FULL PROTOCOL

EFFECTIVENESS OF A NECK STRENGTHENING PROGRAM FOR THE PREVENTION OR MITIGATION OF SPORTS CONCUSSION INJURIES IN STUDENT ATHLETES

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HSR# 17-4360

Revised 12/14/16, Revised 6/9/17, 6/21/17, Revised 7/12/17

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1 SUMMARY

This project will assess the relationships between neck strength and the incidence, severity, and duration of concussions in student athletes in order to evaluate the effectiveness of a neck strengthening training regime as a primary intervention for reducing the risk of sport-related concussion.

2 BACKGROUND

Sport-related concussion is a common injury that results in more than 200,000 emergency department visits annually, 65% of which are children aged 5 to 18.[1] Recognized as a major public health concern,[2] sport-related concussion diagnoses in the United States have increased by 43% overall over the last 5 years.[3] Rates of increase over the same time span were also found to be higher for pediatric (71%) and female (up to 118%) populations, consistent with research indicating that the incidence and clinical outcomes of concussion vary with sex and age[4]; specifically, significantly higher risks and poorer outcomes have been reported for younger and female populations.[1,5-8] Because the developing brains of children and adolescents are uniquely vulnerable to diffuse brain injury,[9] single or repeated concussions have potential for severe acute and long-term complications in these young athletes.[10,11]

Low neck strength is a risk factor thought to contribute to an elevated concussion risk.[2,12] Previous studies have shown that athletes with smaller and weaker necks experience greater resultant linear and angular head displacements, velocities, and accelerations after impact.[2,6,13,14] Because these parameters represent the primary mechanisms contributing to a concussive event, further studies clarifying the relationships between neck strength and the risk and clinical outcomes of concussion are warranted. To date, only 1 study has examined the relationship between neck strength and concussion incidence; in a prospective study of high school athletes, Collins et al[12] measured isometric neck strength parameters using a hand-held tension scale and monitored the concussion rate over several sports sessions. Neck strength was found to be a significant predictor of concussion incidence among high school students, with concussed athletes demonstrating 11% to 22% reduction in neck strength compared with nonconcussed athletes.

Given the increases in the reported incidence of head injuries sustained by young student athletes in the United States, it is essential that high school and university athletics programs have access to inexpensive, effective, and easy-to-implement strategies for the prevention of concussions. Collectively, the results of previous studies suggest that interventions aimed at increasing athletes' neck strength may be effective for decreasing the risk and symptoms of concussion. Imperative to the development of such interventions are additional studies that quantify the extent to which the severity and duration of concussion symptoms are a function of neck strength.

3 STUDY PURPOSE

The purpose of the project is to evaluate the effectiveness of neck strengthening as a primary prevention mechanism against concussion.

4 STUDY PROTOCOL

4.1 OVERVIEW

This project has the following goals:

1. Determine whether baseline measurements of neck strength correlate with the incidence, severity, and duration of concussion symptoms;
2. Determine whether a standardized neck strengthening training regime reduces the risk of concussion and the severity and duration of symptoms; and
3. Determine whether the relationships between neck strength and the clinical symptoms of concussion are independent of gender.

Subjects aged 5 to 22 who are involved in organized, academic or community-based contact/collision sports activities at Gustavus Adolphus College, member schools of the Independent Metro Athletic Conference (IMAC) conference, and The Sanneh Foundation participate in an instructor-led neck-strength training program. Subjects enrolled in the study will be followed for up to 3 years to assess whether the incidence, severity, and duration of concussion symptoms varies as a function of neck strength in young athletes. Anthropometric measurements, neck strength parameters, cognitive assessments, and an eye-tracking assessment will be performed for each subject at baseline, and at yearly intervals thereafter in the absence of a reported head injury. In addition, anthropometric and neck-strength measurements will be recorded at regular intervals during the study to quantify the effectiveness of the strength training regime. Subjects diagnosed with concussion during the study will be assessed for the severity and duration of postconcussion symptoms using eye-tracking methodology and traditional cognitive assessments. Clinical outcomes will be assessed immediately following a concussive event and monitored by research staff until symptoms resolve. Data will be collected by onsite study volunteers trained by Dr. Uzma Samadani or another member of the Brain Injury Research Lab staff at HCMC. All aspects of the study design will be overseen and approved by Dr. Thomas Bergman.

4.2 STUDY DESIGN AND METHODS-BRIEF

Table 1: Study Design Summary

STUDY TYPE	Multicenter, observational, open analytical study
SAMPLE SIZE	1500
SITES	Sports facilities onsite at Gustavus Adolphus, member schools of the IMAC conference, and The Sanneh Foundation.
STUDY DURATION	Approximately 3 years
STUDY ARM(S)	**Single-arm design**

	All subjects will undergo an instructor-led, standardized neck-strengthening training regime
STUDY DESIGN	**Subject recruitment and enrollment** Subjects (aged 5-22) involved in contact/collision sports programs will be recruited from and enrolled at schools and community-based sports facilities. **Intervention** Subjects will be invited to participate in a twice-weekly, instructor-led, neck-strengthening training program. In each training session, subjects will perform a variety of lightly-weighted and nonweighted resistance exercises. **Assessments and timeline** Demographic and sport history information will be collected at screening, and morphometric, cognitive, neck-strength, and eye-tracking assessments will be made at baseline, and annually thereafter in the absence of a reported head injury. In addition, anthropometric and neck-strength measurements will be recorded immediately before and after training sessions at 6-month intervals to track improvements in neck strength. Subjects who experience concussion during the study will undergo assessments for eye-tracking and cognition at the time of the event; a subset of cognitive assessments will also be made on a daily basis following the event, until full recovery is achieved. If recovery is not achieved within a week, eye-tracking will be repeated. If symptoms continue to persist, additional cognitive assessments will be administered and repeated monthly until the subject fully recovers. **Data analysis** Repeated-measures analysis of variance (ANOVA) will be used to evaluate the effectiveness of the training program for increasing neck strength. Relationships among neck-strength parameters and concussion risk and functional outcome measures will be evaluated via logistic and linear regression models. Analyses will be adjusted for sex to evaluate whether the results are independent of gender.
SCHEDULE	Week 1: Initial visit or call prior to enrollment to obtain informed consent; Baseline assessments made within 72 hours of enrollment Weeks 4 to 52: Assessments of neck strength made at 6-month intervals (+/- 3 days)[a] Weeks 4 to 52: Assessments of concussion symptoms (if applicable) until symptoms resolve.

	• Time-of-event (within 1 day of event): Cognitive and eye-tracking assessments • Days 1-7 after event: Daily subset of cognitive assessments • Day 7: Eye-tracking assessment, neck-strength measurement • Weeks 4, 8, and 12 after event (+/- 3 days): Cognitive assessments [a]The neck-strengthening training regime will be administered for the length of the subject's sport program and during the period(s) of time corresponding to the subject's regular athletic training schedule.
BLINDING	This study is nonblinded.

4.3 STUDY OBJECTIVE

The primary objective of the study is to evaluate the impact of neck strength on the incidence and clinical outcomes of concussion among young athletes.

The study also generally aims to determine if implementation of a neck-strengthening program can significantly reduce the duration and severity of concussion symptoms in young athletes.

4.4 STUDY HYPOTHESES

The primary study hypothesis is that increased neck strength reduces in the incidence, severity, and duration of concussion symptoms.

4.5 STUDY ELIGIBILITY AND ENROLLMENT

4.5.1 Study Population

Subjects will be youths aged 5 to 22 who are involved in one or more academic or community-based organized contact/collision athletic sports program(s). Approximately 1500 students will be recruited from Gustavus Adolphus College, member schools of the Independent Metro Athletic Conference (IMAC) conference, and The Sanneh Foundation, and enrolled in the study. The study population will be composed of players from multiple sports, and at a broad range of competitive levels. Study-site coordinators and/or trainers will be advised of the purpose and procedures of the study and will refer subjects to the Investigator for consideration. Subjects who meet all inclusion/exclusion criteria and have appropriate consent to participate in the study may be enrolled. The study is open to all races and both genders.

4.5.2 Duration of Investigation

Enrolled subjects may be followed for up to 3 years. The duration of training and assessment for subjects is anticipated to vary by sport and program. However, all subjects will

complete the neck-strengthening training program twice weekly for the duration of time that they are enrolled in the study.

4.5.3 Informed Consent

Subjects enrolling in the study may not be capable of providing consent in which case consent will be obtained from the subject's parent/guardian/legal representative. Legal guardians will be provided with written consent forms detailing all risks, benefits and alternatives to subject participation.

For subjects aged 8 and above, written informed assent will be obtained from the subject. Informed consent will include a detailed description of the study, including its purpose, procedures, and risks.

The consent form will include information about the assessments conducted at baseline and at follow-up, and a description of the training regime. Research personnel from the Brain Injury Research Lab will prepare an informative video to be placed online, as well as verbally explain the information provided in the consent form and subjects and their representatives will be granted the opportunity to ask unlimited questions in English or any chosen language through the availability of a trained medical translation service.

The subject will be provided with a copy of the IRB-approved/stamped informed consent form. The Investigator or designee will ensure that all of the potential subject's questions and those of the subject's caregiver regarding study participation have been answered, and that the potential subject agrees to study participation. Written informed consent will then be obtained from the subject or the subject's legally authorized representative. A copy of the signed informed consent form shall be given to the subject/proxy, and the original stored on site at the Brain Injury Research Lab. The informed consent process shall be documented in the subject's records. No study-specific procedures will be conducted prior to obtaining consent.

4.5.4 Subject Selection and Enrollment Procedures

Study site coordinators at each school or organization who are advised of the purpose and procedures of the study and will refer subjects to the Investigator for consideration. Once a subject has been identified, he/she will be approached by research personnel from the Brain Injury Research Lab or the study site coordinator and informed consent will be obtained prior to the screening process. Subjects will be considered enrolled in the study at the time the informed consent is obtained and when the subject ID has been assigned.

4.5.5 Inclusion Criteria/Exclusion Criteria

Youth athletes screened as potential study subjects must meet all of the following inclusion criteria and none of the following exclusion criteria.

INCLUSION CRITERIA:

1. Involved in programmatic athletic activities with an ongoing duration of at least 4 weeks.
2. Written informed consent obtained by the subject or subject's legal guardian.
3. Written assent from subjects ages 8 years old and above
4. Subject is between the ages of 5 and 22 years, male or female.

5. Subjects from all racial and ethnic origins will have an opportunity to participate.

EXCLUSION CRITERIA:

1. Corrected vision less than 20/500.

4.6 STUDY TREATMENT

Subjects will engage in an instructor-led, supervised, manual-resistance training program twice weekly. At each session, subjects will perform a variety of nonweighted resistance exercises, previously shown in a clinical trial to be safe and effective for use in pediatric populations (ClinicalTrials.gov identifier, NCT02455037)[15] and lightly weighted exercises using barbells, and commercial neck strengthening equipment (eg, NekkDekk and/or IronNeck).

The effectiveness of the strength training regime over time will be assessed by measuring neck girth and neck strength at the beginning and end of training sessions at 6-month intervals, for as long as the subject continues the sport program or until he/she leaves the study.

4.7 ASSESSMENTS (BASELINE THROUGH END OF STUDY)

Eye Tracking

Subjects' eye movements will be tracked and recorded with an SR Research Eyelink 1000 eye tracker while a 220-second video was played continuously within a square aperture moving around the perimeter of a 17" viewing monitor (aspect ratio 4:3) fixed 55cm away from the patient. The video aperture size is approximately 1/9th the area of the display monitor. The position of the eyes will be obtained at 500Hz with a stabilized chin rest to minimize head movement during the eye tracking session. All subjects will be asked to take off their glasses while being tracked. The visual stimuli are G-rated music videos, children's movie clips, and other documentary film selections. Subjects will not be spatially calibrated to the tracker to enable independent analysis of each pupil position over time. The eye tracking data will be processed to yield 89 eye tracking metrics.

Cognitive Assessments

Subjects will undergo cognitive assessments which have been previously validated in clinical research.

Morphometric Measurements

Height and weight will be measured using a standing scale. Head circumference will be measured at the top of pinna and neck circumference (girth) will be measured at the level of the thyroid cartilage using a flexible metric tape.

Neck Strength Parameters

Neck strength (extension, flexion, left and right lateral measurements) will be assessed using a hand-held commercial dynamometer that is effective for measuring neck strength.[16] Subjects will be permitted to rest between measurements to minimize risk of injury.

4.8 STUDY TIMELINE

4.8.1 Screening/Baseline:

Once a potential study subject is identified, informed consent will be obtained. After this, patients will be asked or undergo

- General medical questions to affirm inclusion/exclusion criteria

If they are eligible for enrollment, they will then undergo:

- Training on all aspects and requirements of the study, including the neck-strengthening training program, concussion and adverse event reporting, and frequency and expectations for follow-up measurements of neck strength
- Morphometric assessments
- Cognitive evaluations
- Eye-tracking algorithm
- Neck-strength assessment

4.8.2 Regular Training Assessments (every 6 months):

- Review subject's impressions of the training program
- Morphometric and neck-strength measurements immediately before and after the training session

4.8.3 Following a Diagnosis of Concussion (within 1 day of event):

- Review subject's general well-being
- Cognitive evaluations
- Eye-tracking algorithm
- Neck-strength assessment
- Date of last menstrual period (females only)

If concussion symptoms persist:

4.8.4 Following a Diagnosis of Concussion (7 days after event):

- Review subject's general well-being
- Cognitive evaluations
- Eye tracking algorithm
- Neck-strength measurements

4.8.5 Following a Diagnosis of Concussion (30, 60, 90 days after event):

- Review subject's general well-being
- Cognitive evaluations

4.9 CONCUSSION AND ADVERSE EVENT REPORTING

Athletic trainers will inform study site coordinators if a concussive event is suspected. The subject will be removed from activity and ultimately returned to activity as per their school or program protocol. The study site coordinator will immediately inform the Investigator of the event.

Monitoring of potential adverse events will be performed on a continuous and ongoing manner by the Investigator, research staff, and/or experienced athletic trainers at each study site. The nature of each adverse event, date and time of onset (when appropriate), outcome, frequency, maximum intensity, action taken, and attribution of each event will be recorded to identify those that are potentially related to the intervention (ie, the training regime). If an adverse experience increases in frequency or severity during the study period, a new record of the experience will be started.

5 INVESTIGATOR TRAINING

Study-site coordinators, athletic trainers at each site, and site volunteers will receive practical training in the execution of the neck-strengthening program, recognition of the symptoms of concussion, and data collection methods prior to the start of the study.

5.1 SUBJECT TRAINING

The Investigator or his/her designee will train the subjects on the correct execution of the resistance training movements, and will document this training in the subject records. Training will include the following steps and tools:

- Review all precautions and potential risks associated with participation in the training program
- Review the execution of each exercise move and the use of any applicable associated equipment
- Invite the subject to ask questions about the exercises or program

Subjects may also contact the Investigator or study-site coordinator at any time during the study to ask questions or request additional training/retraining.

6 EVALUATION OF OUTCOMES

6.1 SAFETY

The safety of the neck-strength training program will be measured and evaluated by the incidence of injuries or other adverse events related to the study treatment.

Improper execution of the exercises will be considered in the review of potential causes for any intervention-related or possibly intervention-related adverse events during the study. Any injury or other adverse event that is determined by the Investigator or the

Investigator's designee to be related or possibly related to the training program will be followed-up with the study subject, athletic trainer or study-site coordinator, and/or the subject's parent/guardian/legal representative to obtain wider perspective on the factors that led to the event.

6.2 OUTCOME ASSESSMENT

Outcomes will be assessed by an experienced researcher with neurologic and cognitive evaluations that are commercially available and validated in traumatic brain injury or cognitive dysfunction. Subjects will be followed for a minimum of 4 weeks after enrollment and a minimum of 1 week following a concussive event unless they or their legal guardians choose to leave the study.

6.3 STATISTICAL METHODS

Data accrued through this study will be reviewed with statisticians from The Minnesota Medical Research Foundation Chronic Disease Research Group. Repeated-measures analysis of variance (ANOVA) will be used to evaluate the effectiveness of the training program for increased neck strength. Relationships among neck-strength parameters and concussion risk and functional outcome measures will be evaluated via logistic and linear regression models. Analyses will be adjusted for sex to evaluate whether the results are independent of gender.

6.4 SAMPLE SIZE DETERMINATION

Sample size estimates were calculated based on unpublished data indicating an incidence of concussion of 11%, and published data on the reduction in concussion risk associated with increased neck strength.[12] Based on this information, a sample of size of 1198 subjects would be needed to detect a correlation of R=0.25 between neck strength and a reduction in the severity of concussion symptoms (based on cognitive assessment scores) with a power of 0.8 at alpha=0.05. Assuming attrition of 15-20%, we therefore believe that approximately 1500 subjects will be needed.

6.4.1 Data Analysis and Complicating Considerations

A potential limitation on data interpretation is that substantial asymmetry in the number of enrolled males vs females could reduce the potential to detect an effect of neck strength on concussion risk. This is more likely to occur if the enrolled population is heavily skewed towards males because of the lower incidence rate of concussion in this demographic. All efforts will be made to enroll a study population with a 50% male-to-female ratio. We will consult with a biostatistician if this target is not reached to reevaluate the adjusted minimum sample size required to detect an effect.

7 INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

7.1 INVESTIGATOR RESPONSIBILITIES

7.1.1 Investigator Accountability

The Investigator is ultimately responsible for equipment accountability including but not limited to hand-held tension devices and eye trackers. The study-site coordinators, or designees, are responsible for maintaining site logs of equipment accountability and use, which will include tracking the receipt and return/disposition of all equipment used in the study (if applicable).

7.1.2 Patient Accountability

A subject /subject caregiver may withdraw their consent to participate in the study at any time and can do so by notifying the Investigator and/or Investigator staff.

7.2 INVESTIGATOR REPORTS

The Investigator will be responsible for the following reports:

Adverse Events:

Adverse events will be reported to the reviewing IRB in compliance with its reporting requirements. For serious adverse events (whether or not related to the intervention) or unanticipated adverse effects of the intervention, this will occur no later than 5 business days of the Investigator becoming aware of the event.

Deviations from the Investigational Plan:

The Investigator is responsible for reporting all protocol deviations. Examples of protocol deviations include, but are not limited to:

- Failure to obtain written informed consent prior to conducting study procedures
- Failure to comply with any requirements of the reviewing IRB

Progress Reports: The Investigator is required to submit annual progress reports to the reviewing IRB. Reports must include the number of study subjects, a summary of all follow up evaluations, a summary of all adverse events and a general description of the study's progress.

Final Report: The Investigator will submit a final report to the IRB within 3 months of termination of the study or termination of that Investigator's participation in the study.

7.3 INVESTIGATOR RECORDS

The Investigator will maintain complete, accurate and current study records, including the following materials:

- Study subject records, including signed informed consent forms and copies of all data collection forms
- Documentation of any participation in the study without informed consent and a brief description of the circumstances justifying the failure to obtain informed consent
- All relevant observations, including records concerning adverse effects of the training regime (whether anticipated or unanticipated)
- Current study protocol and documentation of protocol deviations, including details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects,
- The IRB-approved blank informed consent form and blank data collection forms
- Certification that the investigational plan has been approved by all of the necessary approving authorities
- Signed and dated letters of agreement among the Investigator and all participating study site organizations.

These records shall be maintained for a period of 2 years after the date on which the investigation is terminated or completed.

7.4 MONITORING

After commencement of the study, regular monitoring will be conducted to ensure:

- Ongoing compliance with the study protocol
- Ongoing compliance with any conditions of approval of the reviewing IRB

7.5 SCREENED SUBJECTS NOT ENROLLED

Only data for enrolled subjects will be monitored and entered into the database. Of those subjects who have consent and are screened for the study but are not enrolled for any reason will not be followed and their data will not evaluated, except as may be necessary to assess the reason for the screening failure. The sites may retain the informed consent form and screening documentation for these subjects at their discretion.

8 REIMBURSEMENTS

8.1 SUBJECT COMPENSATION

There will be no costs to the subject or payment for participation in the study to subjects or their legal proxies.

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