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How do the neck muscles influence head acceleration during sport-associated impact events in high school athletes?

Principal Investigator: James T. Eckner, M.D., M.S.

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Principal Investigator: James T. Eckner, M.D., M.S.

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.2, 2.3.2, 4.1, 4.2, 4.3, 6.1.1, 6.1.2, 6.2, 9.2, 9.4.5	Low-Volume exercise group removed from protocol.	Reduce enrollment following COVID pandemic.
1.3	Clarification to criteria defining protocol deviation - updating number of days that create a deviation.	Reducing documentation burden associated with schedule deviations
2.3.1, 2.3.3, 5.2	Removal or MRI contraindication as exclusion criteria.	Low enrollment number. MRI data is not used for primary outcome. Removing this criterion may increase the number of eligible participants.

Table of Contents

STATEMENT OF COMPLIANCE

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Investigators and clinical trial site staff responsible for study conduct, management, or oversight will complete Human Subjects Protection training in best practices for research.

1 PROTOCOL SUMMARY

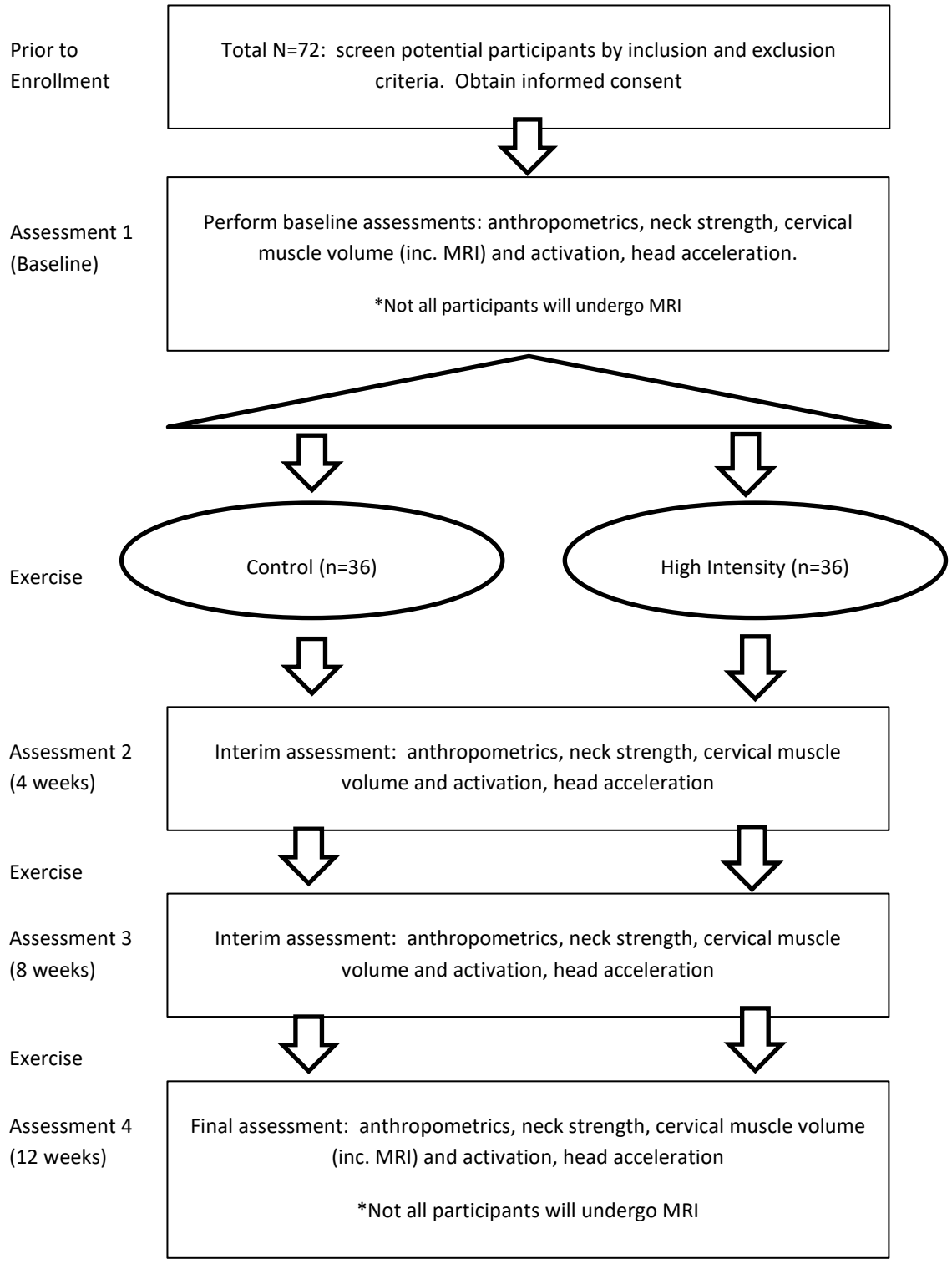
1.1 SYNOPSIS

Title:	How do the neck muscles influence head acceleration during sport-associated impact events in high school athletes?
Study Description:	Sport-related concussion is a common injury associated with significant short- and long-term disability in high school athletes. This project will study up to 72 healthy male and female soccer athletes to determine how neck strengthening exercise affects head acceleration during sport-associated impacts (AIM 1) and define the mechanism relating neck strength and neck muscle volume to head acceleration under different impact conditions (AIM 2). The long term goal of this project is to optimize neck strengthening exercise programs to decrease the risk of concussion in high school athletes.
Objectives:	Primary Objective (AIM 1): To determine the effect of manual resistance neck strengthening exercise on net head acceleration during simulated sport-associated impacts to the head (direct loading condition). Secondary Objective (AIM 1): To determine the effect of manual resistance neck strengthening exercise on net head acceleration during simulated sport-associated impacts to the body (indirect loading condition). Exploratory Objective (AIM 1): To determine the effect of manual resistance neck strengthening exercise over time on neck strength, cervical muscle volume, neuromuscular recruitment, and net head acceleration under direct and indirect loading as well as during voluntary soccer heading. Exploratory Objective (AIM 2): To determine the relative influences of baseline neck strength and cervical muscle volume on net head acceleration during simulated sport-associated impacts to the head and body with and without volitional, anticipatory cervical muscle pre-contraction to brace for the impact.

Endpoints:	Primary Endpoint: Mean area under the net head acceleration vs. time curve during direct loading, with anticipatory bracing, at Assessment Time Point 4. Secondary Endpoint: Mean area under the net head acceleration vs. time curve during indirect loading, with anticipatory bracing, at Assessment Time Point 4.
Study Population:	Up to 72 male and female high school soccer athletes in and around Ann Arbor Michigan.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	University of Michigan.
Description of Study Intervention:	Neck strengthening resistance exercise.
Study Duration:	Approximately 60 months.
Participant Duration:	Approximately 4 months.

1.2 SCHEMA

Refer to **Section 1.3, Schedule of Activities**, for additional detail.



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Initial Phone Screening Day -90 to -2	In-person screening/Intake Day -30 to -1	Baseline Assessment (#1) Day 1	Baseline MRI Day 1 +/- 10 days	Exercise (2x/week) Weeks 1-4	Interim Assessment (#2) 28 +/- 10 days from #1	Exercise (2x/week) Weeks 5-8	Interim Assessment (#3) 28 +/- 10 days from #2	Exercise (2x/week) Weeks 9-12	Final Assessment (#4) 28 +/- 10 days from #3	Final MRI 28 +/- 10 days from #3
Eligibility review	X	X									
Demographics	X	X									
Medical and sport history	X	X									
Screening physical examination		X									
Informed consent		X									
Anthropometric assessment			X			X		X		X	
Randomized group allocation			X								
Neck strength			X			X		X		X	
Cervical Muscle ultrasound			X			X		X		X	
Neck MRI				X							X
Cervical muscle activation			X			X		X		X	
Net head acceleration			X			X		X		X	
Exercise (2x/week) with strength coach					X		X		X		
Adverse event monitoring			X	X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Neck strengthening exercise represents a simple and practical intervention to reduce the risk of sport-related concussion (SRC) in the millions of student-athletes who play a high school sport in the US each year. Athletes whose necks are less able to attenuate forces acting on their heads during an impact will experience greater head acceleration and therefore be at higher risk for sustaining SRC. In fact, the only study to directly assess the neck's influence on concussion risk was a prospective epidemiological investigation demonstrating that for every one-pound increase in neck strength there was a 5% reduction in the odds of sustaining SRC.[12] However, neck strengthening exercise remains under-utilized in the high school athlete population, and there is a gap in our understanding of how the neck influences an athlete's head acceleration under different impact conditions, as well as how these relationships may be modified by exercise. There is a critical need to define these relationships and to develop optimal neck strengthening exercise protocols for high school athletes to reduce their risk of SRC.

This work is expected to have a positive translational impact in the field because *evidence-based prescription of neck strengthening exercise represents a significant advancement over the existing status quo*, which ranges from an uninformed "shooting in the dark" approach to neck strengthening exercise prescription to no neck strengthening exercise at all. Based on our own pilot results and published epidemiological work, we estimate that neck strengthening exercise may have the *potential to prevent as many as 47,000 cases of SRC* in high school athletes annually. While this work will focus on high school soccer athletes, it will have translational potential to inform SRC prevention efforts in broader athlete populations, including youth and collegiate athletes, as well as athletes who participate in sports other than soccer.

2.2 BACKGROUND

Clinical and Societal Significance
Sport and recreation-related concussion (SRC) is a common injury estimated to affect as many as 3.8 million Americans each year, and is now recognized as a major public health concern in the U.S.[45, 50] In the short-term, SRC causes a constellation of physical, cognitive, affective, and sleep-related signs and symptoms limiting an athlete's ability to participate in academic, vocational, and recreational pursuits for a period of days to months. A history of SRC increases an athlete's risk for sustaining subsequent concussions in the short term,[88] as well as for developing depression,[30] dementia,[29] and neurodegenerative diseases including chronic traumatic encephalopathy later in life.[52] Given the myriad of negative short- and long-term consequences of SRC, developing injury prevention strategies is critically important.

The ~7.8 million student-athletes who participate in organized sports at the high school level each year represent the single largest population of athletes at risk for sustaining SRC.[58] In fact, we recently reported in *JAMA* more than one out of every 5 U.S. high school students who participate in contact and semi-contact sports has sustained at least one prior concussion.[82] Further, concussions represent approximately 13% of all athletic injuries in this population.[48] High school-aged and younger athletes whose brains have yet to fully develop are also thought to have a greater physiological susceptibility to concussion than adults.[38]

Overall Scientific Premise
This proposal is built upon the overall scientific premise that concussion occurs as a result of rapid head acceleration following external force application. An early explanation of the positive association between head acceleration and the risk of brain injury was provided by the Wayne State Tolerance Curve (WSTC), which demonstrated that injury risk increased with greater magnitudes and durations of linear head acceleration.[28] Weaknesses of the WSTC include its failure to account for angular acceleration and its focus on more severe brain injury rather than SRC. More recently, our group and others have performed field-based concussion biomechanics research using a helmet-based head impact sensor [Head Impact Telemetry (HIT) System] further supporting the relationship between head acceleration and the associated risk of SRC.[5, 7, 18, 23, 68] We have recently published two reviews summarizing that body of work,[4, 6] which now includes over 40 peer-reviewed scientific publications. The HIT System provides the best *in vivo* biomechanical head impact data available today,[1, 15, 65] but is limited by measurement error associated with imperfect coupling of the in-helmet sensors to the head.[40] Furthermore, most studies using the HIT System have given relatively little consideration to impact durations. Field-based biomechanics research provides an unparalleled ability to collect head acceleration data *in vivo*, but has failed to demonstrate a simple linear or angular acceleration threshold able to reliably discriminate between concussive and non-concussive head impacts.[31, 56] Nonetheless, *it is clear the risk of concussion associated with a given impact increases with increasing linear and angular head acceleration magnitudes and durations*.[66]

Head acceleration causes concussion by inducing brain tissue deformation that leads to microstructural and physiological injury.[53] Since greater head acceleration magnitudes and durations both increase brain tissue deformation, *this provides a mechanistic explanation for the observed relationship between head acceleration and concussion*.

Scientific Premise for AIM 1: *AIM 1 is based on the scientific premise that attributes of an athlete's cervical muscles (i.e., neck strength, cervical muscle volume and neuromuscular recruitment patterns) influence their risk of SRC for a given impact by modifying the resultant acceleration of their head. Therefore, neck strengthening exercise has the potential to mitigate head acceleration during sport-associated impacts to reduce an athlete's SRC risk.* The strongest evidence that the neck can influence an athlete's risk of SRC comes from a large epidemiological study involving 6,704 high school male and female soccer, basketball, and lacrosse athletes.[12] In that study there was a *5% decrease in*

odds of SRC for every one-pound increase in neck strength. However, that study did not address the mechanism relating neck strength to concussion risk so it cannot directly inform the development of neck strengthening exercise programs. In contrast with that epidemiological evidence, two *in vivo* studies using the HIT System to measure head acceleration magnitudes as a proxy measure for concussion risk failed to support the hypothesis that having a larger, stronger neck is associated with lower head accelerations in American football and ice hockey athletes in the field.[55, 67] While these field-based studies share strong ecological validity, a major weakness of both studies was their lack of experimental control. Because impact conditions were not monitored, factors known to influence head acceleration, such as impact anticipation and bracing,[34, 54] may have confounded any underlying association between cervical muscle attributes and head acceleration.

Taking advantage of the greater experimental control achieved in a laboratory environment, we have previously reported on the influence of neck strength and circumference on head accelerations in response to standardized test loads.[22] In 46 male and female contact sport athletes exposed to standardized loads in each plane of motion, we found greater neck strength and circumference were both significantly associated (r= .42 to r= .76) with lower head acceleration, quantified in that study as the changes in linear and angular velocity (ΔV in m/s and Δω in °/s) to account for both acceleration magnitude and duration given their mathematical equivalence to the areas under the linear and angular acceleration curves. Other groups have used similar laboratory-based methodologies to administer sagittal-plane standardized test loads to subjects' heads in pursuit of complementary study aims with similar results.[63, 70, 75] Such experimental designs allow researchers to safely and precisely apply standardized test loads directly to the head, while measuring resultant linear and angular head accelerations with a high degree of accuracy. However, with this standardization, precision, and control comes the loss of ecological validity as such testing paradigms do not closely mimic the circumstances athletes experience during live sport participation. One approach to improving ecological validity while maintaining a high degree of experimental control is to study simulated sport-specific events in a lab environment. Several studies have adopted this approach to either directly or indirectly assess relationships between various cervical attributes and head acceleration during lab-based soccer heading tasks, typically reporting significant associations between greater neck strength and/or circumference and lower head acceleration.[3, 9, 32, 74] However, no study has investigated the effect of a neck strengthening intervention on head acceleration using a soccer heading model.

The strongest direct support for the premise that neck strengthening exercise will decrease head acceleration during sport-associated impacts comes from our own group's pilot data collected in 17 male and female youth and high school athletes.[19] In our pilot study, 13 participants assigned to a supervised 8-week manual resistance neck strengthening exercise program had greater increases in neck strength than 4 participants assigned to a control resistance exercise program not specifically targeting the neck. Athletes in both groups experienced decreases in head acceleration, again quantified as ΔV and Δω. Multiple other researchers have also demonstrated increases in neck strength and circumference with resistance training,[8, 13, 27, 71, 72] but only one other published study has reported the effect of neck strengthening exercise on head acceleration in response to standardized loading.[47] In that study, Mansell et al. randomly assigned 36 male and female collegiate soccer athletes to an 8-week flexion/extension-based isotonic neck strengthening exercise program or a control program not including cervical resistance exercises. The neck strengthening exercise group demonstrated increases in neck strength and circumference, but without a corresponding decrease in peak angular head acceleration during standardized loading in flexion and extension.

Unfortunately, there are limitations associated with both of those interventional studies. A limitation of our own pilot neck strengthening study[19] was its small, unbalanced sample size, which limits statistical power and the generalizability of our results. Furthermore, because we did not measure the resistance applied by the strength coach during the manual resistance exercises, we were unable to assess for evidence of dose-response relationships. The Mansell et al. study[47] was likely limited by a ceiling effect due to its inclusion of only highly-trained Division I collegiate athletes. A potential ceiling effect is supported by our own data demonstrating non-linearity in the relationship between neck strength

and head acceleration.[22] Furthermore those results may not generalize to non-collegiate populations. In addition, that exercise intervention addressed only the sagittal plane, and only sagittal-plane angular head acceleration magnitude was considered as a kinematic outcome. Finally, neither study's laboratory-based standardized test loads were representative of head impact events encountered by athletes during sport participation in the field. *There remains a knowledge gap in how neck strengthening exercise influences an athlete's head acceleration during sport-associated impacts.*

AIM 1 will directly address this knowledge gap by determining the effect of manual resistance neck strengthening exercise on net head acceleration during direct force application to the head, force application to the body with inertial force transmission to the head via a simulated checking/blocking task, and voluntary soccer heading. In designing AIM 1, we have addressed each of the limitations in the previous studies described above.

Scientific Premise for AIM 2: *AIM 2 is based on the scientific premise that anticipatory pre-contraction of the cervical muscles to brace for an impact influences head acceleration. Furthermore, cervical muscle attributes (i.e., neck strength and cervical muscle volume) influence head acceleration differently with vs. without cervical muscle pre-contraction.* This premise is supported by our own work demonstrating that head acceleration, again reported as ΔV and Δω, decreased by 12.3% and 9.7%, respectively, during anticipatory cervical muscle pre-contraction as compared to relaxed, upright sitting.[22] Recent finite element modeling work, as well as numerous other studies in the concussion and whiplash literature, have also reported decreased head acceleration in response to various forms of loading during trials with vs. without anticipation and/or cervical muscle pre-contraction.[34, 41, 44, 57, 63, 70, 75] However, the design of those studies limits the insight they can provide into which cervical muscle attribute is most responsible for controlling head acceleration with vs. without anticipatory pre-contraction. While not the primary objective, our previous work demonstrated greater neck strength and circumference were each significantly associated with lower ΔV and Δω across all directions of head motion under both anticipation conditions (r= .42 to r= .60 for neck strength; r= .60 to r= .76 for neck circumference).[22] In that study, more of the variability in head acceleration was explained by neck strength for 6 of the 7 models under the anticipated condition, but by neck circumference for 6 of the 7 models without anticipation. That finding suggests neck strength and cervical muscle volume may influence head acceleration differently depending on cervical muscle pre-contraction status. We are unaware of other reports to directly quantify the relationships between individual cervical muscle attributes and head acceleration with vs. without anticipatory cervical muscle pre-contraction.

The premise that neck strength and cervical muscle volume may exert differential influences on head acceleration during anticipated vs. unanticipated impacts is further supported when considering each potential cervical contributor to head acceleration. Previous work concluded that since the mechanical properties of the neck's non-contractile tissues (e.g., bone, ligament) are not affected by muscle activation, and because peak head acceleration is reached before either a reflexive or voluntary muscular response has had time to occur, head acceleration is primarily influenced by the mechanical properties of the cervical muscles.[70] Passive muscle stiffness is strongly influenced by the amount of muscle tissue being acted upon.[26, 85] In contrast, the stiffness of actively contracting muscle increases proportionally with muscle activation and torque.[2, 37, 84] Therefore for any volume of cervical muscle, greater neck strength (i.e., torque generation) associated with improved neuromuscular recruitment is expected to confer greater muscle stiffness during maximal anticipatory cervical muscle pre-contraction to brace for the impact. While muscle strength and volume co-vary, these characteristics are known to change independently from one another with aging,[42, 86] disuse,[11, 81] and of greater direct applicability to this proposal, following resistance training.[25] *There remains a knowledge gap in how individual cervical muscle attributes affect head acceleration during sport-associated impacts with vs. without anticipatory cervical muscle pre-contraction to brace for the impact.*

AIM 2 will directly address this knowledge gap by comparing the relative weights of neck strength and cervical muscle volume in predicting net head acceleration during anticipated and unanticipated impacts to the head and body.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with each component of the study include:

Collection of demographic and historical information: Loss of privacy and/or confidentiality is the main potential risk associated with this component of the study. This risk is considered non-serious. Likelihood: rare (< 1%).

Collection of anthropometric data: Subjects may feel embarrassed if they consider their height or weight to be outside of their self-perceived desirable range. There is also potential loss of privacy and/or confidentiality associated with anthropometric data collection. These risk are collectively considered non-serious. Likelihood: infrequent (1-10%).

Cervical muscle volume (MRI) and cross sectional area (ultrasound) assessments: There is no radiation exposure associated with either MRI or ultrasonography and there are no known adverse long term effects associated with either imaging modality. It is possible that subjects may feel uneasy while confined to the small space inside the MRI scanner. It is also possible that during sonographic assessment of the neck muscles the carotid baroreceptors could be stimulated by the transducer head resulting in a syncopal or near syncopal episode (fainting/near-fainting). These risks are considered non-serious. Likelihood: rare (< 1%). Not all subjects will undergo an MRI scan.

Neck strength assessment: Subjects may feel muscular discomfort associated with maximal isometric contraction of their cervical muscles. This risk is considered non-serious. Likelihood: infrequent (1-10%).

Assessment of the head's dynamic response to direct force application: Subjects may initially be concerned about how the direct force application loads will feel. This risk is considered non-serious. Likelihood: likely (10-25%). Subjects could potentially experience neck pain or a headache associated with this loading condition. The most likely etiology for neck pain is anticipated to be mild cervical muscle strain and the most likely etiology for headache is anticipated to be cervicogenic headache. The risk of developing neck pain or headache is considered non-serious. Likelihood: rare (< 1%). It is not expected that any more serious neck or neurological injury (concussion, radiculopathy, spinal cord injury, or vascular injury) will result from this procedure.

Assessment of the head's dynamic response during the standardized checking/blocking and voluntary soccer heading tasks: Subjects could again potentially experience neck pain or a headache associated with these loading conditions. Again, these risks are considered non-serious. Likelihood: rare (< 1%). Specific to the simulated checking/blocking task, subjects could also potentially experience musculoskeletal back, chest, or shoulder pain or "have the wind knocked out of them" due to the impacts delivered to their torsos by the punching bag. The risk of developing musculoskeletal pain or "having the wind knocked out of them" is also considered non-serious. Likelihood: rare (< 1%). It is not expected that any more serious injuries such as fracture or joint dislocation will result from these procedures. Both tasks were designed to simulate the low-end of forces experienced by an athlete while performing a soccer

header or being checked/blocked during live soccer play and are therefore felt to be less risky than their routine participation in sport and no more risk than they experience in normal, everyday recreational activities. In addition, the controlled laboratory conditions under which the headers will be performed will allow ample time to properly align the head with the ball to ensure correct heading technique. The proposed soccer heading task, which involves less than 10 headers performed with an incoming ball velocity of less than 10 m/s, represents fewer headers at a lower velocity, and with a less-inflated ball than would be expected to occur during a high school soccer practice or a physical education class activity focusing on heading skills. Furthermore, this protocol represents an overall smaller combination of repetitions and ball velocities than has been used in existing research studies involving standardized soccer headers. Similar studies in the past have included as many as 20 headers and ball velocities up to 25 m/s. The soccer heading and checking/blocking tasks were developed with input from our expert soccer advisor, Mr. Greg Ryan, the former University of Michigan Women's Varsity Soccer coach, who has extensive soccer coaching experience at the high school level is also of the opinion these controlled tasks will not pose any safety risk to high school soccer athletes, and will be no greater risk than youth members of the general population are exposed to during normal recreational activities.

Kinematic measurements: Light emitting diodes used with a high speed kinematic camera system may become hot to the touch when left to record continuously. Subjects could experience a minor superficial skin burn if a light emitting diode became too hot and was left in place, although this would be unlikely as the diodes are not affixed directly to the skin, but rather to a plastic plate surface affixed to the skin. The risk associated with this is considered non-serious. Likelihood: rare (< 1%).

Skin preparation/application of skin adhesives: Subjects may experience minor skin cuts or irritation associated with skin shaving or the adhesive backing on the surface EMG electrodes or other superficially adherent sensors. The risk associated with this is considered non-serious. Likelihood: infrequent (1-10%).

Fitting of boil-and-bite mouth guards: Subjects could receive minor burn to their hands or mouths while using boiling water to fit mouth guards to their mouth if direct contact with the boiling water occurred. The risk of burn is considered non-serious. Likelihood: rare (< 1%).

Supervised exercise sessions: Subjects are anticipated to experience delayed-onset muscle soreness following resistance training, which is a normal training-related phenomenon. The risk associated with this is considered non-serious. Likelihood: frequent (>25%). It is not expected that any serious training-related injuries will result from participation in study exercise sessions.

2.3.2 KNOWN POTENTIAL BENEFITS

Subjects allocated to both study groups may potentially benefit from the resistance training exercise program administered by the Certified Strength and Conditioning Specialist during the study. Resistance training is anticipated to improve muscle strength and endurance and has the potential to enhance subjects' athletic performance as well as to reduce their risk of sustaining sport-related injury. In addition, subjects will receive a 4-month gym membership,

permitting them unrestricted access to the gym's exercise facilities for the duration of their membership.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All study activities will be approved and monitored by the UM IRB-MED.

The PI, who is a licensed and board certified Physical Medicine and Rehabilitation physician will complete a final in-person eligibility determination for each subject. If the PI is unavailable to perform the in-person eligibility determination, then a qualified designated Co-I will complete the final in-person eligibility determination in the PI's absence. Potential subjects with any historical or physical examination findings felt by the PI, or his designee, to place them at potentially elevated risk for injury will be excluded.

Subject privacy will be protected during laboratory assessments by testing in a private environment closed to the outside in the presence of study personnel only. To ensure the confidentiality of data and personal information, all electronic data will be coded. Only the PI and appropriate study personnel will have access to the key, which will be stored on a password-protected secure computer maintained by the University of Michigan.

Prior to each laboratory testing and exercise session, subjects will complete a brief warm-up routine including static and dynamic neck stretches. All exercise sessions will be administered by a Certified Strength and Conditioning Specialist (CSCS) so the risk of sustaining any exercise-related injury is felt to be lower than that typically present during unsupervised or indirectly supervised resistance training exercise.

Additionally, the following test-specific safety measures will be employed to minimize risk to subjects during laboratory testing:

> *Neck MRI and cervical muscle cross sectional area measurements with ultrasound:* Subjects will undergo ultrasound testing while seated in a chair with bilateral armrests. The tester will be seated immediately adjacent to the subject during the assessment. In the unlikely event of a syncopal episode, the subject will be prevented from falling to minimize potential risk of injury.
>
> *Assessment of the head's dynamic response to direct force application:* During our experience using this technique, concerned subjects have been uniformly relieved after experiencing the first load applied to their head. The testing apparatus is designed to limit forced displacement of the head and the drop height of the weight is set so that no more energy is delivered to the subject's head than is necessary to generate a reliable, measurable dynamic response. In our experience using the direct force application model, measured head accelerations are approximately 10-fold less than the minimum values typically reported in the literature to cause concussion in athletes in the field.
>
> *Assessment of the head's dynamic response during the simulated checking/blocking and voluntary soccer heading tasks:* Subjects will wear a mouth guard during these tasks for dental protection. Both tasks were designed to simulate the low-end of forces experienced by an athlete while performing a soccer header or being checked/blocked during live soccer play and are therefore felt to be no more risk than their routine

participation in everyday recreational activities. In addition, the controlled laboratory conditions under which the tasks will be performed will allow ample time to properly align the head/body with the ball/punching bag to ensure correct heading/blocking technique. The proposed soccer heading task represents fewer headers of lower magnitude than would be expected to occur during a high school soccer practice or a physical education class activity focusing on heading skills. Furthermore, this protocol utilizes an overall smaller combination of repetitions and ball velocities than has been used in previous research studies involving standardized soccer headers.[3, 14, 15, 23, 30, 31, 47, 55, 62] We are not aware of any existing research using a similar checking/blocking task that can be compared to our proposed protocol, but the subjective experience of the volunteers who were involved during protocol development was that no discomfort occurred. During the simulated checking/blocking task, the distance the boxer's punching bag swings before contacting the subject's body is set sufficiently low so as not to displace the subject's feet upon contact with the minimum amount of energy delivered as necessary to generate a reliable, measurable dynamic head response. The soccer heading and checking/blocking tasks were both developed with safety input from a collegiate soccer coach with extensive experience working with high school soccer athletes.

Kinematic measurements: Kinematic recording will be paused between trials to minimize the chances of light emitting diode heating.

Fitting procedures for boil-and-bite mouth guards: While fitting the boil-and-bite mouth guards, after removing the unit from the boiling water subjects will fully submerge it in cold water before placing it in their mouths.

The risk level for all study activities is *no more than minimal* because subjects will not be performing any activities riskier than those they routinely experience in their day-to-day lives. All eligible subjects are high school athletes who are expected to routinely experience minor, and in some cases major, trauma to the head, neck, and body during sport participation, such as regular voluntary heading of a soccer ball. Routine sport participation is felt to be associated with a much greater potential for injury than the controlled experimental procedures associated with this study. In addition, participation in a resistance training exercise program under the direct supervision of a Certified Strength and Conditioning Specialist is felt to be safer than participation in an unsupervised or indirectly supervised resistance training program, as is typical for high school athletes. As such, we feel the potential benefits to subjects, as well as the potential future benefits of this work to athletes like those participating in this study, outweigh the minimal risks to subjects.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Primary Objective (AIM 1): To determine the effect of manual resistance neck strengthening exercise on net head acceleration during simulated sport-associated	Primary Endpoint: Mean area under the net head acceleration vs. time curve during direct loading, with anticipatory bracing, at Assessment Time Point 4.	Head acceleration is used as the study's lab-based proxy measure for concussion risk (greater head acceleration is associated with greater risk). Concussion is most commonly caused by direct force

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
impacts to the head (direct loading condition).		application to the head. This study seeks to determine how manual resistance neck strengthening exercise influences an athlete's head acceleration under direct loading.
Secondary		
Secondary Objective (AIM 1): To determine the effect of manual resistance neck strengthening exercise on net head acceleration during simulated sport-associated impacts to the body (indirect loading condition).	Secondary Endpoint: Mean area under the net head acceleration vs. time curve during indirect loading, with anticipatory bracing, at Assessment Time Point 4.	While a less common mechanism than direct loading to the head, concussion can also be caused by indirect transmission of forces to the head from the body. This study therefore seeks to also determine how manual resistance neck strengthening exercise influences an athlete's head acceleration under indirect loading.
Tertiary/Exploratory		
<u>Exploratory Objective 1 (AIM 1):</u> To determine the effect of manual resistance neck strengthening exercise over time on neck strength, cervical muscle volume, neuromuscular recruitment, and net head acceleration under direct and indirect loading as well as during voluntary soccer heading. <u>Exploratory Objective 2 (AIM 2):</u> To determine the effect of manual resistance neck strengthening exercise on the relative influence of neck strength vs. cervical muscle volume on net head acceleration during direct and indirect loading with and without volitional, anticipatory cervical muscle pre-contraction to brace for the impact.	<u>Exploratory AIM 1 Endpoints:</u> Neck strength (peak force/moment and rate of force/torque development); total cervical muscle volume (estimated based on sex, neck circumference, cervical ultrasound and MRI measurements); cervical muscle activation (agonist muscle activation, antagonist muscle inhibition based on surface EMG); mean area under the net head acceleration vs. time curve during direct and indirect loading, with anticipatory bracing, at Assessment Time Points 1, 2, 3; mean area under the net head acceleration vs. time curve during voluntary soccer heading at Assessment Time Points 1, 2, 3, 4. <u>Exploratory AIM 2 Endpoints:</u> Mean area under the net head acceleration vs. time curve	Resistance training is known to increase muscle strength through more efficient neuromuscular recruitment (i.e., muscle activation patterns) before muscle hypertrophy (i.e., increase in muscle size) occurs. This study seeks to understand the effect of resistance exercise on neck strength, as well as cervical muscle volume and activation patterns. This study also seeks to determine the relative influence of neck strength vs. cervical muscle volume on head acceleration during impacts to the head and body that are anticipated (i.e., with bracing) vs. unanticipated (i.e., without bracing), and will explore whether the relative influence of neck strength vs. cervical muscle volume on head acceleration is influenced by manual resistance neck

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	during direct and indirect loading, without anticipatory bracing, at Assessment Time Points 1, 2, 3, 4.	strengthening exercise. In addition to the direct and indirect loading conditions, which are both passive (i.e., force application is not initiated by the subject), voluntary soccer heading is also included as an exploratory loading condition representing a more active sport-associated impact scenario.

4 STUDY DESIGN

4.1 OVERALL DESIGN

In this single-site randomized clinical trial, 72 high school soccer athletes will complete a series of 4 laboratory assessment sessions before, during, and after a 12-week resistance training program including either high intensity neck strengthening exercises or control exercises not targeting the neck. During each laboratory assessment, measurements will be performed to assess key cervical muscle attributes, as well as the head's net acceleration under multiple loading conditions designed to reflect the range of impact scenarios encountered by athletes during sport participation. The primary loading conditions will be direct force application to the head using the customized loading apparatus designed by our group for our previous research[19, 22] and a standardized checking/blocking task involving impacts to the body with inertial force transmission to the head. In addition, a voluntary soccer heading task will be used as an exploratory loading condition.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The control exercise group will perform only "shoulders-down" resistance exercises not directly targeting the neck so that the effects of the high intensity neck exercise program can be distinguished from changes associated with normal age-related growth and development or generalized effects of resistance training not specifically targeting the neck.

4.3 JUSTIFICATION FOR DOSE

All subjects will exercise 2 days per week under the direct supervision of a study-assigned strength coach (National Strength and Conditioning Association Certified Strength and Conditioning Specialist, CSCS, certification), with a minimum of 1 day of rest between exercise sessions. Subjects will be assigned either to a high intensity neck strengthening exercise group or to a control exercise group performing only "shoulders-down" resistance exercises not directly targeting the neck. All exercises will be performed in accordance with National Strength and Conditioning Association standards.[76] The neck strengthening program will include manual resistance exercises in sagittal-plane flexion and extension, coronal-plane lateral flexion to the left and right, and axial-plane rotation to the left and right, as well as dumbbell shoulder shrugs as previously described by our group.[19] For each group, the exercise program

will progress in volume and intensity over the duration of the study, to accommodate muscular fitness adaptation. Such progression is considered vital to the long-term efficacy of resistance exercise programming.

The volume load of neck strengthening exercise will be calculated using a modified protocol previously employed by our group for the elbow flexors.[61] For shoulder shrugs the volume load for each exercise session will be defined as the product of the dumbbell weight x the force of gravity (g= 9.8 m/s2) x the number of repetitions performed during the exercise session, to yield a volume load for the exercise session in N. During manual resistance exercise, the strength coach will hold a hand-held dynamometer against the subject's head to measure and record the force applied during manual resistance. For both dumbbell shrugs and manual resistance exercises, the total cumulative exercise volume load will be defined as the sum of the individual session volume loads over all exercise sessions completed by the subject. Since subjects assigned to the control group will not perform neck strengthening exercise, their exercise volume load will remain zero throughout the study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the final lab assessment (#4) and final MRI, as shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form, or assent form with parental consent for minors
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 13-19
4. Participated in a soccer team, club, or other soccer program/organization within the preceding 2 years
5. Be willing to adhere to the assigned exercise regimen

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria on self/parental-report or screening examination, as appropriate, will be excluded from participation in this study:

1. Prior history of trauma-induced neck injury of sufficient severity to require treatment by a medical provider within 30 days of injury or to limit sport participation for > 1 day (note: having received

routine chiropractic treatment in the absence of a recent traumatic injury to the neck will not be considered to meet this criterion)
2. Any prior history of whiplash injury, stinger/burner, or cervical radiculopathy diagnosed by a medical provider
3. Any prior history of bone, disk, neural, or ligamentous abnormality identified on cervical spine medical imaging performed for any reason that is felt by the PI (or designee) to present a risk to study participation
4. Any prior history of surgery involving the cervical spine (note: having undergone non-spine surgery to the soft tissue structures in the neck will not necessarily exclude participation, but will be considered on a case-by-case basis by the PI, or his designee, with consultation from the performing surgeon when deemed appropriate)
5. Self-report of moderate or severe neck pain (rated as 5 or greater on a 10-point pain scale) lasting > 1 day in the previous 6 months that required treatment by a medical provider or that limited sport participation for > 1 day (note: having received routine chiropractic treatment in the absence of moderate-severe neck pain will not be considered to meet this criterion)
6. Self-report of low back pain (any severity) associated with morning stiffness occurring 30 days or more in the previous 3 months
7. Prior episode(s) of unexplained upper extremity numbness, tingling, or weakness suspicious to the PI, or designee, for a stinger/burner or cervical radiculopathy
8. Prior history of concussion in the previous 6 months diagnosed by a medical provider or suspected by the subject, or the parent/guardian of a minor (if no medical evaluation was sought)
9. Personal history of migraine headaches within the previous 3 years diagnosed by a medical provider
10. Personal history of anxiety disorder diagnosed by a medical provider
11. Parental/guardian history of anxiety disorder diagnosed by a medical provider
12. Prior personal or parental history of the following medical conditions known to be associated with atlanto-axial instability diagnosed by a medical provider: rheumatoid arthritis or other systemic inflammatory disease with joint involvement, Down Syndrome, mucopolysaccharoidosis, Ehlers-Danlos Syndrome, Marfan Syndrome
13. Known exposure to or infection with head lice in the previous 30 days
14. Serious allergic reaction to nickel/metal jewelry
15. Known or suspected pregnancy (for females)

16. Presence of significant abnormality on a standardized screening neurological and musculoskeletal physical examination performed by the PI, or designee, including: pain with palpation or active range of motion of the cervical spine, abnormal active range of motion of the cervical spine, positive Spurling test, upper motor neuron signs (spasticity, hyper-reflexia (grade 4+), Hoffman sign, >2 beats of ankle clonus, Babinski sign/up-going toes), upper extremity reflex asymmetry, marfanoid body habitus (all of the following: arm span to height ratio > 1.05, hand length to height ratio > 0.11, foot length to height ratio > 0.15, upper body segment to lower body segment ratio < 0.89), or hypermobile joints (Beighton score > 4) or abnormal Schober test (< 5cm difference between standing and full forward flexion).
17. Prior participation in a resistance exercise training program including exercises specifically intended to target the neck muscles within 3 months of enrollment, or intention to begin participating in such an exercise program outside of the study protocol during the upcoming 12-week study period
18. Unable to speak and understand English.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who do not meet the study inclusion/exclusion criteria as determined during the initial phone screening assessment or initial in-person screening evaluation. A minimal set of screen failure information will be retained to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a time sensitive factor (e.g., diagnosed concussion within the past 6 months) may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

High school-aged soccer athletes will be recruited primarily through the athletics programs at local high schools, following local approval at each individual institution. Coaches, managers, athletic trainers, or other team/athletics personnel will be asked to post and/or distribute paper and/or electronic recruitment materials to those athletes who are members of the school's soccer teams. In addition, we will also recruit through other non-school-based local soccer clubs, camps, and programs in a similar manner, including recruitment through local soccer and/or fitness facilities. Lastly, we will advertise on the Michigan Institute of Clinical Health Research (MICHR) UM Health Research website (https://umhealthresearch.org), in UMHS clinics, and through public advertisements and outreach as necessary. UM Health Research is a secure registry database that matches people to clinical research studies, and is supported by the Michigan Institute for Clinical and Health Research.

Interested individuals (and/or their parents/guardians if minors) will complete an initial self-reported screening evaluation (either electronically with phone review or during a single phone session, per individual preference and availability) with a member of the study to assess study inclusion and exclusion criteria and to describe the details of the study. Those who pass the initial screening assessment and are interested in participating after hearing full study details will be scheduled for a final in-person eligibility assessment by the PI, or his designee, which will include a targeted screening physical examination.

Potential subjects passing both components of the screening assessment will then be invited to enroll in the study and those wishing to do so will complete the informed consent process (assent for minors with accompanying parent/guardian consent). All subjects will provide written informed consent using UM IRB-MED approved informed consent documents with a qualified member of the study team. Minor children under the age of 18 will provide written assent and a parent/guardian will provide written consent. During the in-person consent process the consenting study team member will review the entire informed consent document with the subject (and parent/guardian when applicable), including all potential risks associated with the study and will provide an opportunity to ask any questions they may have.

To promote study recruitment and retention, subjects will be compensated for their participation in this study. Compensation will be incrementally disbursed upon successful completion of each of the four laboratory testing sessions, with greater amounts provided for each successive testing session to incentivize full study completion. Subjects will also receive a 4-month membership at a local fitness facility as well as paid parking during study-associated appointments through the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is participation in a supervised exercise program. Participants will perform two exercise sessions per week, with at least one day between sessions. All participants will perform a standardized set of general resistance exercises targeting the chest, shoulders, back, upper and lower extremities, and core. In addition, those participants allocated to the high intensity neck strengthening group will also perform manual resistance exercises in sagittal plane flexion and extension, coronal plane lateral flexion in both directions, and axial plane rotation in both directions, as well as dumbbell shoulder shrugs.

6.1.2 INTERVENTION ADMINISTRATION

The supervised exercise program will be administered by a Certified Strength and Conditioning Specialist. Manual resistance exercises will be performed lying horizontally on a standard weight lifting bench using a similar protocol as previously described by our group.[19] For each repetition, the CSCS will apply steady manual resistance through the both the concentric and eccentric phases of cervical range of motion. Shoulder shrugs will be performed at a tempo allowing for steady controlled movement to be maintained throughout the concentric and eccentric phases with a brief pause at the top of the shrug motion using the maximum load comfortably completed by each participant for the target number of repetitions while maintaining correct form. The high intensity neck strengthening exercise program will increase in volume and intensity over the study duration to accommodate muscular fitness adaptation. All exercises were performed in accordance with National Strength and Conditioning Association standards.[76]

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized using a centralized electronic randomization tool with equal allocation to the control and high-intensity neck strengthening groups. Balanced block randomization will be used to ensure equal sex and age category balance between the groups. Age category will correspond to high school under-class (i.e., age 13.0 - 16.49 years at the time of randomization) vs. upper-class (i.e., age 16.50 – 19.99 years) status given the typical maturation occurring in adolescents through the high school years. Subjects will be considered enrolled in the trial upon randomization and available data will be included in the intention to treat analysis. The Study Statistician, Strength Coach, Study Coordinator, and PI (or his Co-I designee when necessary to make a determination of AE relatedness to the study) will not be blinded to subject group allocation. Other members of the study team, including those responsible for performing the laboratory- and radiology-based assessment will be blinded to group allocation status. Subjects will not be informed of their group allocation status, although they will be aware of whether or not they are performing neck strengthening exercises during their exercise sessions. Subjects will be instructed not to discuss whether they are performing neck strengthening exercises with study team members during either laboratory- or radiology-based assessment sessions.

6.3 STUDY INTERVENTION COMPLIANCE

Subjects will be given the opportunity to make-up any missed exercise sessions within 7 days of the originally scheduled date, so long as at least one day of rest is scheduled between successive exercise sessions. Subjects will be considered to have successfully completed the exercise protocol if at least 20 of the 24 exercise sessions are attended, with no more than 2 missed sessions during any 4-week block.

6.4 CONCOMITANT THERAPY

Participation in a resistance training exercise program including exercises specifically intended to target the neck muscles either in the 3 months prior to study enrollment or a plan to begin participating in such an exercise program outside of the study protocol at any point during the 12-week study period are criteria for exclusion.

6.4.1 RESCUE MEDICINE

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the exercise intervention does not necessarily mandate immediate discontinuation from the study. If a subject is unable to continue participating in their assigned exercise intervention due to injury, illness, or other reason, they will still be eligible to complete all or part of the next scheduled study assessment(s) so long as they are able to do so within 7 days of discontinuation of the intervention, they have completed at least 4 exercise sessions since their last assessment was performed, and they remain able to participate in the upcoming lab-based (and MRI, as applicable) assessment. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the PI or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Date and reason for study intervention discontinuation
- Eligibility for and ability to perform upcoming study assessments

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy, unless written clearance to continue study participation is provided by the treating obstetrician or other physician managing the pregnancy
- Significant study intervention non-compliance

- If any clinical adverse event (AE) or other medical condition or situation occurs that precludes the subject's ability to participate in the study or such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to participate in study exercise program for 14 or more consecutive days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who are randomized and drop out subsequently will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 4 scheduled visits or more than 14 days and is unable to be contacted by the study team.

The following actions must be taken if a participant fails to return for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, multiple telephone calls, emails, and/or text messages, and, a certified letter or equivalent may be sent to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Methodology for measuring kinematic outcome: Net head acceleration will be measured under direct force application, as well as standardized checking/blocking and voluntary soccer heading tasks at 4 time points (see Section 1.3). Our rationale for including loading conditions involving direct force application to the head as well as force application to the body with resultant transmission of inertial forces to the head (the simulated checking/ blocking task) is that concussions can, by definition, occur as a result of both of these mechanisms.[51] Voluntary soccer heading is being used as a second, more ecologically-valid direct loading condition. The order of testing will be randomized across subjects and practice trials will be performed for each task prior to data collection to familiarize subjects with each procedure.

Loading conditions:
Standardized direct force application to the head in forced flexion, extension, lateral flexion, and axial rotation. We will use a customized laboratory testing apparatus to deliver controlled forces to the head via headgear connected to cable with in-line weight-drop, similar to as previously described by our group.[19, 22] The results of three trials will be averaged, in each direction during active isometric neck muscle pre-contraction (as if bracing in anticipation of being struck in the head during live play) as well as during relaxed upright sitting (to simulate an unanticipated blind-side impact)

conditions.[19, 22] An effort will be made to prevent subjects' knowledge of the precise timing of force application during the unanticipated condition using strategies such as wearing blinders and being exposed to ambient white noise. sEMG will be used as biofeedback to ensure appropriate neck muscle activation under both conditions, in a similar manner as in our previous pilot study.[19]

Standardized impacts to the body will be applied in the coronal plane by swinging a boxer's heavy punching bag suspended from the ceiling like a pendulum into the subject's lateral shoulder to simulate a sport checking or blocking event. Subjects will stand on a force plate in an athletic ready position so that the punching bag surface lightly touches the lateral aspect of their shoulder while hanging at rest. The punching bag will be drawn back in a standardized manner and released to elicit lateral flexion of the head and neck in the coronal plane upon impact to the shoulder (monitoring to ensure they are not displaced from the force plate). The results of three trials will be averaged during active pre-contraction of the neck and torso muscles (as if bracing in anticipation of being checked or blocked by an opponent during live play) as well as a relaxed upright standing (to simulate an unanticipated blind-side collision) conditions. An effort will again be made to prevent subjects' knowledge of the precise timing of force application during the unanticipated condition using strategies such as wearing blinders and being exposed to ambient white noise. sEMG will again be used to ensure appropriate neck muscle activation under both conditions, as above.

Standardized voluntary soccer headers will also be performed in the sagittal plane. One heading task will involve an active heading strategy with the goal of returning a soccer ball directly back in the direction from which it was pitched with as much velocity as possible, as if performing an attacking/offensive soccer header. A second heading task will be similar, except with a goal of gently directing the soccer ball to the ground in the direction from which it was pitched as if performing a glancing header to pass the ball to the foot of a teammate. For both tasks, a standard soccer ball inflated at the low end of the recommended inflation range) will be pitched to the subject from a soccer machine using similar methodology as has been applied in previous soccer heading studies.[33, 35, 60, 74] The results of three trials will be averaged under both heading strategies.

Net head acceleration measurement:
For each loading condition, net head acceleration will be measured using a kinematic camera system in a similar manner as previously described by our group.[19, 22] Subjects will wear optoelectronic markers (infrared emitting diodes) to allow tracking of head position in space and relative to the torso. Signal processing will be performed in a similar manner as previously described by our group to calculate head accelerations.[19, 22] For the checking/blocking and soccer heading tasks, subjects will wear a thin force sensor on their shoulder (for checking/blocking) or forehead (for soccer heading) to identify the time of impact between their shoulder/forehead and the punching bag/soccer ball, respectively. In the unlikely event that head kinematics patterns are not sufficiently stereotyped under a given loading condition for between-subject comparisons of AUC for the net head acceleration vector, which does not directly account for directionality, then we would decompose the net acceleration vector into its individual linear and angular components. Participants will also wear a second inertial measurement unit (body-worn sensor) on their heads to provide redundant head acceleration data as a back-up in the unlikely event that the kinematic camera data cannot be adequately resolved. Additionally, if the force sensing resistor used to identify the onset of head acceleration during the checking/blocking and soccer heading tasks unexpectedly fails for a given trial, we would alternatively use a similar technique to the one we have previously employed to identify the onset of head acceleration from the kinematic dataset via a trailing window.[20, 46]

Methodology for measuring cervical muscle attributes: Given that muscular adaptation to resistance exercise results in strength gains attributable to both improved neuromuscular recruitment and muscle hypertrophy, we will assess neck strength as well as cervical muscle volume and neuromuscular activation.

Neck strength

Neck strength will be measured both in terms of the peak force/moment and rate of force/torque development in cervical flexion, extension, axial rotation, and lateral flexion using a customized laboratory testing apparatus similar to that previously described by Dr. Vasavada.[80] Measured force values will be converted to moments, in N·m, by multiplying each force value by the neck's estimated moment arm.

Cervical muscle volume
The total cervical muscle volume will be measured using magnetic resonance imaging (MRI) without contrast in a similar manner as previously described by Dr. Vasavada.[89] The volume of individual cervical muscles will be calculated by integrating the cross sectional areas (CSA's) across slices multiplied by slice center-to-center spacing and total cervical muscle volume will be calculated as the sum of volumes of the individual muscles.

Estimated cervical muscle volume will also be calculated at each assessment using a predictive regression equation developed by Dr. Vasavada's lab, which has been shown to accurately account for 87% of the variance in MRI-based total cervical muscle volume based on overall neck circumference and sex.[89] We will further refine this regression-based estimate by incorporating the sonographic anatomical cross-sectional areas (CSA's) of key cervical muscles measured at each assessment time point, with validation of the expanded model using our MRI-based cervical muscle volume measurements. We will assess the sternocleidomastoid (SCM), upper trapezius (TRAP), splenius capitis (SPL), and semispinalis capitis (SEMI) muscles, which we have previously studied with acceptable test-retest reliability (intra-class correlation coefficients, ICC= .91 to ICC= .99) and validity as compared to criterion-standard MRI CSA measurements (R= .76 to R= .97).[21] In the unlikely event that we are unable to adequately predict total cervical muscle volumes using Dr. Vasavada's regression equation,[89] we would alternatively assess cervical muscle hypertrophy using total neck circumference and the sonographic anatomical CSA measurements of the SCM, TRAP, SPL, and SEMI muscles.

Cervical muscle activation
We will quantify neuromuscular recruitment of the cervical muscles in terms of agonist muscle activation and antagonist muscle inhibition, using a similar surface electromyography (sEMG) protocol as during our pilot neck strengthening study.[19] Briefly, after standard skin preparation sEMG electrodes placed over the SCM, TRAP, SPL, and SEMI muscles will measure muscle activation during maximum voluntary contraction and under each loading condition. Raw sEMG data will be normalized with respect to each muscle's maximum amplitude, with agonist muscle activation and antagonist muscle inhibition calculated as the mean normalized sEMG amplitude (percentage of maximum) of the agonist and antagonist muscles during maximum voluntary contraction in each plane of motion. The mean activation level of each cervical muscle will also be measured during the loading tasks, allowing assessment of agonist activation and antagonist inhibition, as well as agonist-antagonist co-contraction and muscle activation onset latencies during loading.

Estimated cervical muscle stiffness
We will estimate cervical muscle stiffness by imposing cervical muscle volume, head kinematics, and sEMG data onto Dr. Vasavada's multi-body dynamic neck model[78] in a similar manner as previously used to accurately estimate joint stiffness in an elbow model.[36]

All results will be collected by the study team through the conduct of this research study and are for research purposes only. As such, no medical record review will be performed and no study results will routinely be reported to participants. Individual participant or parent/guardian requests for study results will be considered by the PI on a case-by-case basis and requested information will be provided at the discretion of the PI when feasible for the study team to do so.

8.2 SAFETY AND OTHER ASSESSMENTS

Potential participants meeting any exclusion criteria (See Section 5.2), either during the initial phone screen or the final in-person screening assessment which includes a brief screening physical examination, may potentially be at slightly increased risk for injury as a result of study participation and so out of caution will be excluded from study participation.

Potential participants with disqualifying findings on the screening physical examination (and their parent/guardian if they are a minor) will be notified verbally at the time of the screening examination, and will subsequently be notified in writing, of the specific disqualifying physical exam finding. They will be advised to follow up with their primary care physician.

Participants will be asked at the beginning of each study-associated exercise and testing session whether they have experienced any AE's as described below in Section 8.3.4. Participants will also be observed by the study team during each study visit for AE's.

Any moderate or severe AE's will be reported to the PI, or his designee, for determination of the need for medical follow up. If immediate emergent medical care is deemed necessary 9-1-1 will be called. If urgent, non-immediate, medical care is deemed necessary the participant will be referred to a local Emergency Department or Urgent Care Center via their own private transportation. If non-urgent medical care is deemed necessary, the participant will be referred to their own physician's office. If no medical care is deemed necessary, the participant will be advised to monitor their condition and contact their own physician if their condition worsens prior to their next study visit.

All study MRI's will be reviewed by the Study Radiologist for quality control purposes, as well as to screen for incidental findings of clinical significance. If incidental clinically significant findings are identified, the Study Radiologist will note them in the research MRI report and will alert the PI (or his designee if he is unavailable) to their presence. The PI (or his designee) will subsequently contact the subject (and their parent/guardian if they are a minor) by phone to notify them of the incidental finding and advise them to follow up with their primary care physician. In addition, a written notification of the incidental finding, including a copy of the research MRI report, will be sent to the subject, as well as to their primary care physician, or an alternative physician providing them medical care if this is their preference.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Note: delayed onset muscle soreness is a normal, anticipated occurrence following resistance exercise training and is therefore not considered an AE for the purposes of this study.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator or his designee, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.2.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.2.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study intervention assessed by the PI, or his designee, based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. The study-assigned exercise program will always be considered suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other exposure/event (e.gs., drug, chemical, toxin, pathogen, activity, environmental factor, traumatic event). The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. If medically appropriate, a rechallenge procedure may be employed, with a positive response to rechallenge considered as confirmation of definite relatedness.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other or other exposure/event, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it

can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other disease or exposure/event provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.2.3 EXPECTEDNESS

The PI, or his designee, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in Section 2.3.1, or if it is not known to be associated with any non-disqualifying underlying disease, disorder, or condition affecting the participant.

8.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or if communicated to the study team between visits. The study team will not prompt participants for any specific solicited AE's, but will ask about unsolicited AE's at each study visit using the following general question: "Have you noticed any new illness, injury, or other health-related concerns since your last study visit?"

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed by the PI or his designee with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator or project manager will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.4 ADVERSE EVENT REPORTING

AE and SAE reporting to IRBMED will occur per IRBMED standard reporting guidelines. Reporting to the DSMB will occur in conjunction with annual DSMB meetings as scheduled per the DSMB Charter. Additionally, any serious adverse event deemed possibly, probably, or definitely related to study procedures, or were IRBMED standard reporting guidelines otherwise necessitate more immediate reporting, will be reported to the DSMB on the same schedule as reports to IRBMED or within 14 calendar days of identification, whichever occurs first.

Note that if a series of related, expected AE's of moderate severity appear to be occurring at a frequency greater than previously known or expected, the study team will report this to IRBMED and the DSMB within 14 calendar days of identifying the trend.

Unrelated, non-serious AE's (expected or unexpected) will not be reported to IRBMED or the DSMB unless there appears to be a trend of events occurring at a frequency greater than previously known or expected, in which case the study team will also report this trend to IRB-MED as well as the DSMB within 14 calendar days of identifying the trend.

8.3.5 SERIOUS ADVERSE EVENT REPORTING

Related, unexpected SAE's resulting in death or any life-threatening outcome will be reported to IRBMED and the DSMB within 7 calendar days of becoming aware of the event. Other related, unexpected SAE's will be reported to IRB-MED and the DSMB within 14 days of becoming aware of the event.

Unrelated, unexpected SAE's will be reported per standard IRBMED guidelines and in conjunction with regularly scheduled DSMB meetings.

Note, there are no related, expected SAE's associated with this study.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

If the study team becomes aware of new knowledge regarding related, unexpected AE's/SAE's that may affect other current or future study participants, the study team will seek input from the DSMB as to whether/how to communicate this information to other current participants and/or whether/how to amend the IRB-MED approved informed consent documents for future participants. Re-consenting will be performed for subjects actively involved in the study if deemed necessary by the PI, IRMBED, or DSMB.

8.3.7 EVENTS OF SPECIAL INTEREST

N/A

8.3.8 REPORTING OF PREGNANCY

If a study participant becomes pregnant during the study period, or becomes aware of a previously unidentified pre-existing pregnancy during the study period, they will be permitted to continue study participation at the discretion of their treating obstetrician (or other physician responsible for managing their pregnancy, e.g., family medicine physician) and a letter of clearance for ongoing study participation will be requested to document this clearance.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The study team will report unanticipated problems (UPs) to IRBMED. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are actual AEs or SAEs will be reported to IRB-MED as described above in Section 8.3.5-8.3.6.
- Any other UPs representing newly identified possibility of previously unsuspected harm will be reported to IRB-MED within 14 days of the study team becoming aware of the problem.
- If IRB-MED concurs that a UP exists, the UP will be reported to appropriate institutional and external officials as required under IRB-MED's reporting policies and procedures.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If UPs are identified that may affect current or future study participants, the study team will seek input from the DSMB as to whether/how to communicate this information to current participants and/or whether/how to amend the IRBMED approved informed consent documents for future participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint:

There will be evidence of a dose-response effect for neck strengthening exercise on net head acceleration under direct load application proportional to the volume load of exercise.

Secondary Efficacy Endpoint:

There will be evidence of a dose-response effect for neck strengthening exercise on net head acceleration under indirect load application proportional to the volume load of exercise.

9.2 SAMPLE SIZE DETERMINATION

Our power calculation is based on AIM 1. Assuming net head acceleration (on the logarithmic scale) will follow linear trends over time, then our power calculation is based on comparison of the slope of this change, which has 9/14 of the variance, i.e., 36% less variance, than the underlying log(net head acceleration) measurements. As a result, the standardized effect size (Cohen's d value) of the slope is approximately 1.25 times greater than that of the underlying log(net head acceleration) measurements. Based on our own pilot data,[19] we expect observed standardized effect sizes to be between .6 and 1.0 for log(net head acceleration), depending on the variability of the individual measurements across the 4 directions of motion. These values correspond with a 20% overall reduction in un-transformed net head acceleration. A total of 30 subjects in each exercise group (control and high intensity), will provide power of between .83 [for standardized effect size for log (net head acceleration) of .6 and 1.0 [for standardized effect size for log(net head acceleration) of 1.0] depending on the actual observed standardized effect size in the population. To account for the possibility of a drop-out rate of up to 20%, we will plan to enroll up to a total of 72 subjects.

9.3 POPULATIONS FOR ANALYSES

All participants will be included in the analysis, including participants contributing only a partial data set. The only exception would be in cases where the PI, study statistician, and Exercise Physiology/Engineering/Radiology study CoI-lead (for volume-load vs. lab-based vs. imaging-based data) agree there is legitimate threat to the validity of data collected in any individual participant due to technical error not identified at the time of assessment that cannot be resolved through post-processing (e.g., incorrect gain settings leading to signal saturation or failure of MRI field of view not covering the full extent of cervical musculature to be measured).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Prior to the analysis, all data will be examined and transformed as necessary to achieve approximate normality. Descriptive statistics will be used to characterize the distribution, central tendency (mean, median), and variability (standard deviation, range, interquartile range) of each continuous variable. All subjects will be included in the analysis and an alpha of .05 will be considered significant for statistical testing.

9.4.2 ANALYSIS OF THE PRIMARY AND SECONDARY EFFICACY ENDPOINTS

We expect a percentage reduction in net head acceleration as the volume load of exercise performed increases over the 12 week exercise program, so we will assess net head acceleration on a logarithmic scale to allow us to model and detect a constant change. For example, a 20% reduction in net head acceleration corresponds to a difference of log(.8) on the log-scale, regardless of the initial value of net head acceleration. We will use linear mixed models to describe the longitudinal changes in log(net head acceleration) over the volume loads of exercise performed at each of the four study time points, and to test the significance of this change across the three exercise groups.

9.4.3 SAFETY ANALYSES

AEs and SAEs will be summarized by severity, relatedness, and expectedness using counts, with each AE counting only one time for a given participant, and will be presented in a table format.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics (including demographics, cervical muscle attributes, and net head accelerations under each loading condition) to assess for the presence of any baseline differences between the groups before participation in the study-assigned exercise intervention. Categorical and continuous variables will be assessed using chi-square tables and ANOVA, respectively.

9.4.5 PLANNED INTERIM ANALYSES

Consistent with the original proposal submitted to and funded by NIH, a blinded interim analyses will be performed by the study statistician in Study Year 3, or upon protocol completion by 15 participants in the treatment group, whichever marker of the study mid-point comes first. The results of the interim analysis will be reviewed by the PI and shared with the study team for dissemination as preliminary study results, but will not be used to halt ongoing study activities.

In addition, the strength of the estimated total cervical muscle volume prediction algorithm with respect to MRI-based measured total cervical muscle volume will be reassessed by the study statistician on an ongoing basis throughout the study period. Pending determination of the strength of the estimated total cervical muscle prediction algorithm, the MRI portion of the study protocol will be amended to minimize the time and expense associated with MRI acquisition and analysis for the remainder of the study.

In the event that an immediate DSMB review is required in response to any AE(s), SAE(s), or UP(s) (see Sections 8.3.5-8.3.6 and 8.4.2), new study enrollment will temporarily be suspended until the DSMB has met and assessed the need for ongoing modification to study enrollment and/or study intervention activities. Ongoing study activities will continue without interruption unless an unexpected, study-related SAE occurs, in which case ongoing study activities associated with the portion of the study protocol deemed to have caused the SAE will be temporarily suspended pending DSMB review and recommendations.

9.4.6 SUB-GROUP ANALYSES

We will include sex as a covariate in the statistical models, as well as explore possible interactions between sex and other independent variables, to identify any sex-based differences in the relationship between exercise volume load and the net head acceleration outcome.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.8 EXPLORATORY ANALYSES

We will construct linear models with net head acceleration as the outcome and combinations of neck strength and/or cervical muscle volume as the predictor(s) for direct and indirect force application under both the anticipated and unanticipated conditions. Rather than comparing the B coefficients of the neck strength and cervical muscle volume terms, which are scale-dependent, we will instead quantify the impact of each cervical covariate on net head acceleration by calculating the differences in R^2 values of statistical models with vs. without each cervical variable. These differential R^2 values indicate the importance of each cervical variable in the model, accounting for the other. There is no known analytic solution in the statistical literature to confirm statistically whether one differential R^2 value is higher than the other unless the null hypothesis is zero differential R^2,[14] which is not the case here. Instead, we will use the bootstrap as a nonparametric tool to assess the variability in the differential R^2 values.[24] By bootstrapping the subjects a sufficient number of times, we can obtain a set of differential R^2 values and use them to construct 95% confidence intervals around the differential R^2 values of both cervical variables during the anticipated and unanticipated conditions. If the confidence intervals are non-overlapping, we will conclude that the cervical variable associated with a greater decline in R^2 value upon its removal from the full model is significantly more impactful on the net head acceleration for the given anticipation condition.

We will compare the magnitudes of the B coefficients associated with each cervical independent variable at each time point in the linear mixed model analyses predicting log(net head acceleration). The effect of neck strengthening exercise on the exploratory net head acceleration during soccer heading outcomes will be analyzed using a similar statistical analysis plan as described above in Section 9.4.2.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

IRB-MED-approved informed consent forms describing in detail the study intervention, study procedures, and risks will be given to each participant and written documentation of informed consent (or assent with parent/guardian consent) will be obtained prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

A waiver of informed consent for screening purposes will be obtained from IRB-MED to allow potential participants to be screened for study eligibility prior to undergoing the informed consent process in an effort to save ineligible individuals from the inconvenience of unnecessary study-related procedures if they are not eligible to participate in the study. Those individuals who are eligible and interested in participating in the study will complete the informed consent (or assent with parent/guardian consent for minors) process in person with the PI, or a designated member of the study team.

Informed consent (or assent with parent/guardian consent for minors) is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent/Assent forms will be UM Institutional Review Board (IRBMED)-approved and the participant (and parent/guardian for minors) will be asked to read and review the document. A member of the study team will explain the research study to the participant (and parent/guardian for minors) and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's (and parent's/guardian's for minors) comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants (and parent/guardian for minors) will have the opportunity to carefully review the written consent form and discuss/ask questions prior to signing. All participants, regardless of age, will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document (or assent document with the parent/guardian signing the consent document) prior to any procedures being done specifically for the study. Participants (and their parent/guardian for minors) will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/assent document will be given to the participants for their records. The informed consent/assent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants (and their parent/guardian for minors) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Any children who become adults during the course of the study will not be re-consented after their 18th birthday.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Participant confidentiality and privacy are strictly held in trust by the study team. This confidentiality is extended to cover biological imaging results in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of IRB-MED.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the UM Institutional Review Board (IRB-MED), members of the DSMB, or other regulatory agencies may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information and research data, which is for purposes of statistical analysis and scientific reporting, will be securely stored at the University of Michigan for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB-MED and Institutional policies. At the end of the study, the study database will be de-identified and stored at the University of Michigan.

The study team will not apply for a Certificate of Confidentiality for this study.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Michigan. After the study is completed, the data will be de-identified and archived for potential use in the future by the study team. Permission to store de-identified data will be included in the informed consent. A copy of MRI data will also be maintained in the research section of participants' electronic medical records at the University of Michigan/Michigan Medicine.

When the study is completed, the study team will maintain access to de-identified study data.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**DSMB Safety Officer**
James T. Eckner, M.D., M.S. Associate Professor	Hugh J.L. Garton, M.D., M.H.Sc. Professor
University of Michigan Dept. of PM&R	University of Michigan Dept. of Neurosurgery
325 E. Eisenhower Pkwy Ann Arbor MI 48108	1500 E. Medical Center Drive SPC 5338 Ann Arbor, MI 48109
734-936-7200	734-936-7010
jeckner@med.umich.edu	hgarton@med.umich.edu

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of 3 individuals with the appropriate expertise, including biostatistics, pediatric neurosurgery, and pediatric sports medicine. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet annually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the PI and the National Institutes of Health Program Officer assigned to this project.

10.1.6 CLINICAL MONITORING

Clinical study monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with good clinical practice, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the Michigan Institute of Clinical and Health Research. Clinical monitor responsibilities will include:

- Review of study documents, creation of the Clinical Monitoring Plan (CMP), and on-site study initiation visit prior to the start of enrollment
    - The CMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- On-site and/or virtual interim data and regulatory monitoring visits approximately every 6 months throughout the trial with review of approximately 50% of enrolled participants' charts.
- On-site study close-out visit upon completion of the trial.
- Provision of copies of monitoring reports to the PI and study coordinator/program manager within 14 days of visit.
- Planned independent audits will not be conducted outside of the CMP, although it is possible that a random audit could be scheduled by the University of Michigan Office of Research Compliance Review (OCRC).

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be reviewed for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological imaging is collected, documented (recorded), and reported in compliance with the protocol, IRB guidelines, and the Human Research Protection Program (HRPP) Operations Manual.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study team at the University of Michigan under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs) and expected adverse reactions data) will be entered into REDCap, a secure, HIPAA compliant data capture system provided by MICHR. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years from the date of final ClinicalTrials.gov reporting. These documents will be retained for a longer period, however, if required by local regulations.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol document or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It is the responsibility of the PI to use continuous vigilance to identify and report deviations not affecting participant safety as ORIOs in compliance with the current standard ORIO reporting guidance issued by IRBMED.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the PI.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with IRB-MED has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
AUC	Area Under the Curve
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSA	Cross-Sectional Area
CSCS	Certified Strength and Conditioning Specialist
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EMG	Electromyography
FFR	Federal Financial Report
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIT	Head Impact Telemetry
HRPP	Human Research Protection Program
ICC	Intra-Class Correlation Coefficients
IRB	Institutional Review Board
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SCM	Sternocleidomastoid
sEMG	Surface electromyography
SEMI	Semispinalis Capitis
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SPL	Splenius Capitis
SRC	Sport and Recreation Related Concussion
TRAP	Upper Trapezius
UM	University of Michigan
UP	Unanticipated Problem
US	United States
WSTC	Wayne State Tolerance Curve

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	5/22/2019	Additional discussion of risk	Per IRB Request
1.1	5/22/2019	Expansion of exclusion criteria for screening exam	Per PM&R Spine Physician recommendation
1.2	10/19/22	Permission for virtual IMV's	Per MICHR Monitor request
2.2	12/20/22	Removed low-volume exercise group from protocol	Reduced enrollment following COVID pandemic
2.2	12/20/22	Clarifications to criteria defining protocol deviation- updating number of days that create a deviation.	Reducing documentation burden associated with schedule deviations

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