4):241-249.

3.0 Inclusion and Exclusion Criteria

3.1 Describe the criteria that define who will be included or excluded in your final study sample.

Response:

Inclusion Criteria:

1. Age **10-18 years.** Any race, ethnicity, or sex. Civilian or US Veteran. Concussion within 10 days of first clinic visit.
2. Symptom score >5 on the Post-Concussion Scale (PCS).[17]
3. Low risk for cardiac disease (defined as no cardiopulmonary symptoms and meet no more than one risk factor for heart disease).[18]
4. Submaximal symptom-limited threshold on the Buffalo Concussion Treadmill Test.[1]
5. Willing to exercise.
6. Medications, except for βeta-blockers, are acceptable.

Exclusion Criteria:

1. Glasgow Coma Scale (GCS) score <12 at time of injury. Justification: indicates moderate or severe TBI.
2. Lesion on CT/MRI (via review of emergency room medical records) and/or focal neurologic deficit. Justification: indicates moderate or severe TBI.
3. Inability to exercise because of orthopedic injury, significant vestibular dysfunction, visual abnormality, or increased cardiac risk. Justification: unsafe to perform treadmill test or provide exercise as treatment.
4. βeta-blocker use. Justification: affects autonomic function, reduces exercise capacity and blunts exercise heart rate, invalidating interpretation of the treadmill test.
5. Major depression. Justification: affects autonomic function, unlikely to comply with intervention.
6. Unwilling to exercise. Justification: will not be compliant with intervention or control condition.
7. Cannot understand English. Justification: cannot be compliant with intervention.

3.2 Describe how individuals will be screened for eligibility.

Response: Patients will be screened for eligibility at the UB Concussion Management Clinics in Buffalo and in Niagara Falls**.** Potential subjects will be identified after a standard clinical evaluation that consists of a thorough history and physical examination by physicians with extensive experience in concussion management. They will sign informed consent and have the opportunity to ask questions.

Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response:

Children and teenagers. Inclusion is justified since this is the population that suffers the highest incidence of sport-related concussion in the US and for whom valid and objective physiological data would improve concussion diagnosis and reduce the risk of returning these athletes to sport or cognitive activity prematurely. The risk of the study to this age

group is minimal. Safeguards in place to protect the rights and welfare of these vulnerable subjects include parental consent and assent of the child; daily recording of symptoms; regular visits with the treating physician and our clinical and research experience evaluating and treating concussed children and students on a regular basis with excellent results.

3.3 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

Response: We will exclude non-English speaking subjects because this is an unfunded study that requires fluent English to follow instructions during the treadmill test, complete the required questionnaires, and comply with the exercise intervention.

4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

Response:

Using our published data on rate of recovery with exercise treatment in concussion,[1,7] and our pilot data on rate of recovery in subjects aged 14-19 years, we calculate that **50** subjects in each treatment group (exercise or stretching) will be sufficient for the Primary Aim of time to physiologic recovery. Analyses will be on a per protocol basis. Based on our pilot work,[1,7] we estimate a potential 10% attrition rate so we will enroll **55** subjects into each category for a total of **N = 110 subjects**.

Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

4.2 Describe when, where, and how potential subjects will be recruited.

Response: Patients will be screened for eligibility at the UB Concussion Management Clinics in Buffalo and in Niagara Falls. Potential subjects

will be identified after a standard clinical evaluation that consists of a thorough history and physical examination by physicians with extensive experience in concussion management.

4.3 Describe the methods that will be used to identify potential subjects.

Response:

These concussion centers receive referrals from other doctors, emergency rooms and athletic trainers. Clinic patients satisfying inclusion criteria will be approached for participation.

Identification of potential human subjects: study physicians at each site.

Recruitment: study coordinators and research assistants at each site.

Methods of recruitment: physicians at each site will identify potential subjects and refer them to the study coordinators and research assistants for a description of the study and opportunity to ask questions. The potential subject will be screened against this projects' Inclusion and Exclusion criteria. If the subject fits these requirements, the study coordinator will explain the project and answer questions before the subject signs the consent form. Prospective subjects and, if appropriate, the parent or LAR, will have a 15 minute waiting period to consider enrollment.

4.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: Not applicable.

5.0 Multi-Site Research (Multisite/Multicenter Only)

5.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*

- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response: Not applicable

5.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response: Not applicable

6.0 Study Timelines

6.1 Describe the duration of an individual subject's participation in the study.

Response: 3-5 weeks.

6.2 Describe the duration anticipated to enroll all study subjects.

Response: 24 months

6.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Response: 6/30/17

7.0 Study Endpoints

7.1 Describe the primary and secondary study endpoints.

Response:

1. Time to concussion recovery, which is defined as reporting a normal level of symptoms; exercise tolerant (i.e., cycle or treadmill exercise to 17 or above on the Borg RPE scale without symptom exacerbation); and receiving confirmation of normal physical examination by blinded physician assessment.

2. Incidence of delayed recovery (≥30 days) between the groups.

7.2 Describe any primary or secondary safety endpoints.

Response: Symptom reports between the intervention and control groups.

8.0 Procedures Involved

8.1 Describe and explain the study design.

Response: Randomized controlled trial of sub-threshold aerobic exercise therapy versus placebo stretching in subjects in the acute phase after concussion.

8.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Response:

Visit 1: If eligible, and after consent, subjects and controls will fill out a standardized concussion symptom checklist and subjects will be tested for exercise tolerance on a treadmill on day of enrollment with pre-determined stopping criteria. Those who achieve a HR > 150 bpm will be excluded from the study since, based upon our pilot data, they are close to full recovery. Those who achieve a HR > 120 but < 160 bpm and who cannot exercise to exhaustion (defined by RPE < 17) will be randomly assigned to sub-threshold aerobic exercise or to a stretching program (keeping HR near resting levels). Those who do not achieve a HR > 120 bpm will return in one week for a repeat treadmill test (Visit 2). If they achieve HR > 120 bpm but cannot exercise to exhaustion at Visit 2 (i.e., exercise intolerant), they will be randomly assigned to sub-threshold aerobic exercise or to a stretching program (keeping HR near resting levels). This strategy is based on our pilot data showing that subjects who do not achieve HR > 120 bpm at Time 1 typically require a week of rest to achieve that level. Furthermore, subjects must be able to demonstrate some level of exercise tolerance to have a reasonable sub-threshold (80% of achieved HR) exercise treatment prescription.

Subjects randomized to aerobic exercise treatment will be given an HR monitor and a specific HR intensity to perform 30 minutes per day. They will be prompted by text/email to do their exercise at the same time each day. Subjects randomized to stretching will be given a written progressive stretching program and contacted by text/email each day to document that they have stretched for 30 minutes per day (and that they have not participated in structured aerobic exercise during the entire study). After randomization to treatment group, all subjects will be seen weekly for up to 3 weeks (Visits 3-5) to have treadmill testing and complete a cognitive activity questionnaire to determine physiological recovery.

At each study visit, participants will be administered the King-Devick (K-D) test for impairment in saccadic eye movements immediately prior to, and following, testing for exercise intolerance. Saccadic and other types of eye movements are frequently abnormal in patients following concussion, and the K-D test is a brief (2 minute) task that objectively measures subcortical pathways. Participants will be given the K-D test, while standing, before the start of exercise. Five minutes after completion of the treadmill test, the K-D test will be repeated.

All subjects will be prompted to enter their symptom data into a form on a dedicated website between 7-10 PM each evening (after that day's exercise, for those in the exercise group).

Based on our pilot work, it is extremely difficult to retain subjects once they have recovered from concussion. Therefore, the study is over for each subject at recovery (defined as at a normal symptom level and normal exercise tolerance) or at 4 weeks post randomization (Visit 5), with the assumption that the majority of subjects will have recovered by Visit 5 (which is true for >80% based upon our pilot work).

To monitor for risk, subjects will report symptoms daily to a dedicated website (with text reminders to report between 7 and 10 PM each day) and can text the RAs with any concerns. They will be instructed that there may be temporary exacerbation of symptoms on some days with aerobic or stretching exercise and to stop exercise if that occurs and simply wait until the following day to resume. We have been very successful with this approach in our clinical practice and in our published studies.[3,4,7]

8.3 Describe procedures performed to lessen the probability or magnitude of risks.

Response:

The risk of treadmill testing is minimal since two research assistants (RAs) conduct the test and we have pre-determined stopping criteria for the symptom-exacerbation threshold. The risk of sub-threshold exercise is minimal since the exercise intensity is controlled closely by the HR monitor and is one that they achieved safely at the time of the initial treadmill test. The risk of a gently progressive stretching program is minimal. Subjects with vestibular signs who are not safe for treadmill exercise will have exercise tolerance determined by stationary cycle, again with two RAs present.

8.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Response: Standard treadmill or stationary cycle to assess exercise capacity and HR monitor to wear at home during exercise treatment sessions to ensure proper exercise intensity is not exceeded.

8.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Response: Validated concussion symptom checklist and a recording form for treadmill or cycle exercise (**see attached**). Physical examination by an experienced physician using a standardized reporting form. *What data will be collected including long-term follow-up.*

Response: Heart rate, level of exercise tolerance, and concussion symptoms.

8.6 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response: Not applicable.

9.0 Data and Specimen Banking

9.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.

Response: Not applicable.

9.2 List the data to be stored or associated with each specimen.

Response: Not applicable.

9.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: Not applicable.

10.0 Data Management

10.1 Describe the data analysis plan, including any statistical procedures.

Analyses will be based on per protocol analysis. Baseline characteristics will be analyzed to assess cluster differences between aerobic and stretching groups. We will assess group-wise differences in normally distributed variables (age, total physical examination findings, total symptom severity scores on initial visit, and days to initial visit) using ANOVA. Chi-square test will be used to assess group-wise differences in sex and prior concussions. The Mann-Whitney test will be used for the main outcome measure (days to recovery). We will use Kaplan-Meier curves and multivariable Cox proportional hazards models adjusted for patient characteristics (age, sex, prior concussion, and time since injury). Mean daily symptom severity score with 95% CI for the first three weeks will be considered in linear regression models and distributional checks of residuals undertaken to determine the most appropriate model. Missing values will be calculated as the average of day-before and day-after scores. Repeated measures ANOVA will be used to assess differences in

symptom recovery time between groups. A p-value less than 0.05 will determine statistical significance and all tests will be 2-sided.

Provide a power analysis. Response: We use data from a pilot study of exercise versus stretching in concussed patients[19] and estimated 4.2 and 7.8 as the standard deviation of the days to recovery for the aerobic exercise and stretching exercise groups, respectively. We use an underlying normal distribution to simulate time to recovery data with the above standard deviations. Using a two sample two-sided t-test, we calculate an 80 percent chance to detect a clinically significant mean difference of 3.7 days in recovery time between groups with **50 subjects in each group**.

10.2

Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Response:

Identifiers: The identities of all research subjects will be held in strict confidence to the extent required by law. In accordance with the Health Insurance Portability and Accountability Act, a confidential and unique subject ID number will be used to identify each subject on source worksheet forms and in all communications. Limited personal health identifiers (date of birth and dates of study visits) will appear on research materials or entered into the central electronic database.

The subject ID log may be viewed by a site monitor to ensure adherence to procedure but will not be removed from the site or reproduced. No names or other identifying data will be used in any report or publication of this study.

Confidentiality: The Site Investigator will assure that the privacy of subjects, including identity and medical information, will be maintained at all times. All coded data will be maintained in locked file cabinets and/or on computers equipped with security programs. Review of medical records to obtain study-related data will only occur for research purposes and will be kept confidential and de-identified within the research database. Information obtained directly from research subjects through exam, interview, monitoring equipment, or worksheet will be captured as coded research data and entered into the secure electronic database.

Sharing Study Results: To protect the integrity of this research study, individual results of screening and/or study participation will not be shared with the subject or the primary care provider. If, however, there is a medical concern identified during screening or during participation that puts the subject at medical risk, the subject will be notified and asked to

contact his/her primary physician. The site study PI will speak with the primary care provider if the subject provides permission to do so. After conclusion of the study, a copy of the published results may be provided to each participant.

10.3 Describe any procedures that will be used for quality control of collected data.

Response: Data entry procedures will be standardized and evaluated for fidelity. Data validation procedures such as logic checks and duplicate entry will be developed and implemented to ensure fidelity. Procedures to de-identify data and ensure confidentiality will be written and implemented.

10.4 Describe how data and specimens will be handled study-wide:

Response: Data will be collected electronically and transferred to secure computer databases electronically. Data will be backed up on a regular basis to each University's secure backup database. Hard copies of personal data will be filed in a locked cabinet in a locked office accessible to only the principal investigator at each site. Participant's identity will be coded and will not be associated with any published results. The code numbers and identities will be kept in a locked file of the Principal Investigator. Names, phone numbers, addresses, or any other information uniquely identifying subjects will not be written on or associated with any samples. Other parties will have only a coded Patient Identification Number.

Although results from this research may be published, or otherwise disclosed to outside parties, such results will not identify subjects in any way. Study subjects will be given emergency phone numbers and email addresses to contact the RAs or PIs with any questions or issues throughout the course of the study.

10.5 What information will be included in that data or associated with the specimens?

Response: All participants will be assigned a unique identification number at enrollment. This number will include a code to indicate their sequence in the enrollment process. This unique study identification number will be used by all investigators. Data on each subject will include: age, gender, date of injury, basic demographic and health information (e.g. HR, BP, Height, Weight, Gender, Age, Race, presence of certain conditions including ocular motor performance), HR and RPE for symptom exacerbation on the treadmill, daily symptom reports, daily accounts of work and school hours, and daily reports of exercise.

10.6 Where and how data or specimens will be stored?

Response: Information obtained directly from research subjects through exam, interview, monitoring equipment, or worksheet will be captured as coded research data and entered into the secure electronic database.

10.7 How long the data or specimens will be stored?

Response: Until 5 years after study conclusion.

10.8 Who will have access to the data or specimens?

Response: The site PIs, Co-investigators and RAs.

10.9 Who is responsible for receipt or transmission of the data or specimens?

Response: Site RAs.

10.10How data and specimens will be transported?

Response: Electronically via secure email.

11.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

11.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Subjects will meet weekly with the RAs and with the study physician and will report any problems. They can also text the RA with any problems or concerns. We will review the data once 10 subjects have completed the study to assess for any potential harm. We assume that all subjects will recover from their concussion and we will monitor daily symptom reports. If any subject appears to be deteriorating (i.e. has increased symptoms for a week or more), subject will be contacted and asked to see the treating physician.

11.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: The primary safety data reviewed will be the daily symptom reports as described above. We will also review the report of each treadmill test to ensure that the test is being completed in the manner found to be safe for subjects.

11.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Daily symptom reports are recorded on a dedicated study website with password protection and during weekly visits with the study physicians.

11.4 Describe the frequency of data collection, including when safety data collection starts.

Response: Symptom collection starts Day 1 and continues daily until the end, at Visit 5.

11.5 Describe who will review the data.

Response: Study RAs, investigators and physicians.

11.6 Describe the frequency or periodicity of review of cumulative data.

Response: After every 10 subjects complete the study.

11.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: Recovery from concussion follows a fairly predictable course that includes a decrease in daily symptom scores. We will complete a cursory review of data to see if there are participants demonstrating a regular increase in symptoms and arrange to have a physician examine any subject that appears to be showing health decline.

11.8 Describe any conditions that trigger an immediate suspension of the research.

Response: Any SAE such as cardiac event or serious injury.

12.0 Withdrawal of Subjects

12.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Response: If subjects do not complete at least 75% of their daily symptom reports and/or if they do not complete at least 3 of 4 required treadmill tests.

12.2 Describe any procedures for orderly termination.

Response: We will terminate exercise prescription for any subject that shows an extended increase in symptoms over a period of one week.

12.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Response: Subjects that do not complete a daily symptom report will be contacted by text or phone call and reminded to report symptoms. When a subject has missed 25% of daily recording of symptoms or missed more than one clinic visit s/he will be informed that they are no longer in the study. They will also be informed that withdrawal from the study will not influence their access to medical care. We do not foresee a partial withdrawal situation. Once a subject has withdrawn from the study no further data collection will occur.

13.0 Risks to Subjects

13.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a

description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Response: There is a possibility of return of symptoms during exercise testing for individuals with concussion. Should this occur, the test session will be stopped immediately according to our predetermined stopping criteria (treadmill testing will be stopped once the participant reports that overall concussion symptoms have increased by ≥3 points from pre-exercise baseline on a visual analog Likert scale, or once the subject wants to stop or develops significant fatigue or breathlessness). We will not test anyone on a visit who reports a baseline Likert score ≥7 - they will be rescheduled to return on another day. In our clinical work, any exacerbation of symptoms during or after exercise testing has been temporary. During the exercise test there is a small risk of injury from falling off the treadmill, but we will not treadmill test participants if they cannot demonstrate appropriate balance. In addition, participants will perform the treadmill test under supervision of two people to minimize any risk of falling. Participants with vestibular dysfunction will perform exercise testing on a stationary bicycle. Participants may also become tired and experience muscle soreness and breathlessness common to exercising, although the exercise intensity is very low to start with and is progressed in a gradual manner. We will minimize any cardiac risk of exercise by starting at a very low exercise intensity level, by advancing exercise intensity very gradually, and by including only subjects who are at low risk for heart disease. There is no risk from a gentle progressive stretching program other than temporary muscle soreness.

We have experience performing exercise tests on hundreds of individuals, and to date, no participants in our prior studies or clinical assessments have experienced adverse cardiac effects during these tests. This includes research subjects and patients.

RAs will be trained in basic life support and an automatic external defibrillator (AED) will be in close proximity. We have a written emergency protocol in place. RAs will have the site PI's cell phone number and will call the PI on his cell phone to report any adverse consequences. The PI will be in the clinic or the building and readily available for any issues or problems during the exercise tests. If for some reason the PI cannot be in close proximity, he will assign a physician to be available for any questions or problems that may arise.

13.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Response: Not applicable.

13.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: None. Low level exercise is not harmful to a pregnant female or her fetus.

13.4 If applicable, describe risks to others who are not subjects.

Response: Not applicable.

14.0 Potential Benefits to Subjects

14.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Response:

The potential for direct benefit to the participant is that aerobic exercise may speed recovery. In addition, the procedures we have developed for the assessment of exercise tolerance serve as a biomarker for recovery and all subjects will benefit from the knowledge that they are physiologically recovered from concussion and ready to return to activity safely.

The impact that the results of the proposed research will exert on the concussion research field is to advance understanding of the physiology of concussion. If aerobic exercise speeds recovery, this would have important implications for the treatment of concussion. This could be of enormous benefit to concussion patients of all ages and circumstances.

14.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

Response: Not applicable.

15.0 Vulnerable Populations

15.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children*

(HRP-416)" to ensure that you have provided sufficient information.

- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response: Children and students.

16.0 Community-Based Participatory Research

16.1 Describe involvement of the community in the design and conduct of the research.

Response: Not applicable.

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

17.0 Sharing of Results with Subjects

17.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response: Subjects cannot be blinded to exercise test results. In addition, any information we gather that is useful will be shared with the treating physician with the permission/request of the subject. Information will be shared in the form of a medical report.

18.0 Setting

18.1 Describe the sites or locations where your research team will conduct the research.

Response: Concussion clinics and laboratories at UB (Farber Hall and Niagara Falls).

Identify where your research team will identify and recruit potential subjects.

Response: Patients meeting eligibility criteria at the UB concussion clinics will be asked if they are willing to meet with the RA regarding possible inclusion in a study of concussion outcomes.

18.2 Identify where research procedures will be performed.

Response: UB Concussion clinics at the Main Street Campus and the Niagara Falls clinic.

18.3 Describe the composition and involvement of any community advisory board.

Response: Not applicable.

18.4 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: Not applicable.

19.0 Resources Available

19.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response: The staff at the UB study sites has extensive experience with clinical studies in concussed patients. Each site has experienced and qualified researchers and research assistants, who have recruited for, enrolled and completed multiple studies on different aspects of concussion.

Describe other resources available to conduct the research: For example, as appropriate:

19.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: The UB concussion clinics see more than 100 concussion patients per year. We need to recruit approximately 50% of these subjects for purposes of the study.

19.3 Describe the time that you will devote to conducting and completing the research.

Response: we estimate that the PI and CO-I's will each devote 10% of their time to the study.

19.4 Describe your facilities.

Response: Each site has dedicated clinical space for the enrollment of patients, dedicated computers, as well as treadmills and exercise cycles required for the exercise testing.

19.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response: They will all be under the care of clinicians (physicians, psychologists, physical therapists and other health care professionals) experienced with caring for concussed patients.

19.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All RAs and staff are required to pass the CITI course. The PI and collaborating investigators will train each RA in the process of completing the treadmill test, the neuropsychological tests on computer and all data collection procedures

Prior Approvals

19.7 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response: Not applicable.

20.0 Recruitment Methods

20.1 Describe when, where, and how potential subjects will be recruited.

Response: Physicians at both UB clinics will identify potential subjects and refer them to the study coordinator and research assistants for a description of the study and opportunity to ask questions. The potential subject will be screened against this project's Inclusion and Exclusion criteria. If the subject fits these requirements, the study coordinator will explain the project and answer questions before the subject signs the consent form. Prospective subjects and, if appropriate, the parent or LAR will have a 15 minute waiting period to consider enrollment.

20.2 Describe the source of subjects.

Response: The concussion clinics receive referrals from other doctors, emergency rooms, athletic trainers and self-referrals. Clinic patients satisfying inclusion criteria will be approached for participation.

Describe the methods that will be used to identify potential subjects.

Response:

Identification of potential human subjects: study physicians at each clinic will identify potential subjects with acute concussion. Athletic trainers at schools will provide interested students information to contact our RCs.

Recruitment: study coordinators and research assistants at each site.

20.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: Not applicable.

20.4 Describe the amount and timing of any payments to subjects.

Response: Subjects will be paid $150 for their participation. $25 after the first visit, $25 after the second visit, and $100 on study completion.

Local Number of Subjects

20.5 Indicate the total number of subjects to be accrued locally.

Response: 110

20.6 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Response: 110 subjects to be screened and 100 subjects to complete the study.

21.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

21.1 Where and how data or specimens will be stored locally?

Response: Data will be collected and entered electronically in an excel data base. Data will be backed up on a regular basis to the University's secure backup server. Hard copies of personal data will be filed in a locked cabinet in a locked office accessible to only the principal investigator and Research Coordinator (Dr. Hinds). Participant's identity

will be coded and will not be associated with any published results. The code numbers and identities will be kept in a locked file accessible only by the Principal Investigator and the Research Coordinator (Dr. Hinds). Names, phone numbers, addresses, or any other information uniquely identifying subjects will not be written on or associated with any samples. Other parties will have only a coded Patient Identification Number.

21.2 How long the data or specimens will be stored locally?

Response: Until 5 years after the study is over.

21.3 Who will have access to the data or specimens locally?

Response: The site PI, Co-investigators and RAs.

21.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response: The site PI, Co-investigators and RAs.

21.5 How data and specimens will be transported locally?

Response: On password protected computers.

22.0 Provisions to Protect the Privacy Interests of Subjects

22.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response: Subjects will only interact with the study physicians, co-investigators and RAs.

22.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response: Subjects will only be asked questions that they would normally encounter in a medical visit. However, if any question or procedure appears to make a subject uncomfortable the subject will be instructed that participation in the research is entirely voluntary and they may withdraw at any time without consequences.

22.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response: Information about subjects will be obtained via subject report, behavioral observation and the medical record.

23.0 Compensation for Research-Related Injury

23.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response: Not applicable.

23.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response: Not applicable.

24.0 Economic Burden to Subjects

24.1 Describe any costs that subjects may be responsible for because of participation in the research.

Response: None

25.0 Consent Process

25.1 Indicate whether you will be obtaining consent

Response: assent and parental permission will be obtained by the RA for participants 13 years or older but not yet 18 years of age.

Describe where the consent process take place

Response: In a room adjacent to the concussion clinic.

25.2 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response: prospective subjects and, if appropriate, the parent or LAR will have a 15 minute waiting period to consider enrollment.

25.3 Describe any process to ensure ongoing consent.

Response: This is a short term study. Not applicable.

25.4 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: We will follow "SOP: Informed Consent Process for Research (HRP-090)".

Non-English Speaking Subjects

25.5 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: Not applicable.

25.6 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Response: Not applicable.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

25.7 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: Not applicable.

25.8 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: Not applicable.

Subjects who are not yet adults (infants, children, teenagers)

25.9 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response: consent may only be obtained from biologic or adoptive parents or an individual legally authorized to consent on behalf of the child to general medical care.

25.10For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: legal counsel or authority will review our protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

25.11Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: Since the research presents only minimal risk to children, we will obtain parental consent from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

25.12Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response: any legal guardian or parent can consent on behalf of a child.

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response: assent will be obtained from all children.

25.13When assent of children is obtained describe whether and how it will be documented.

Response: it will be obtained at the time of identification as a potential subject in the presence of one of the child's parents. The child will sign an assent form. Prospective subjects and, if appropriate, the parent or LAR will have a 15 minute waiting period to consider enrollment.

Cognitively Impaired Adults

25.14Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response: Not applicable.

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

25.15List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

Response: Not applicable.

25.16For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: Not applicable.

25.17Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: assent and parental permission will be obtained by the RA for participants older than 12 but not yet 18 years of age. Consent will be obtained from those who are 18 or older.

25.18For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: Not applicable.

26.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

26.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response: We will be following "SOP: Written Documentation of Consent (HRP-091)."

27.0 Drugs or Devices

27.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: Not applicable.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

27.2 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: Not applicable.

27.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

1147 Response: Not applicable.

Data Analysis

Analyses were based on per protocol analysis. Baseline characteristics were analyzed to assess cluster differences between aerobic and stretching groups. We assessed group-wise differences in normally distributed variables (age, total physical examination findings, total symptom severity scores on initial visit, and days to initial visit) using ANOVA. Chi-square test was used to assess group-wise differences in sex and prior concussions. The Mann-Whitney test was used for the main outcome measure (days to recovery), which was not normally distributed. This outcome was demonstrated by Kaplan-Meier curves and assessed using multivariable Cox proportional hazards models, which were adjusted for patient characteristics (age, sex, prior concussion, and time since injury) based on prior literature.[34] Mean daily symptom severity score with 95% CI for the first three weeks was considered in linear regression models and distributional checks of residuals were undertaken to determine the most appropriate model. Missing values were calculated as the average of day-before and day-after scores. A repeated measures ANOVA was used to assess differences in symptom recovery time between groups. A p-value less than 0.05 determined statistical significance and all tests were 2-sided. Statistical analyses were performed using STATA version 14 (College Station, Texas).