EYE-TRAC Advance: Technology Verification (ETA-TV) Cohort 2

NCT02877732

April 12, 2016

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Clinical Research Protocol
EYE-TRAC ADVANCE: TECHNOLOGY VERIFICATION COHORT 2

Protocol Number:	ETA-TV
Version:	2.3
Version Date:	April 12, 2016
Investigational Device:	EYE-SYNC
Study Phase:	Feasibility/Exploratory
Sponsor:	Jamshid Ghajar, MD, PhD, FACS Stanford Concussion and Brain Performance Center 1050 Arastradero Road, Suite A 233 Palo Alto, CA 94304
Funding Organization:	Office of Naval Research
Site Investigator:	Name: Title: Telephone: Fax: E-mail:

Approval:

_____ _____

Site Investigator Signature (Name and Title) *Date*

This confidential information about feasibility/exploratory study is provided for the exclusive use of investigators of the EYE-SYNC Goggles and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Dr. Ghajar and the Stanford Concussion and Brain Performance Center with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: ETA-TV_34662

Protocol Title: EYE-TRAC Advance: Technology Verification

Version: 2.3

Protocol Date: April 12th, 2016

_____ _____

Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Site Contact _____

Address _____

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Phone Number _____

Email _____

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LIST OF ABBREVIATIONS

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ANAM	The Automated Neuropsychological Assessment Metrics
ANAM-SRT	The Automated Neuropsychological Assessment Metrics Simple Reaction Time Subtest
CCS	Concussion Subject
CFR	Code of Federal Regulations
CRF	Case Report Form
CTR	Control Subject
DEM™	Developmental Eye Movement™
ETA	EYE-TRAC Advance
ETA-TV	EYE-TRAC Advance: Technology Verification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HX	History
ICC	Intra-class Correlation Coefficient
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PHI	Personal Health Information
PI	Principal Investigator
SCAT	Sports Concussion Assessment Tool
SSRI	Selective Serotonin Re-uptake Inhibitor
UADE	Unanticipated Adverse Device Event

PROTOCOL SYNOPSIS

TITLE	EYE-TRAC Advance: Technology Verification
SPONSOR	Jamshid Ghajar, MD, PhD, FACS
PRINCIPAL INVESTIGATOR	Jessica Little, PhD
FUNDING ORGANIZATION	Office of Naval Research
NUMBER OF SITES	4-5
RATIONALE	There is a lack of understanding regarding the mechanisms that cause concussive signs and symptoms, and there is no definitive consensus on how to best evaluate or treat an individual with concussion. As a result, it is difficult to evaluate when it is necessary for an athlete to be removed from play after a possible head injury. Current sideline assessments may be subject to the athlete's lack of effort during baseline testing, leading to inaccurate interpretation post-concussion, or learning effects. To avoid inaccurate variability in performance that may complicate trainers' decisions, there is a high demand for an objective sideline measure to better determine the outcome of an athletic head injury. The current EYE-TRAC Advance (ETA) study uses a predictive visual tracking paradigm to measure gaze error variability. The addition of EYE-TRAC Advance: Technology Verification (ETA-TV) will help to fill knowledge gaps that exist in the current ETA protocol and contribute to the overall goal of accurately assessing possible impairment following a force to the head.
STUDY DESIGN	This is a prospective multi-center cohort feasibility and exploratory study.
PRIMARY OBJECTIVE	We propose to prospectively study a cohort of 18-25-year-old athletes to establish the reliability of EYE-SYNC data and the utility of the EYE-SYNC goggles as a sideline concussion assessment tool. A clinical research study will be conducted to 1) determine if eye-tracking, assessed on the sideline by EYE-SYNC goggles, is a potential marker of injury that can be used in conjunction with other sideline evaluations to inform decisions regarding removal of athletes from play and 2) to use the EYE-SYNC goggle data as a post- injury recovery curve monitor.
SECONDARY OBJECTIVES	To describe interrelationships among relevant variables used to describe concussion and EYE-SYNC.

NUMBER OF SUBJECTS	N = 100 (50 Concussion Subjects, 50 Controls) * Please note that we will continue to consent subjects, until we are able to complete 100 eligible participants for Cohort 2.
SUBJECT SELECTION CRITERIA	Inclusion Criteria: Athletes between the age of 18 – 25-years-old. 20/30 or better eyesight (corrected vision allowed). English fluency. CCS - those who experience impact where concussion is highly suspected as evidenced by impairment on any of the SCAT-3 Domains: Symptoms, Immediate Memory, Physical Signs, and Orientation. CTR - a teammate of the CCS who did not experience impact but who was participating in the same sport and session along with the injured teammate at the time of injury. Exclusion Criteria: Clinical diagnosis of a neurological condition including the following: Stroke, Multiple Sclerosis, Epilepsy, Brain Tumor/Cancer, dyslexia, Nystagmus and/or other major neurological condition. Clinical diagnosis of any of the following eye-sight abnormalities: Uncorrected Amblyopia, Uncorrected Myopia, Uncorrected Presbyopia, Uncorrected Farsightedness or Uncorrected Astigmatism. Psychiatric history with any of the following: **LIFETIME** a. Clinical diagnosis of a Psychotic Disorder, Bipolar Disorder: LIFETIME b. Clinical diagnosis of ADHD or ADD: LIFETIME **LAST YEAR** c. Clinical diagnosis of Major Depressive Disorder d. Clinical diagnosis of Substance Abuse Disorder within the LAST YEAR. e. Major Anxiety Disorder within the LAST YEAR. **MEDICATION** g. Use of a psychotropic medication. Cannot have participated previously in any ETA-TV study visits (for instance, a subject that has completed any study visit as a control subject cannot participate as a concussed subject at a later time point)..
INVESTIGATIONAL DEVICE / INTENDED USE	The EYE-SYNC® portable assessment system consists of two primary components enclosed in a portable aluminum case. The eye tracker is a handheld isolated display environment with embedded eye tracking sensors. The eye tracker is connected to a high-performance Windows tablet though a customized docking station. Included accessories with EYE-SYNC are a U.S. tablet power supply adapter and disposable sanitary masks. Subjects are asked to follow a dot as it moves on the screen.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The proposed study will occur within an 18-month window. Active enrollment will continue through the last month of the study or intended sample size is reached. Subject participation begins with enrollment, followed by baseline testing, and follow-up assessments (2 days post-injury, 7 days post-injury (+/- 1 day); and 14 days post-injury (+/- 3 days)). Testing follows consent for all subjects and continues through last

	practice/game in study period. Study windows are only to be used in rare situations. Please discuss with Stanford Principal Investigator/Study Sponsor for approval.
CONCOMMITANT MEDICATIONS	No psychotropic medication.
EFFICACY EVALUATIONS	**DEM:** The Developmental Eye Movement Test is an evaluation of saccadic eye movements. In this test, the subject reads the numbers presented on a card from left to right and top to bottom as quickly as he/she can without making any errors. **ANAM-SRT:** The Automated Neuropsychological Assessment Metrics (ANAM) is a computerized neurocognitive assessment tool designed to measure a wide range of cognitive functions. The Simple Reaction Time subtest is used as an index of attention (i.e., reaction time and vigilance) and visuo-motor response timing. **SCAT-3:** The Sport Concussion Assessment Tool (SCAT) is a widely used sideline concussion assessment tool used to evaluate the presence of neurocognitive impairment following a concussion. In the symptom evaluation, the subject self-reports the presence and severity of 22 concussion- related symptoms on a likert scale from 0-6. The SCAT3 tests the subject's orientation using Maddocks questions, and also includes the administration of the Standardized Assessment of Concussion (SAC). The SAC includes sections that test immediate memory and balance (modified BESS).
PRIMARY ENDPOINT	Our primary endpoint will be the acquisition of sufficient data to establish integrity and reliability of EYE-SYNC data and to compare and characterize trajectories of EYE-SYNC measurements in injured versus non-injured athletes.
SECONDARY ENDPOINTS	Our secondary endpoint will be to characterize interrelationships among variables relevant to concussion including DEM, ANAM-SRT, and SCAT-3 scores with EYE-SYNC.
OTHER EVALUATIONS	History and Demographics
SAFETY EVALUATIONS	N/A – EYE-SYNC is a minimal-risk noninvasive assessment tool, not an invasive assessment or treatment modality.
PLANNED INTERIM ANALYSES	When approximately 50% of subjects have completed the study, an interim analysis for safety will be conducted. Serious adverse events will be monitored by all site Investigators, Dr. Jamshid Ghajar, and the Stanford Concussion and Brain Performance Center (SCBPC) Coordinators on an ongoing basis throughout the study.

STATISTICS **Primary Analysis Plan and Rationale for Number of Subjects**	*Descriptive Statistics:* We will provide descriptive statistics for all subjects included in our study. Specifically, for continuous variables such as age, and scores from DEM, ANAM-SRT, SCAT-3, and EYE-SYNC, we will provide means, medians, standard deviations and interquartile ranges. For categorical variables such as race, ethnicity and previous history of injury, we will present frequency distributions. We will utilize graphical tools such as histograms and box plots to describe distributions of continuous variables. If needed to adhere to modeling assumptions, we may consider transformations of outcomes, such as a log transformation. *Handling of Missing Data:* We anticipate minimal missing data in this study. We expect that a small proportion of subjects recruited for the longitudinal study (1%) will not complete all visits. We will fully describe missing data for each variable and any pertinent patterns of missingness (e.g., how missingness is related to specific baseline measurements or time, if at all). The statistical methods we propose are particularly flexible for missing data and allow for systematic missingness that is related to observed features. *Statistical Tools for Each Aim:* Our first aim addresses the integrity of data generated by EYE-SYNC. Specifically, in Aim 1A, we will characterize the feasibility of collecting and generating data in real-time as injuries occur by considering the proportion of time we are able to collect 3 subsequent measures using EYE-SYNC on the sideline in the field from a case using data from cases included in *Cohort 2* (described above). We deem EYE-SYNC to be a promising tool to be used on the field if we are able to make use of it 90% of the time. This will be tested using a one-sided exact binomial test. With 50 cases, we have excellent power to evaluate feasibility. More specifically if we use a decision rule such that we conclude EYE-SYNC to be a promising and practical tool to be used in the field if we have complete information on 40 of the 50 cases, we have over 95% power when the true rate of complete data is 90% with a type I error of 0.04 under the null hypothesis that an unacceptable rate of complete data is 70%. The goal of Aim 2 is to assess whether data from EYE-SYNC correlates with clinically meaningful endpoints. To that end, we will create *Cohort 2* by collecting data (in replicates of 3) at immediately post impact, 2 days from injury, 7days from injury and 14 days from injury from 50 cases (defined as those who experience impact where concussion is highly suspected) and 50 matched controls (a teammate who did not experience impact but who was participating in the same sport and session along with the injured teammate at the time of injury). Using mixed effects regression techniques, we will examine whether the trajectory of EYE-SYNC changes over time for those injured differs significantly from those who were not injured. In

	addition, we will characterize trajectories of change in EYE-SYNC over time for those injured and for athletes who are injury free. Such models account for the correlation of scores within a subject over time as well as for the matched pairing of cases and their corresponding teammates. In addition, such models are robust to assumptions regarding missing data. The goal of Aim 3 is to describe interrelationships among relevant variables used to describe concussion and EYE-SYNC. This aim is fairly exploratory but will pave the way for future studies. We will rely on mixed effects techniques to characterize relationships of interest.

1.0 PURPOSE OF THE INVESTIGATION

1.1 Name of investigational device

EYE-SYNC®

1.2 Intended use of the investigational device

We intend to conduct a clinical trial including 50 Concussion Subjects and 50 Controls to compare trajectories of EYE-SYNC measurements in injured versus non-injured athletes and characterize variables related to concussion in relation to EYE-SYNC data.

1.3 Objectives of the clinical investigation

1.3.1 Primary objectives

Specific Aim 1: Establish integrity and reliability of EYE-SYNC data

- Specific Aim 1A: Characterize feasibility of collecting data using EYE-SYNC in real-time on the field.

Specific Aim II: Compare and characterize trajectories of EYE-SYNC measurements in injured versus non-injured athletes.

Specific Aim III: Characterize interrelationships among variables relevant to concussion including DEM, ANAM-SRT and SCAT-3 scores and EYE-SYNC.

1.4 Anticipated duration of the clinical investigation

The proposed study will occur within an 18-month window. Active enrollment will continue through the last month of the study or intended sample size is reached.

2.0 CLINICAL PROTOCOL

2.1 Protocol number and title

ETA-TV_34662: EYE-TRAC Advance: Technology Verification

2.2 Protocol version number and date

Version 1.0, October 26, 2015

Version 2.0 January 26, 2015

Version 2.1 March 17, 2016

Version 2.2 April 4th, 2016

Version 2.3 April 12th, 2016

2.3 Study design

2.3.1 General study design

This is a prospective multi-center cohort feasibility and exploratory study.

2.3.2 Study design schematic

The proposed study will occur within an 18-month window. Subject participation begins with enrollment, followed by baseline testing, and follow-up assessments.

Figure 1. Eighteen-month study plan

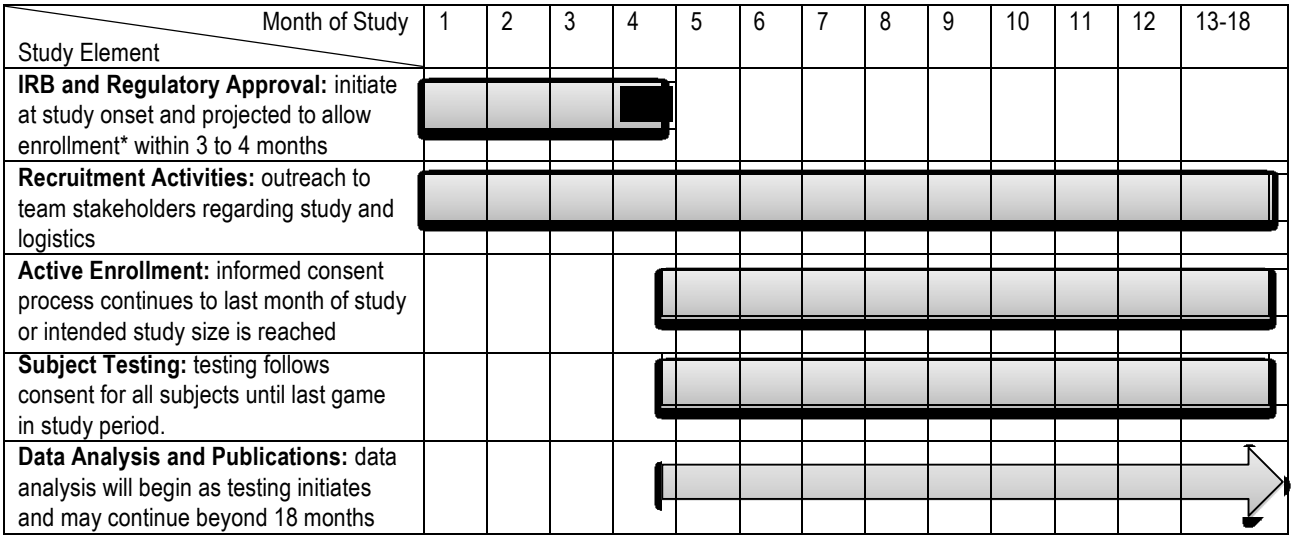

Figure 2. Sample Individual Subject Study Timeline

Cohort 2	**N=50 CCS** **N=50 CTR** Impact Sustained						
Phase	Prior to game	**Visit 1**		**Visit 2**		**Visit 3**	**Visit 4**
		Post-Concussion Immediate at **Sideline** – EYE-SYNC, Level of Alertness. **Within 3 hrs*** – SCAT-3, ANAM-SRT, DEM		**Post Concussion** 2 days		**Post Concussion** 7 days** (+/- 1 day) **CCS&CTR**	**Post Concussion** 14 days** (+/- 3 days) CCS&CTR
		CCS	**CTR**	**CCS**	**CTR**		
Informed Consent	X						
Inclusion and Exclusion Criteria and demographics			X[2]	X[3]			
History of injury				X	X		
SCAT-3 Symptom		X[1]	X	X	X	X	X
SCAT-3 Balance, Orientation and Immediate Memory		X[1]	X	X	X	X	X
DEM		X	X	X	X	X	X
ANAM-SRT		X	X	X	X	X	X
Level of Alertness questions[4]		X[5]	X	X	X	X	X
EYE-SYNC (3 times consecutively)		X[5]	X	X	X	X	X

*DEM, SCAT-3, ANAM-SRT must be performed within 3 hours of impact for Concussed subject (CCS) and within 3 hours post competition or practice for the control subject.

** The study window is only to be used for rare situations where the subject is unable to be seen on the exact date they are scheduled to come in. Please notify the site Investigator immediately for approval if subject needs to be seen within the study window that is provided.

1. Those that display impairment on any of the SCAT-3 domains: Symptoms, Immediate Memory, Physical Signs and Orientation will be registered as CCS subject.
2. CTR subjects: Those that meet the inclusion and exclusion criteria under cohort 2 (section 2.4.3 and 2.4.4), was actively participating in the same game along with the CCS subject at the time of injury.
3. During Visit 2, before performing any study procedures CCS subject must meet all the inclusion and exclusion criteria under cohort 2 (section 2.4.3 and 2.4.4). If subject does not meet all the criteria, CCS subject will be a screen failure. If possible, perform CTR study assessment after confirming that CCS is eligible to continue participation on Visit 2.
4. Level of Alertness questions must always be completed before performing the EYE-SYNC
5. EYE-SYNC must be performed at sideline immediately post impact.

2.4 Subject selection

2.4.1 General characteristics of the proposed subject population(s)

Male and female athletes, aged 18-25 years, will be recruited from athletic programs at collaborating study sites for Cohort 2.

2.4.2 Anticipated number of research subjects

Throughout the course of 18 months, the study will enroll 100 subjects in Cohort 2.

Cohort 2 will include 100 subjects; 50 Concussion Subjects (CCS) who have sustained an impact where concussion is highly suspected, as evidenced by impairment on either of the SCAT-3 domains: Symptom, Physical Signs, Orientation, Immediate Memory and 50 control subjects (CTR) who are teammates of the CCS and who did not experience impact, but who were participating in the same sport and session along with the injured CCS at the time of injury.

2.4.3 Inclusion criteria

- Athletes between the age of 18-25 years-old
- 20/30 or better eyesight (corrected vision allowed).
- English fluency.
- CCS - those who experience impact where concussion is highly suspected as evidenced by impairment in any of the SCAT-3 Domains: Symptoms, Physical Signs, Immediate Memory and Orientation. An Injured Athlete is concussed if he/she is FAIL on the Physical Signs, Score = 0 on the Orientation or Scoring below the cutoff scores on the Symptom Checklist and/or Immediate memory SCAT-3 domains.

    - Symptoms: Rating of 2 or higher on any of the following items:
        - Headaches
        - Nausea or Vomiting
        - Dizziness
        - Balance Problems
        - Blurred Vision
        - Feeling Slowed Down
        - Feeling like “in a fog”
        - “Don’t feel right”

    - Physical Signs:
        - Balance (Leg Stances): Number of Error(s) on any of the following 7 subtests classifies a subject as concussed.
            I. Double Leg Stance: At least 3 errors
            II. Single Leg Stance: At least 3 errors with either dominant or non-dominant foot
            III. Tandem Stance: At least 3 errors or more.
        - Balance (Tandem Gait): FAIL on at least 2 of 4 trials:
            I. FAIL per trial: more than 14 seconds to complete a trial

II. FAIL per trial, if one or more of the following errors are made
   a) If step off the line;
   b) Separation between heel and toe
   c) Touch/grab the examiner or an object

- Orientation: Score = 0 on any of the following 5 items
  - Date: Score = 0 (any date different from current)
  - Month: Score = 0 (any month different from current)
  - Day of the week: Score = 0 (any different from current)
  - Year: Score = 0 (any different from current)
  - Time: Score = 0 AND answer is MORE than + or – 1 hour apart from the correct time.
- Immediate Memory
  - Recall Total Score = less than 13 words recalled.

- CTR - a teammate of the CCS who did not experience impact but who was actively participating in the same sport and session along with the injured teammate at the time of injury

2.4.4 Exclusion criteria

- Clinical diagnosis of a neurological condition including the following: Stroke, Multiple Sclerosis, Epilepsy, Brain Tumor/Cancer, dyslexia, Nystagmus and/or Other major neurological condition.
- Clinical diagnosis of any of the following eye-sight abnormalities: Uncorrected Amblyopia, Uncorrected Myopia, Uncorrected Presbyopia, Uncorrected Farsightedness, Uncorrected Astigmatism.
- Psychiatric history with any of the following:

  LIFETIME
  a. Clinical diagnosis of a Psychotic Disorder, Bipolar Disorder
  b. Clinical diagnosis of ADHD or ADD
  Within LAST YEAR
  c. Clinical diagnosis of Major Depressive Disorder
  d. Clinical diagnosis of Substance Abuse Disorder
  e. Clinical Diagnosis of Major Anxiety Disorder.
  MEDICATION
  f. Use of a psychotropic medication
- Cannot have participated previously in any ETA-TV study visits (for instance, a subject that has completed any study visit as a control subject cannot participate as a concussed subject at a later time point).

2.5 Study Procedures

Post-concussion immediate and scheduled follow-up visits
Data Collection:

2.5.1 Visit 1

1. Visit 1 occurs immediately post-impact. The "Immediate" time frame for "post impact" is quantified as taking place as part of the naturalistic evaluation of the athlete suspected of sustaining a concussion. This will likely be immediately after the identification of a "hit" or other event that would lead to an athlete being evaluated for a possible concussion. At Visit 1, Level of Alertness, EYE-SYNC, DEM, ANAM-SRT, and SCAT-3: Symptom reporting, Physical Signs, Orientation, and Immediate Memory will be obtained (the above tests in combination will be referred to as 'Testing Battery').
    a. Post-impact the subject undergoes EYE-SYNC measurement immediately at the sideline. EYE-SYNC to be performed 3 times consecutively.
    b. Individuals enrolled as a Concussed Subject (CCS) are defined as those who experience impact where concussion is highly suspected as evidenced by impairment on any one of the SCAT-3 domains: Symptoms, Immediate Memory, Physical Signs or Orientation
    c. For each CCS subject enrolled, immediately enroll a Control Subject (CTR). A CTR subject is defined as a teammate who did not experience impact, but who was actively participating in the same sport and session along with the injured teammate at the time of injury. The CTR subject also receives the Testing Battery. Prior to performing the Testing Battery, ensure the CTR subject meets the Inclusion and Exclusion criteria – Cohort 2 as per section 2.4.3 and 2.4.4.
    d. CTR subject will complete Demographics during Visit 1.

2.5.2 Visits 2, 3 and 4

1. CCS must meet the inclusion and exclusion criteria prior to performing any assessments on Visit 2 (2 days post-injury). If CCS is ineligible, both CCS and CTR will discontinue participation in the study.
2. History of injury data for CCS and CTR subjects are collected during Visit 2.
3. Following CCS eligibility to continue participation in study, testing battery will be performed by both CCS and CTR.
4. During Visit 3 and Visit 4, all the assessments in the testing battery will be completed both by CCS and CTR.

The Day of injury is Day 1. Following visit 1, the testing battery will be collected for both the CCS and the CTR subject at three additional time points. Visit 2 will occur at 2 days post-injury. Visit 3 at 7 days post-injury (+/- 1 day), and Visit 4 at 14 days post-injury (+/- 3 days). It's important that subjects are seen exactly at 2, 7, and 14 days post-injury. For instance, if subject sustains an injury on January 3, 2016 – Visit 2 will be on January 5th, visit 3 will be on January 10th and visit 4 will be January 17th.

The study windows are meant for unforeseen circumstances. Please notify the site Investigator for approval if the subject needs to be seen within the study window.

During all the visits in cohort 2 EYE-SYNC must be performed after administering level of alertness questionnaire and to be performed 3 times consecutively.

Please note: If a CTR subject sustains a concussion at any point while enrolled as a control, he/she will be withdrawn from the study and the paired CCS subject will continue on with the study visits without a CTR subject. The CTR subject will not be allowed to enroll as a CCS subject for the study.

If a CCS subject sustains a second concussion, he/she will be withdrawn from the study and the paired CTR subject will continue on with the study visits without a CCS subject.

3.0.1 Withdrawal of subjects

If a subject first agrees to participate and then changes his/her mind, the subject is free to withdraw consent and discontinue participation at any time. The subject's decision will not affect his/her ability to receive medical care and the subject will not lose any benefits to which he/she would otherwise be entitled.

If a subject decides to withdraw consent to participate in this study, the subject should notify the site Investigator. The subject may ask to have their data withdrawn from the study database. The subject has the right to refuse to allow his/her data to be studied now or saved for future study.

The Protocol Director may also withdraw a subject from the study without consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff (non-compliance).
- The Protocol Director decides that continuing participation could be harmful to the subject.
- Pregnancy
- The subject becomes no longer eligible to complete follow-up sessions due to no longer meeting eligibility requirements.
- Need of treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

If subjects are withdrawn from the study due to non-compliance or protocol director decision the subject will have the option to withdraw the data.

3.1 Study Outcome Evaluations

3.1.1 Study endpoints

Our primary endpoint will be the acquisition of sufficient data to establish integrity and reliability of EYE-SYNC data and to compare and characterize trajectories of EYE-SYNC measurements in injured versus non-injured athletes.

Our secondary endpoint will be to characterize interrelationships among variables relevant to concussion including DEM, ANAM-SRT, and SCAT-3 scores with EYE-SYNC.

If subjects are withdrawn from the study due to non-compliance or Protocol Director decision the subject will have the option to withdraw the data as described above.

3.1.2 Planned Data Analysis and Sample Size Determination

Descriptive Statistics: We will provide descriptive statistics for all subjects included in our study. Specifically, for continuous variables such as age, and scores from DEM, ANAM-SRT, SCAT-3, and EYE-SYNC, we will provide means, medians, standard deviations and interquartile ranges. For categorical variables such as race, ethnicity and previous history of injury, we will present frequency distributions. We will utilize graphical tools such as histograms and box plots to describe distributions of continuous variables. If needed to adhere to modeling assumptions, we may consider transformations of outcomes, such as a log transformation.

Handling of Missing Data: We anticipate minimal missing data in this study. We expect that a small proportion of subjects recruited for the longitudinal study (1%) will not complete all visits. We will fully describe missing data for each variable and any pertinent patterns of missingness (e.g., how missingness is related to specific baseline measurements or time, if at all). The statistical methods we propose are particularly flexible for missing data and allow for systematic missingness that is related to observed features.

Statistical Tools for Each Aim: Our first aim addresses the integrity of data generated by EYE-SYNC. Specifically, in Aim 1A, we will characterize the feasibility of collecting and generating data in real-time as injuries occur by considering the proportion of time we are able to collect 3 subsequent measures using EYE-SYNC on the sideline in the field from a case using data from cases included in *Cohort 2* (described above). We deem EYE-SYNC to be a promising tool to be used on the field if we are able to make use of it 90% of the time. This will be tested using a one-sided exact binomial test. With 50 cases, we have excellent power to evaluate feasibility. More specifically if we use a decision rule such that we conclude EYE-SYNC to be a promising and practical tool to be used in the field if we have complete information on 40 of the 50 cases, we have over 95% power when the true rate of complete data is 90% with a type I error of 0.04 under the null hypothesis that an unacceptable rate of complete data is 70%.

The goal of Aim 2 is to assess whether data from EYE-SYNC correlates with clinically meaningful endpoints. To that end, we will create *Cohort 2* by collecting data (in replicates of 3) Immediately Post Impact, 2 days from injury, 7 days from injury and 14 days from injury from 50 cases (defined as those who experience impact where concussion is highly suspected) and 50 matched controls (a teammate who did not experience impact but who was participating in the same sport and session along with the injured teammate at the time of injury). Using mixed effects regression techniques, we will examine whether the trajectory of EYE-SYNC changes over time for those injured differs significantly from those who were not injured. In addition, we will characterize trajectories of change in EYE-SYNC over time for those injured and for athletes who are injury free. Such models account for the correlation of scores within a subject over time as well as for the matched pairing of cases and their corresponding teammates. In addition, such models are robust to assumptions regarding missing data.

The goal of Aim 3 is to describe interrelationships among relevant variables used to describe concussion and EYE-SYNC. This aim is fairly exploratory but will pave the way for future studies. We will rely on mixed effects techniques to characterize relationships of interest

3.1.3 Data and Safety Monitoring and Training

The research team will consist of investigators and research assistants familiar with the administration of EYE-SYNC goggles, desktop eye-tracking, and ANAM-SRT. Appropriate personnel will undergo extensive training in the administration of Developmental Eye Movement Test (DEM) and SCAT3 to establish high inter-rater reliability. Additionally, the Stanford will provide Academic Research Organization services (coordination and monitoring), data management and statistical analysis.

3.0 RISK ANALYSIS

3.1 Anticipated risks

All of the research procedures are minimal risk and non-invasive. This is not a treatment study and no alternative procedures or courses of treatment are available. The only alternative for subjects is to not participate. No standard treatment will be withheld. However, all research is subject to some minimal risk and may include:

1) Some of the interviews/questionnaires will ask personal information. All personal information is treated as confidential and will be de-identified.

2) Subjects may experience some fatigue as a result of participating in some of the cognitive tests. The amount of fatigue may be similar to, i.e. studying for an exam, or attending a class.

3) Subjects may experience some watering of the eyes from keeping their eyes open during administration of the EYE-SYNC test. Blinking can relieve this.

4) It may be inconvenient for subjects to travel to scheduled appointments, when travel is necessary.

5) There may be risks or discomforts related to study procedures that are not currently foreseeable.

3.2 Adverse event reporting

3.2.1 Adverse event definitions

Unanticipated adverse device event (UADE): Any serious adverse event on health or safety or any life-threatening problem or death caused by, or associated with, a device, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Associated with the investigational device: There is a reasonable possibility that the adverse event may have been caused by the investigational device.

Life-threatening adverse event: Any adverse event that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the event **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event: An adverse event is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

Unanticipated adverse event: Any adverse event, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol.

3.2.2 Recording and assessment of adverse events

All observed or volunteered adverse events (serious or non-serious) regardless of treatment group (Control or Concussed), if applicable, or suspected causal relationship to the investigational device or, if applicable, other study related procedure will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse events felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the sponsor.

3.2.3 Causality and severity assessment

The sponsor will promptly review documented adverse events and abnormal test findings to determine 1) if there is a reasonable possibility that the adverse event was caused by the investigational device or other study treatments; and 2) if the adverse event meets the criteria for a *serious adverse event*.

If the sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the adverse event will be classified as *associated with the use of the investigational device or other study treatments* for reporting purposes. If the sponsor's final determination of causality is "unknown but not related to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case history.

3.2.4 Reporting adverse events to the FDA

For any observed or volunteered adverse event that is determined to be a UADE, the sponsor will submit an expedited safety report to the FDA's Center for Devices and Radiological Health. The expedited safety report will consist of:

- a completed Form FDA 3500A
- a cover letter analyzing the significance of the event

A copy of this safety report will be provided to all participating study investigators.

The completed Form FDA 3500A and cover letter will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor first receives notice of the adverse event.

If, following receipt and investigation of follow-up information regarding an adverse event that was previously determined not to be a UADE, the sponsor determines that the event does meet the requirements for expedited reporting, the sponsor will submit a completed Form FDA 3500A and cover letter as soon as possible, but in no event later than 10 working days, after the determination is made.

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor will submit additional information concerning the reported adverse event as requested by the FDA.

3.2.5 Reporting adverse events to the responsible IRB

For any adverse event determined to be a UADE, the sponsor will submit the completed Form FDA 3500A and cover letter to the IRB as soon as possible and, in no event, later than 10 working days after the sponsor first receives notice of the adverse event.

Follow-up information to reported adverse events will be submitted to the IRB as soon as the relevant information is available.

3.3 Withdrawal of subjects due to adverse events

If a subject is withdrawn from continued exposure to the investigational device or, if applicable, other study treatment or diagnostic product(s) due to an observed or volunteered adverse event, appropriate reports will be filed with the FDA and IRB, the subject's withdrawal will not affect his/her ability to receive future medical care, and the subject will not lose any benefits to which he/she would otherwise be entitled.

Adverse events or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the adverse event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor.

The subject may ask to have their data withdrawn from the study database. The subject has the right to refuse to allow his/her data to be studied now or saved for future study.

4.0 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The EYE-SYNC® portable assessment system consists of two primary components enclosed in a portable aluminum case. The eye tracker is a handheld isolated display environment with embedded eye tracking sensors. The eye tracker is connected to a high-performance Windows tablet though a customized docking station. Included accessories with EYE-SYNC are a U.S. tablet power supply adapter and disposable sanitary masks. Subjects are asked to follow a dot as it moves on the screen.

5.0 MONITORING PROCEDURES

Monitoring of the study for compliance with the clinical protocol will be conducted periodically (at a minimum, annually) by qualified staff of the Stanford Concussion and Brain Performance Center. The address of the Stanford Concussion and Brain Performance Center is listed below.

Stanford Concussion and Brain Performance Center
1050 Arastradero Road, Suite A233
Palo Alto, CA 94304
Phone: +1.650.497.7045
Fax: +1.650.498.2566

The sponsor\ and the collaborating institution study sites will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

6.0 INFORMED CONSENT

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor will prepare the informed consent form (ICF) and HIPAA authorizations based on samples attached, and provide the documents to their local IRB or Central IRB for approval. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Sponsor will retain an IRB-approved copy of the ICF in the study master file. A copy of he approved ICF and HIPAA will be submitted to Stanford.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study.

A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

7.0 IRB INFORMATION

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. UADEs will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to the Stanford Concussion and Brain Performance Center prior to the site initiation visit. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

8.0 ADDITIONAL RECORDS AND REPORTS

8.1 Data handling and record-keeping

A Case Report Form will be completed for each subject enrolled into the study. The site-investigator will review, approve and sign/date the completed CRF; the sponsor's signature serving as attestation of the sponsor's responsibility for ensuring that all data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

8.2 Record maintenance and retention

The sponsor will maintain records to include:

- Any FDA correspondence (e.g., Form FDA 3500A, notice of device recall or disposition, and failure to obtain informed consent reports)
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports.
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed Investigator's Agreements
- Curriculum vitae (all research staff at site)
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor and listed sub-investigators and staff
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Instructions for on-site preparation and handling of the investigational device and other study-related materials
- Signed informed consent forms
- Completed Case Report Forms
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of sponsor correspondence to sub-investigators, including notifications of adverse event information
- Subject screening and enrollment logs
- Subject identification code list
- Investigational device accountability records
- Interim data analysis report(s)
- Final clinical study report.

All subject-specific data and Case Report Forms (CRFs) will be coded with a non-identifiable subject number, and the subject identification code list, will be stored so as to protect the subjects' confidentiality. Specifically, each subject is assigned an ID number that is kept separate from the subject's personal health information (PHI). Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

Confidentiality of all subject-specific data and CRFs will be maintained by using only computers for data storage that are password protected and accessible only to study personnel; anonymizing all data if used for publishing the results of the study; keeping all data storage media, like CDs, memory sticks, and printouts within locked areas. Only the study personnel will have access to any data being stored. Electronic files are protected using password protection and paper records in locked rooms. The Principal Investigator may share the results of these studies with the subjects and/or their caring physician if clinically warranted and authorized.

The Sponsor will retain the specified records and reports for a minimum of three years past the completion of the research.