AD_____

AWARD NUMBER: W81XWH-14-1-0561

TITLE: Comprehensive Study of Acute Effects and Recovery After Concussion

PRINCIPAL INVESTIGATOR: Michael McCrea, PhD, ABPP

CONTRACTING ORGANIZATION: Medical College of Wisconsin, Inc.
Milwaukee, WI 53226-3548

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	30 Sep 2015 - 29 Sep 2016

4. TITLE AND SUBTITLE

Comprehensive Study of Acute Effects and Recovery After Concussion

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0561

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Michael McCrea, PhD, ABPP

Professor & Director of Brain Injury Research, Department of Neurosurgery

E-Mail: mmccrea@mcw.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226-3548

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: Utilizing a multi-dimensional research model, this study integrates biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, with the ultimate goal to more fully inform a neurobiopsychosocial model of mTBI risk, recovery and outcome. With the goal of baseline testing 900 athletes and enrolling 50 injured athletes and 50 contact and 50 non-contact controls over the course of 3 years, the project is progressing on schedule and on budget. In the first 2 years of the study, we have enrolled 865 at baseline and accrued 62 concussed athletes in the multidimensional postinjury protocol, along with 54 non-injured control athletes. All groups are undergoing follow up evaluations within 6 hours of injury, 48 hours after injury, and 8, 15, and 45 days after injury. These evaluations include advanced brain neuroimaging, blood biospecimen collection, and clinical testing measures assessing balance, neurocognition, symptoms, and psychological health, which will be correlated with data from the Head Impact Telemetry system (HITS). Data analyses are underway, with our investigative team developing advanced database platforms and analysis techniques. Major progress has been achieved with regard to an advanced platform and "pipeline" for MRI data processing, quality control and integration. Ongoing collaboration with co-investigators and our project partners has guided us to a successful launch of this comprehensive study, which will lead to advancing the science of mTBI and improving clinical care in military, sports, and civilian populations. This project's focus on high school and lower level collegiate athletes makes it fully distinct from the NCAA-DoD CARE Consortium. The combined findings from both studies are predicted to have major translational impact on the science and clinical care for concussion in all populations, including the settings of military medicine and civilian trauma.

15. SUBJECT TERMS
Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	26	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. INTRODUCTION:

During the acute phase, mild traumatic brain injury (mTBI) is known to cause serious disruption in normal biological, cognitive, and behavioral function. While research over the last decade has significantly advanced the science of mTBI, a comprehensive neurobiopsychosocial model of mTBI has yet to be achieved. With the goal of conducting a comprehensive study of mTBI, we hypothesize that there will be a significant correlation between biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, which will more fully inform a neurobiopsychosocial model of mTBI. The overarching aim of this proposal is to investigate the predictive and correlative value of multiple diagnostic and prognostic markers of mTBI in a common injured sample and single study design, including:

- Advanced brain neuroimaging to study changes in brain structure and function
- Blood biomarkers to study changes in brain biochemistry and physiology
- Head impact sensor technologies to study the kinetics and kinematics of concussion and the effects of repetitive, subconcussive head impacts
- Genetic testing to study the influence of genetics on risk of mTBI and post-concussive recovery
- Clinical measures of postconcussive symptoms, neurocognition, balance, psychological health, and other functional capacities to correlate with neurobiological, neuroimaging, biomechanical and genetic markers of injury

Please see section 9 (Appendices, Table 2) for a more detailed summary of this study's technical objectives and specific scientific aims.

2. KEYWORDS:

Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major tasks of this project are designed to successfully achieve the specific technical objectives and scientific aims of the study (see Appendices). Please find below a summary of the major tasks, projected timeline, level of completion as of the current reporting period, in accordance with the approved Statement of Work (SOW).

We have completed a significant amount of work toward accomplishment of the major tasks and subtasks for the current reporting quarter and year, as described below. The major tasks and subtasks for this project are also being coordinated and completed in sequence with planning and execution of the NCAA-DoD Grand Alliance Advanced Research Core (ARC), given the scientific and operational benefits of synchronization between the two projects.

Major Tasks from Statement of Work (SoW)	Timeline (months)	Date or % of completion
Major Task 1: Finalize Project Contracting, Regulatory, and Operational Processes	1-6	100%
Major Task 2: Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4	1-6, Ongoing	90%
Major Task 3: Data Collection (post-IRB approval)	7-48	65%
Major Task 4: Data Management, Analysis & Dissemination	1-48	40%

What was accomplished under these goals?

The tables below provide an update on the status of our progress associated with each of the Major Tasks and Subtasks for the project, in accordance with the approved SoW for this project.

Major Task 1: Finalize Project Contracting, Regulatory, & Operational Processes	**Months 1-6**

Subtask 1 - Contracting

- Received modification to add additional funds on November 5, 2015; modification formally processed by MCW
- Renewed Banyan Biomarkers subcontract through December 31, 2016

Subtask 2 – Human Subjects Research

- Full IRB approval granted on April 14, 2015, data collection underway
- First continuing progress report submitted to IRB on February 2, 2016; approved on March 22, 2016
- Continuing progress report submitted to HRPO on March 24, 2016; approved on July 10, 2016
- Amendments submitted and approved by MCW IRB (and HRPO when determined significant)
- Reportable events submitted and acknowledged by MCW IRB and HRPO
- Post Morten Human Surrogate (PMHS) testing protocol approved locally on Apr 4, 2016, approved by HRPO on May 27, 2016

Subtask 3 – Project Staffing and Operations

- Staff hired and trained for fall 2016, including baseline testing technicians and head impact sensor operators
- Hired a programmer analyst and a research scientist to support MR infrastructure and pipeline model

Subtask 4 – Project Management

- Standing weekly laboratory meeting to facilitate project planning and monitor progress continued

- Additional meetings with core subject matter experts occurring at regular intervals to ensure consistency with ARC protocol, plan for data dissemination, and plan for data pipelining
- Investigator meeting was held on April 21-22, 2016 in Milwaukee, WI

Major Task 2: Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4	**Months 1-6**

Subtask 1 – Overall Protocol Implementation and Management

- Overall, the project is progressing on schedule and on budget.
- Based on successful enrollment and data collection in fall 2015, plans were executed to expand the enrollment of high school athletes to maximize the study impact and complement the efforts of the CARE Consortium ARC (all D1 college athletes); goal is to increase high school enrollment to complement current high school and NCAA Division III college sample, staying within current project budget and period of performance
- Completed baseline testing on 317 athletes from July 18, 2016 to August 22, 2016, bringing total baseline enrollment to 865
- 625 athletes are active under protocol for Fall 2016, including 228 athletes equipped with the Head Impact Telemetry System (HITS) and 23 equipped with the Prevent Mouthguard
- Of the 625 under protocol, 466 are collegiate athletes and 161 high school athletes
- To date, 62 athletes with concussion were enrolled into the post-injury protocol; an additional 54 non-concussed controls have been enrolled in the parallel protocol.

Subtask SA1 – Advanced Neuroimaging Protocol

- Technical manual for neuroimaging protocol finalized by lead imaging investigator
- Continued development of a robust MRI Informatics Core function at MCW to support pre- and post-processing, advanced algorithm development, analysis pipelines, data scaling techniques, etc. to support this and other studies
- Bi-weekly meetings with imaging investigator team to ensure consistency with ARC protocol, plan for data dissemination, and plan for data pipelining
- Developed Pipeline Model for neuroimaging data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination, which includes implementation of XNAT database and use of Isilon server
- Radiology team following protocol to review MR for incidental findings
- Continued collaboration with GE to implement latest GE TBI research protopak 2 for GE 750 3.0T MRI at MCW
- In collaboration with NCAA-DoD CARE Consortium Advanced Research Core (ARC), significant progress on all aspects of the pipeline augmentation to support quality control and advanced pre- and post-processing methodologies and analytics
- Preliminary analysis of neuroimaging data complete for some modalities for presentation at our 2016 investigator meeting
- Priorities for further MRI data analysis and publications identified and in progress

Subtask SA2 – Blood Biomarkers

- Continued meetings with MCW CTSI Translational Research Unit (TRU) to ensure biospecimen team coverage during assessment time points
- Continued correspondence with Banyan Biomarkers and MCW CTSI TRU to ensure all supplies, protocols, and staffing plans are in place for baseline and postinjury testing
- Baseline and follow up testing samples for injured and contact sport controls sent to Banyan for analysis on February 15, 2016; received data on April 14, 2016
- Preliminary analysis of blood biomarker data presented at our 2016 investigator meeting.
- Preliminary biomarker data presented at 2016 AAN Sport Concussion Meeting in Chicago
- Publication of findings from first flight of biomarker analysis, comparing concussed and control athlete levels at baseline and during the acute phase (<6 hours and 24-48 hours post), is in process
- Ongoing biomarker analysis being conducted in parallel to ARC analysis in Division I college athletes
- Additional priorities for further biomarker data analysis and publications identified and in progress

Subtask SA3 – Head Impact Sensors

- Data collection specifics finalized to reflect ARC to ensure data integration across studies
- Continued collaboration with ARC Head Impact Measurement (HIM) core team around plan for testing and deployment of non-helmeted sensors so to identify technologies fit for research data collection across the current study and ARC
- Coordinating plan for laboratory testing of candidate head impact sensor systems for validation and to inform field deployment of sensor systems for live data collection in this study and ARC
- HIM data analysis being conducted in parallel to ARC analysis in Division I college athletes
- Continued engagement of MCW investigators key to head impact measurement element of study in planning around Pipeline Model for head impact measurement data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination
- Developing stepwise approach to head impact measurement data analysis based on pre-defined hypotheses, core metrics, and analytical methods
- Priorities for further HIM data analysis and publications identified and in progress
- Conducting bi-weekly sessions with HIM team members to do detailed review of head impacts recorded in concussed athletes to assist in correlating HITS data with other study elements (clinical, neuroimaging, biomarker, genetics)
- Preliminary analysis of head impact sensor data presented at our 2016 investigator meeting and multiple conferences
- HITS equipment sent to Riddell for reconditioning to prepare for Fall 2016
- Implemented HITS at 8 data collection sites for the Fall 2016 football season, including Flex sensors
- Limited rollout of Prevent Mouthguard sensor system (Cleveland Clinic) was accomplished for fall 2016 at 3 performance sites. Data collection is ongoing, with plans

for analysis after the season. Findings to help inform plan for use of non-helmeted sensors in the CARE ARC.

Subtask SA4 – Genetic Testing

- Finalized protocol on DNA extraction by engaging MCW Tissue Bank services for extraction and Indiana University for consultation and analysis, IBC, IRB, and HRPO approved
- Coordinated genetics protocol elements, data processing, pipeline and analytics with ARC
- Samples from fall 2015 & 2016 baseline testing processed and stored locally; will wait until the end of baseline data collection for group analysis

Major Task 3: Data Collection (post-IRB approval)	**Months 7-48**

Subtask 1 – Baseline Data Collection Protocol

- Successful baseline data collection on 317 athletes for the Fall 2016 season, bringing total baseline enrollment to 865
- 625 athletes are active under protocol for Fall 2016, including 228 athletes equipped with the Head Impact Telemetry System (HITS) and 23 equipped with the Prevent Mouthguard

Subtask 2 – Postinjury Data Collection Protocol

- To date, 62 athletes with concussion were enrolled into the post injury protocol
- Attrition rate is low (8.7%) with 45 missed visits out of 515 between injured and control groups, including injured subjects who missed a 6 hour evaluation due to late reporting
- Injury accrual ahead of schedule with a total of 62 concussed subjects enrolled and followed in the postinjury protocol (target accrual at this point: 35)

Subtask 3 – Control Group Testing

- To date, 54 non-concussed controls have been enrolled in the parallel follow-up protocol

Major Task 4: Data Management, Analysis & Dissemination	**Months 7-48**

Subtask 1 – Data Management

- Data quality control plan reviewed and revised from existing procedures to handle all data elements
- Finalizing plan for integration of core data elements from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing) with clinical data in REDCap database
- Finalizing plan for connectivity between central REDCap database and repositories holding larger raw data sets from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing)
- Finalized development of separate databases and repositories to hold larger raw datasets from neuroimaging and head impact measurement cores
- Core data elements for current study continually cross-walked with ARC as changes in ARC occur

- Continued engagement with Federal Interagency TBI Research (FITBIR) Informatics System to discuss data submission for head impact measurement data, MR data, and biospecimen data
- 2015 baseline and post-injury clinical data submitted to FITBIR
- 2016 baseline clinical data submitted to FITBIR this past quarter
- Work under way with FITBIR Ops Team for curation and transfer of imaging and biomarker data to FITBIR
- Study PI (McCrea) a member of the NINDS working group for formation of Common Data Elements (CDE) for sport-related concussion. Case Report Forms (CRF) and information on database structure from this study provided to NINDS to facilitate the CDE project.

Subtask 2 – Data Analysis

- Preliminary analysis of clinical, neuroimaging, head impact measurement, and blood biomarker data presented at our 2016 investigator meeting and various conferences
- Ongoing analysis of clinical, imaging, biomechanics and biomarker data underway
- Continued development of pre-defined core metrics and analytical plan to test specific hypotheses within each study core (clinical, head impact measurement, neuroimaging, blood biomarkers, and genetic testing)

Subtask 3 – Dissemination

- The multidimensional and comprehensive research design employed by this study and select preliminary findings have been presented at multiple national and international forums on traumatic brain injury and sport-related concussion over the past year. Please see list of publications and presentations in section 6 (Products) below.
- Continued meetings and discussions with subject matter experts and investigative team to develop analytic plan for dissemination, discussing in particular "early wins" to publish prior to completion of data collection
- Manuscript priority list developed at 2016 investigator meeting, with focus on "early win" publications from data across all modalities (clinical, neuroimaging, biomarkers, head impact measurement)

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

To continue our on-time progress toward accomplishment of the major tasks and subtasks for this project, we plan and will prioritize the following objectives during the next reporting period:

1. **Advanced Neuroimaging Protocol:**
    a. *Imaging Pipeline:* We will continue to refine the pipeline for neuroimaging data processing, transfer, storage, quality control, integration with larger dataset, analysis and dissemination continuously to ensure accuracy. A more robust technology cluster is being leveraged for more efficient and accelerated data processing capabilities.
    b. *Analytics*: We will continue with our a stepwise approach to neuroimaging data analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims, with focus on early win manuscripts.
    c. *Radiology*: Incidental findings will be further evaluated to assess incidence rates and possible relation to mTBI.
2. **Blood Biomarker Protocol:**
    a. *Analysis*: We will conduct our next flight of biospecimen analyses, comparing biomarker levels in concussed and and control samples, when an appropriate number of samples is available to facilitate efficient and cost-effective analysis. This will not be an issue, based on our rate of enrollment and accrual.
    b. *Analytics and Dissemination*: We will continue our stepwise approach to biomarker analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims.
3. **Head Impact Measurement Protocol:**
    a. *Non-helmeted Sensor Technology:* We will continue data collection using the Cleveland Clinic Prevent Mouthguard during the fall 2016 season. These data to be analyzed after completion of the current data collection season.
    b. *HITS*: We will continue data collection using the Riddell Speed and SpeedFlex helmets and sensors in addition to Riddell Speed helmets and sensors during the fall 2016 and 2017 seasons
    c. *Pipeline*: We will further operationalize the pipeline model for HITS and other head impact measurement data processing, transfer, storage, integration with larger dataset, analysis and dissemination prior to implementation to ensure accuracy.
    d. *Quality Control:* We will continue to maintain and further refine a multi-level protocol for monitoring and evaluating data quality.
4. **Genetic Testing Protocol:**
    a. *Analytics*: We will continue development of a stepwise approach to genetic analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims. Analyses to be completed closer to the end of the study, based on accumulating sample size.
5. **Postinjury Data Collection:**
    a. *Contact Sport and Non-Contact Controls*: We will continue with our ongoing recruitment of contact sport controls and do our heaviest recruitment of non-contact sport controls in the winter and spring sports seasons. We do not anticipate any difficulty meeting our targeted samples size for the control groups.

6. **Data Management:**

   a. *Database*: We will continue to refine the architecture and function of our electronic REDCap database according to the protocol specification and required data elements, in parallel to the same for the ARC, in compliance with the NINDS CDE and in working with FITBIR for data transfer.

   b. *FITBIR*: We will continue to work on data submission for clinical and quantitative blood biomarker data. Additional discussions are underway with FITBIR to develop the transfer of imaging and head impact sensor data.

   c. *Quality Control*: We will continue to develop and implement processes to monitor data quality associated with all aspects of the protocol (clinical testing, head impact measurement, neuroimaging, biomarkers, genetic testing).

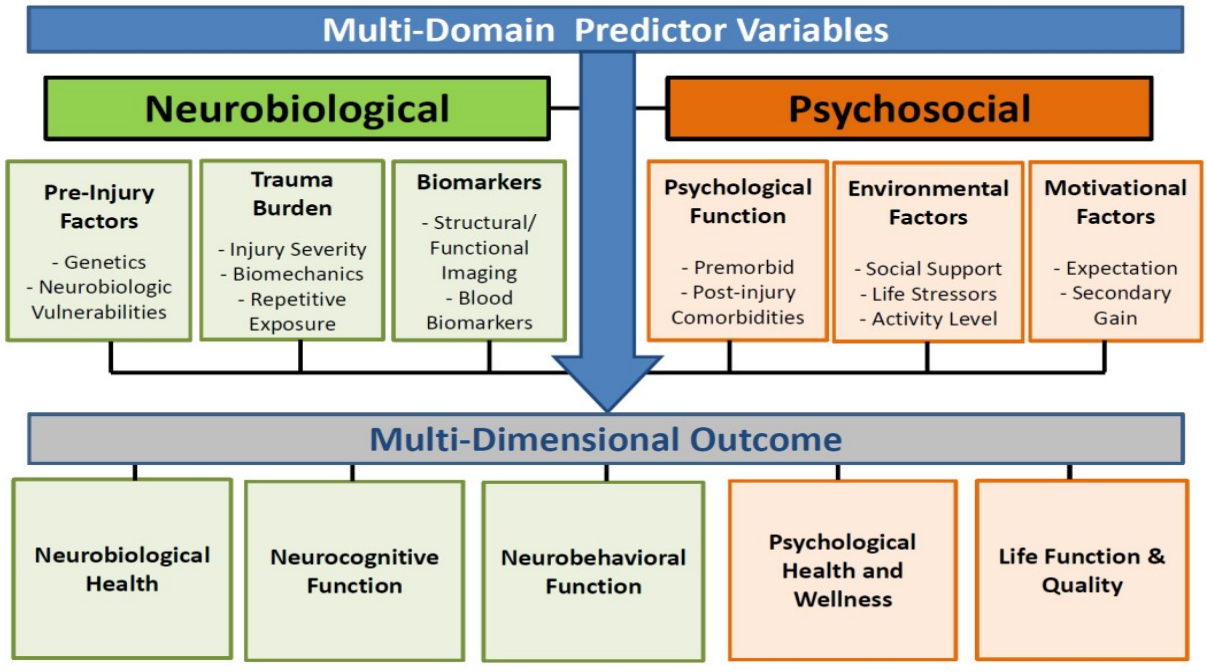
4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

COMPREHENSIVE APPROACH TO STUDY OF TBI

Most importantly, this study will allow us to investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective *in a common injured sample and single study design* (see **Figure 1**). This work will enable a longitudinal perspective on factors that influence both short-range and long-term outcomes after mTBI, and will foster DoD-funded collaboration aimed at informing the broader science of mTBI in military, sports and civilian populations.

Figure 1. Neurobiopsychosocial Model of mTBI



ADVANCED TECHNICAL DEVELOPMENT:

Our investigative team of TBI researchers and imaging scientists has collaboratively developed a cutting-edge, multi-modal MRI protocol targeted specifically at the pathophysiology of SRC and mTBI that will provide benefit to the TBI research community.

Our MRI protocol combines conventional anatomical imaging with advanced, motion compensated MRI acquisition techniques, diffusion kurtosis/tensor imaging (DKI/DTI), susceptibility weighted imaging (SWI) and quantitative susceptibility mapping (QSM), resting state metrics of functional connectivity (rs-fMRI), and blood flow imaging with arterial spin labeling (see **Table 1**). The protocol features a multi-band (8x) accelerated pulse sequence that achieves a high sampling rate while retaining high spatial resolution (2mm isotropic) for robust signal detection in rs-fMRI that is consistent with acquisitions in Human Connectome Project related studies. In addition, we have deployed three advanced pulse sequences and associated innovative data processing and modeling tools that show promise as diagnostic and prognostic biomarkers for diffusion kurtosis imaging (DKI), quantitative susceptibility mapping (QSM), and 3D arterial spin labeling (ASL).

Table 1. MCW Multi-Modal MRI Protocol for Acute Sport-Related Concussion

Targeted Modality	Acquisition Protocols	Reconstruction Requirements	Acquisition Time
	Localizer	Standard	0:30
	Sensitivity map generation	Standard	0:30
Cerebral blood flow	3D enhanced ASL prototype	Standard, flow, transit time corrected flow	4:36
Micro hemorrhage & gray-white matter transition	SWI/QSM (2x1 ARC) prototype	Standard SWI, offline "Orchestra" phase-based imaging and QSM	4:00
Anatomy, gray-white matter segmentation	PROMO MPRAGE prototype	Standard	4:11
Anatomy, edema detection	PROMO T2 FLAIR prototype	Standard	4:42
Anatomy, pial surface segmentation	PROMO T2 prototype	Standard	4:12
White matter integrity & microstructure	DTI/DKI DTI-Distortion Cal	Standard DTI, offline post-processing of DKI from standard DICOM images, including distortion correction	5:30 0:30
Resting state functional connectivity	rs-fMRI with multi-band prototype acquisition (human connectome project harmonized) rs-fMRI-Distortion Cal	Offline "Orchestra" multi-band reconstruction (auto-calibration, slice-GRAPPA unaliasing) Offline, used for rs-fMRI distortion correction	6:00 0:30
Myelin mapping	Inhomogenous broadened magnetization transfer (IhMT) prototype	Standard, quantified MT, quantified IhMT	4:48
		Total Acquisition Time:	40:00

The technical implementation of this innovative TBI imaging protocol has been highly successful based on:

- *Engagement*: This project represents a major collaborative, multidisciplinary effort by highly skilled imaging and neuroscience researchers at MCW.
- *Scanning time*: 40-minute acquisition time.
- *Compliance*: Athletes respond favorably to the procedures and short scanning session.
- *Quality Control*: High resolution imaging with minimal technical error or artifact.
- *Automation*: Customized protocol is essentially a turn-key option for scanner operators.
- *Analytics*: Customized analysis procedures unique to each pulse sequence and modality.
- *Translation*: Targeted modalities and pulse sequences capable of rollout in clinical settings.

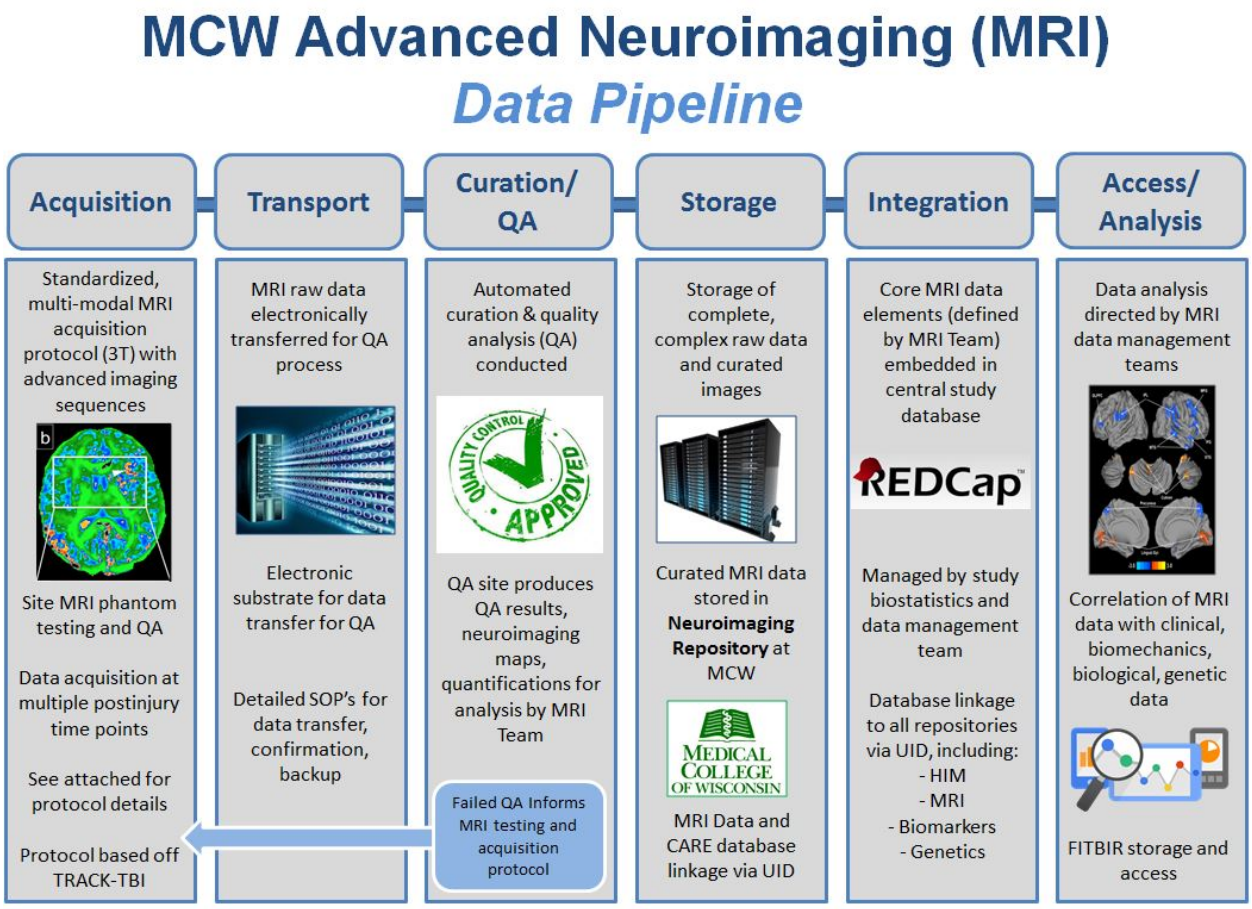
We have cross-walked our MRI acquisition protocol with the GE Research Protopak I/II for TBI and the acquisition protocols for other large research networks such as TRACK-TBI (G. Manley, PI) in order to facilitate eventual sharing/merging of like-set imaging data and enable comparisons of TBI imaging biomarkers across populations at risk (civilians, athletes, military service members). This exercise indicates a high degree of overlap between study protocols. We have merged our acquisition developments with the GE Healthcare traumatic brain imaging "Protopak 2" content to further build cross-study compatibility. This paves the way for further optimization of innovative MRI protocols to be included in other large-scale, national TBI research efforts (e.g., NCAA-DoD Grand Alliance).

POWERFUL IMAGING PIPELINE AND INFORMATICS PLATFORM

Our work supported the development and construction of a technologically advanced platform for MRI post-processing, analytics, transfer and storage that provides a powerful engine to support and accelerate our future research efforts toward advancing the science and clinical utility of MRI biomarkers for concussion and TBI.

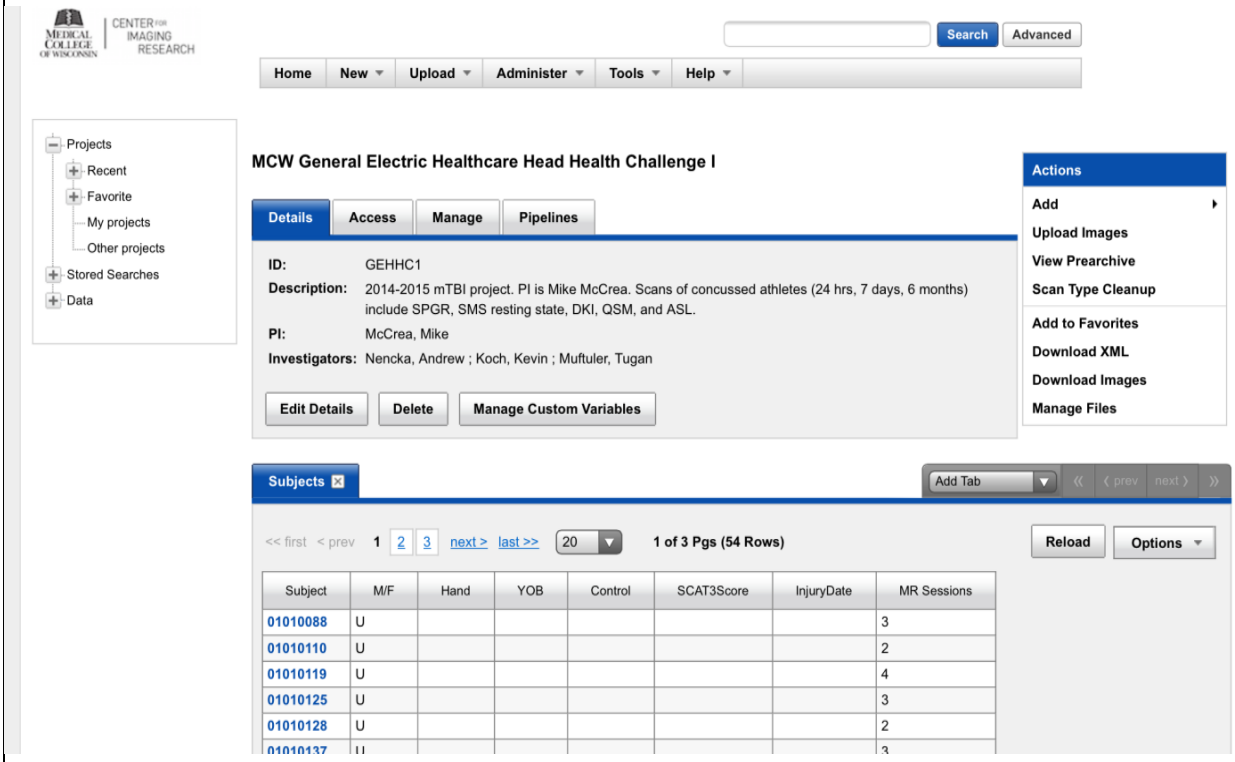
Although not initially proposed in this work, the development of an imaging informatics infrastructure has been part of this first year's progress. Each imaging session includes 12 series, 11,130 images, and over 10 gigabytes of data. Further, a subset of the prototype acquisitions, including the simultaneous multi-slice resting state fMRI and the quantitative susceptibility mapping series require off-line reconstruction of the raw k-space "p-files." With enrollment proceeding as expected and four imaging sessions for each subject, along with a large group of collaborating investigators, a central, organized, automated, and accessible database solution was required. **Figure 2** illustrates the stepwise architecture of our "pipeline" for imaging acquisition, transport, curation and quality control, storage, analysis and integration with other rich clinical datasets (see **Figure 2**). This approach was modeled after centers leading other large research efforts employing advanced MRI in the study of concussion and TBI, such as TRACK-TBI (G. Manley, PI).

Figure 2. MCW Advanced Neuroimaging Pipeline



The eXtensible Neuroimaging Archive Toolkit (XNAT, www.xnat.org) was selected to serve as the central repository for this work (**Figure 3**). XNAT offers a number of compelling features that make it ideally suited for this job. A web-based user interface facilitates team member access to the repository, which is organized hierarchically by project, subject, session and series. DICOM images acquired on the research-dedicated MCW Discovery MR750 can be directly pushed to a DICOM listener integrated into the XNAT deployment, and then automatically integrated into the image database, or archived data sets may be uploaded through the web interface. Underlying the web interface is a PostgreSQL database that can be accessed through a representational state transfer application program interface (REST API). This powerful architecture enables programmatic queries of the image and metadata database and scripting of custom processing pipelines. We have built a Python interface for scripting XNAT processing through the REST API. Work is ongoing to further integrate raw "p-file" storage and automatic Orchestra-based p-file reconstruction via "son of recon" programs automatically initiated by the acquisition pulse sequence through this XNAT REST API. While processing pipelines are prototyped outside of the XNAT framework, finalized pipelines are to be integrated into the XNAT service to further streamline data processing.

Figure 3: MCW XNAT Web Interface for this Brain Injury Research



This XNAT deployment is, in practice, a constellation of computing hardware installed in the MCW Research Computing Center. Three separate servers are each running an instance of XNAT, including a gateway server for data transfers with off-site collaborators and a pair of servers to host redundant XNAT instances of the central database. Images in the central database are stored on an 1.2 PB Isilon storage system, which is backed up through snapshots, mirroring to an additional Isilon storage system, and magnetic tape archiving. The XNAT deployment is further designed to offload processing intensive tasks to other resources of the MCW Research Computing Center, including a 538-core MPI cluster, a large (3Tb) memory system, and four general purpose graphical processing unit (GPU) systems, each with four Nvidia K40 GPUs. Each of these computing units are interconnected with 10 gigabit Ethernet, while internal communication for each unit is maintained with infiniband connections. The XNAT servers are further connected to the general MCW network and pass through the Froedtert Hospital firewall for direct DICOM image pushes to the McKesson PACS for over reads of selected image series.

The XNAT deployment is being further extended to support other mTBI studies at MCW, including the Advanced Research Core of the NCAA/DoD CARE project and the locally conducted GE-NFL Head Health Challenge phases I and II. Reciprocally, data to be acquired in ongoing projects will be used to further refine the data handling and processing software deployed in XNAT. Through this work, MCW will ultimately host the definitive sport related concussion imaging database in this XNAT deployment.

A software developer has joined the team to further accelerate the refinement of this XNAT platform and add automation. To streamline the process of imaging over reads by radiologists on this team, the process of sending images to McKesson PACS has been automated such that once an exam is imported, relevant images are parsed, tagged, and transferred to PACS. Additionally, further automation has been achieved in pre-processing imaging data. Diffusion processing pipelines, including geometric distortion correction, registration, and parameter estimation are now launched automatically when data are imported into the database. Similar automated pipelines are in place for the registration of anatomical images to the Montreal Neurological Institute's template. Pipelines for fMRI processing have been deployed on the Research Computing Center cluster to interactively launch more extensive processing. Continuing work will further advance the automation of such processing.

The XNAT deployment in support of this work is archiving imaging data, serving as the single source of truth for both raw and processed data. The pipeline architecture is ensuring rigorous, consistent processing across the large number of scanning sessions. The pipelines further output quantitative quality assurance metrics which enable the objective sorting of data.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to report at this time, although we anticipate that our efforts toward building a unique, technologically advanced TBI MRI informatics system has great potential for technology transfer and product deployment in the future. The XNAT platform at MCW has grown to support other large neuroimaging studies focusing on TBI, epilepsy, and Alzheimer's disease.

What was the impact on society beyond science and technology?

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery) (see Figure 1).

In parallel, the aims of this proposal align directly with the DoD's priorities to develop evidence-based approaches to improving the medical care, health and welfare of our military service members affected by TBI. The findings of this study are expected to directly impact the current and future state of military medicine relevant to the diagnosis, treatment and prevention of mTBI in military service members. To date, we lack an integrated neurobiopsychosocial model of mTBI in civilians that can effectively guide evidence based approaches to best practice in the diagnosis, assessment and management of persons affected by mTBI.

The proposed work will foster several lines of collaboration with other DoD-funded investigators conducting innovative TBI research, all aimed at informing the broader science of mTBI in

military, sports and civilian populations. This study is designed to significantly advance our understanding of mTBI in such a way to not only benefit the military and sports medicine sectors, but also improve care for patients in our society affected by mTBI.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Non-Helmeted Sensor Technology: In collaboration with the ARC HIM Core team, we continue to assess the landscape of non-helmeted head impact sensors that a) have proper level of preliminary validation to support their use in research efforts, b) have a platform for large scale production to meet our needs, and c) are feasible for field use (with acceptable athlete compliance). As noted above, we conducted a limited rollout of the Prevent mouth guard sensor in the fall 2016 football season. Data collection is underway, to be followed by analysis and report out of these data.

We continue to evaluate all options for non-helmeted sensors focusing on both the safety of athletes and accuracy of data collection. Our team is conducting internal laboratory testing of candidate sensors at MCW, and collaborating with other groups doing the same elsewhere to best inform adoption of viable technologies for field deployment.

Actual or anticipated problems or delays and actions or plans to resolve them

Head Impact Sensor Technology: As noted above, we continue to encounter challenges in identifying non-helmeted head impact sensors that a) have proper level of preliminary validation to support their use in research efforts, b) have a platform for large scale production to meet our needs, and c) are feasible for field use (with acceptable athlete compliance). We continue to evaluate all options for non-helmeted sensors focusing on both the safety of athletes and accuracy of data collection. Please see above the planned approach with respect to continued data collection and analysis for the Prevent mouth guard sensor.

Non-Contact Controls: In keeping with our common approach, we will continue with our ongoing recruitment of contact sport controls and do our heaviest recruitment of non-contact sport controls in the winter and spring sports seasons. We do not anticipate any difficulty meeting our targeted samples sizes for the study control groups.

Changes that had a significant impact on expenditures

We are currently underspending for this project, due to a combination of factors outlined below. We anticipate that spending for the overall period of performance for the project will come in at budget. The following changes had an impact on spending during the current reporting period:

- Salaries & Fringe
    - We did not conduct baseline testing in Spring 2015 or 2016 which resulted in a surplus of baseline technician hours.
    - The biomechanics technicians require less time to manage only one head impact sensor system at their respective sites.

- The fringe benefit rate for MCW decreased to 20% in FY17.

- Equipment
  - Funds will be used over years 3-4 to pay for Isilon server purchase.
- Supplies
  - Other than a small amount to purchase i1 mouth guard system and Prevent mouthguards, we have not used the majority of funds budgeted for non-helmeted sensor system.
- Travel
  - There has been limited conference travel and no IPR attendance travel to date.
- Subcontracts
  - Banyan subcontract period of performance did not start until Jan 1, 2015. Costs were shifted into years 2-3.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

- Significant Amendments submitted to MCW IRB:
  1. Research MR Sequences Considered Device and i1 Mouthguard Discontinuation due to UPIRTSO. Approved by the MCW IRB on Oct 15, 2015, submitted to HRPO on Oct 10, 2015
  2. Addition of Prevent Mouthguard with impact monitoring. Approved by the MCW IRB on Jul 27, 2016, approved by HRPO on Aug 15, 2016
- Reportable Events submitted to MCW IRB:
  1. First incident of chipped tooth while wearing i1 mouth guard. Acknowledged by MCW IRB on Sept 14, 2015. Two additional incidences of chipped teeth while wearing i1 mouth guard. Acknowledged by MCW IRB on Oct 15, 2015. UPIRTSO report acceptance by HRPO on Feb 17, 2016
- PMHS testing submitted to VA Research and Development Committee
  1. PMHS testing protocol of head impact measurement sensors registered with Zablocki VAMC, Approved by the Subcommittee for Research Safety on Mar 4, 2016 and approved by the Research and Development Committee and authorized by Associate Chief of Staff for Research and Development on Apr 4, 2016, approved by HRPO on May 27, 2016

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications

Meier TB, Nelson LD, Huber DL, Hayes RL, McCrea MA. (in prep). Prospective assessment of acute and sub-acute blood markers of brain injury following sport-related concussion.

Shah A, Murtha J, Humm J, Sjoquist D, Chiariello R, LaRoche A, Stemper B, McCrea M. (awaiting publication). Comparison of Head Impact Measurement Data Collected During Routine Participation of Division III College Football Players. Biomed Sci Instrum.

Books or other non-periodical, one-time publications

Nothing to report for the current funding period

Other publications, conference papers, and presentations

Hainline B, McCrea M. The NCAA-DoD CARE Consortium: A Unique Collaboration. Presentation at the BigTen Ivy League TBI Summit; July 14, 2016, Philadelphia, PA.

Huber, D, Thomas, D, Danduran, M, Meier, T, McCrea, MA, Nelson, LD. Leveraging mobile technologies to assess athletes' activities after sport-related concussion. Poster presented at the Milwaukee Regional Research Forum (MRRF); Oct 24, 2016, Milwaukee, WI.

McCrea M. Future Directions in TBI Research: Leveraging Sports Concussion Research Toward a Neurobiopsychosocial Model. Presentation at the University of Calgary; February 27, 2016, Calgary, CA.

McCrea M. Advances in the Neurobiology of Concussion. Presentation at the International Brain Injury Association Congress; March 1, 2016, The Hague.

McCrea M. State of the Science in Sport-Related Concussion: How Far Have We Come and Where Do We Go Next? Presentation at the Sports Neuropsychology Society Annual Concussion Symposium; April 30, 2016, Houston, TX.

McCrea M. Neurobiopsychosocial Model of Concussion Recovery. Presentation at the American Academy of Neurology Sports Concussion Conference; July 8, 2016, Chicago, IL.

McCrea M, Giza C. The New Neurometabolic Cascade and A Comprehensive Model of Concussion; Looking to Science to Drive Clinical Practice. Presentation at the National Academy of Neuropsychology Conference; November 6, 2015, Austin, TX.

McCrea M, Giza C. Modern Advances in Mild Traumatic Brain Injury: From Basic Science to Clinical Translation. Presentation at the American Academy of Clinical Neuropsychology Conference; June 10, 2016, Chicago, IL.

McCrea M, Iverson G. Mild Traumatic Brain Injury and Postconcussion Syndrome: How Does the Science Translate to Clinical Practice? Presentation at the International Neuropsychological Society Conference; February 4, 2016, Boston, MA.

*Meier TB, Nelson LD, Huber DL, Hayes RL, McCrea MA. Prospective assessment of acute and sub-acute blood markers of brain injury following sport-related concussion. Data blitz and poster presented at the American Academy of Neurology 2016 Sports Concussion Conference; July 8-10, 2016, Chicago, IL.

Shah A, Chiariello R, LaRoche A, Stemper B, McCrea M. Project Head to Head II: Year one review. Poster presented at the Annual National Neurotrauma Symposium; June 26-29, 2016, Lexington, KY.

Shah AS, Stemper BD, Murtha JK, Chiariello RA, Humm JR, LaRoche A, McCrea M. Subconcussive head impact exposure for concussed and non-concussed division III football athletes. Conference paper and presentation at the Summer Biomechanics, Bioengineering and Biotransport Conference; June 29-July 2, 2016, National Harbor, MD.

Shah A, Stemper B, LaRoche A, Wang Y, Chiariello R, Nelson L, McCrea M. Correlation between significant subconcussive head impact exposure and post-season clinical changes in football players. Poster presented at t the American Academy of Neurology 2016 Sports Concussion Conference; July 8-10, 2016, Chicago, IL.

Wang Y, Nelson L, LaRoche A, Nencka A, McCrea M. Dynamic changes of cerebral blood flow during acute and subacute stages of sports-related concussion. Data blitz and poster presented at the American Academy of Neurology 2016 Sports Concussion Conference; July 8 -10, 2016, Chicago, IL.

- **Website(s) or other Internet site(s)**

Nothing to report for the current funding period

- **Technologies or techniques**

Please see section 4 (Impact) above on MR imaging informatics platform technologies developed as part of this effort.

- **Inventions, patent applications, and/or licenses**

Nothing to report for the current reporting period

- **Other Products**

1. REDCap database built for clinical data collection, being refined for MR, head impact measurement, and blood/genetic data.
    a. Our REDCap database for this study will be leveraged to facilitate a project led by the NINDS toward development of Common Data Elements (CDE) for sport-related concussion.
2. XNAT database platform developed for neuroimaging raw data.
3. Custom database platform designed for head impact measurement raw data.
4. EMC Isilon server set up for data storage.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Our investigative team for the current project includes clinical and scientific experts within and across all core elements of the study, including clinical, head impact measurement, neuroimaging, biomarkers, and genetic testing. In addition to our key personnel, we have engaged subject matter experts from the ARC investigative team to ensure proper linkage between the two projects for purposes of protocol synchronization and eventual data integration. The following list includes all personnel contributing to work associated with the current project, regardless of funding source.

Name	Project Role	Percent Effort	Contribution to Project
Michael McCrea, PhD	PI	25%	Oversight of project, responsibility for scientific integrity, operational execution, fiscal performance
Lindsay Nelson, PhD	Co-I, Clinical Core	25%	Project design and execution; Database engineering and refinement of clinical protocol
Timothy Meier, PhD	Neuroscience Faculty, MRI & Biomarker Cores	25%	Implementation of protocol for multi-modal MRI data and biomarker acquisition, processing, storage, integration, and analysis
Melissa Lancaster, PhD	Clinical Post-doc	25%	Execution, processing and analysis associated with clinical and neuroimaging studies
Andrew Nencka, PhD	Imaging Faculty, MRI	15%	Lead technical expert on multi-modal MRI protocol for current study;

	Core		Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Shi-Jiang Li, PhD	Co-I, MRI Core	7.5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Matthew Budde, PhD	Co-I, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Kevin Koch, PhD	Imaging Faculty, MRI Core	5%	Technical lead for ARC MRI core and liaison to current study; Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
L. Tugan Muftuler, PhD	Imaging Faculty, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Yang Wang, MD, PhD	Imaging Faculty, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Ron Hayes, PhD	Co-I, Banyan Biomarkers, Biomarker Core	5%	Development and implementation of protocol for biomarker collection, processing, storage, integration, and analysis
Brian Stemper, PhD	Co-I, Head Impact Measurement Core	20%	Co-lead of ARC head impact measurement (HIM) core; assist in development and implementation of protocol for head impact measurement data acquisition, processing, storage, integration, and analysis
Alok Shah, MS	Engineer, Head Impact Measurement Core	36%	Development and implementation of protocol for HIM data acquisition, processing, storage, integration, and analysis
John Humm	Engineer, Head Impact Measurement Core	2.5%	Assist in development and implementation of protocol for HIM data acquisition, processing, storage, integration, and analysis
Jennifer Hill, MA, CCRC	Program Manager, Project	25%	Operational and fiscal management of project

	Coordinator		
Katie Krahn	Program Coordinator	30%	Support project functions related to participant scheduling, reimbursement, inventory management
Ashley LaRoche, CCRC	Study Coordinator	60%	Operational coordination of project, regulatory and IRB processes, protocol implementation
Robyn Furger, MA CCRC	Research Coordinator	10%	Assisting in protocol planning and operations, clinical data collection and entry
Alexa Wild	Research Assistant	60%	Assisting in protocol planning and operations, clinical data collection and entry
Amy Nader	Research Assistant	40%	Clinical data collection and entry
Nicholas Guzowski	Research Assistant	35%	Clinical data collection and entry
Abby Klemp	Research Assistant	30%	Clinical data collection and entry
Mary Gonring	Research Assistant	30%	Clinical data collection and entry
Daniel Huber	Research Technologist	50%	FITBIR liaison and data quality specialist
Rachel Chiariello	Research Technologist	30%	Development of HIM data pipeline and injury identification
Lezlie Espana	Research Technologist	20%	MRI data quality assurance and processing
Habib Al Saleh, PhD	Research Scientist	25%	MRI data quality assurance and pipeline
Brad Swearingen	Programmer Analyst	15%	MRI pipeline construction and maintenance

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Changes to McCrea Other Support

Added:

GE Healthcare and Abbott Laboratories
Advanced MRI Applications for Mild Traumatic Brain Injury (mTBI) & Blood Biomarker Candidate Study for Mild Traumatic Brain Injury
11/30/15-3/1/17
This clinical trial is being conducted for hypothesis generation in population of mild traumatic brain injury (mTBI) patients using advanced applications for magnetic resonance imaging (MRI) and corresponding clinical neuropsychological assessments. The purpose of the companion

blood biomarkers trial is to measure potential blood-based biomarkers of mild traumatic brain injury and evaluate associations with clinical data, neurocognitive testing, and magnetic resonance imaging data.
Role: Site Co-Principal Investigator (0.6 calendar months)

What other organizations were involved as partners?

Organization Name	**Location**	**Contribution to the Project**
Froedtert Hospital	Milwaukee, WI	Facilities
Zablocki VA Medical Center	Milwaukee, WI	Facilities, Collaboration
Banyan Biomarkers, Inc.	Alachua, FL/San Diego, CA	Collaboration
Indiana University	Indianapolis, IN	Collaboration
Carroll University	Waukesha, WI	Facilities, Collaboration
Concordia University of Wisconsin	Mequon, WI	Facilities, Collaboration
Carthage College	Kenosha, WI	Facilities, Collaboration
Wisconsin Lutheran College	Milwaukee, WI	Facilities, Collaboration
Franklin High School	Franklin, WI	Facilities, Collaboration
Marquette University High School	Milwaukee, WI	Facilities, Collaboration
Wauwatosa East High School	Wauwatosa, WI	Facilities, Collaboration
Whitefish Bay High School	Whitefish Bay, WI	Facilities, Collaboration

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:
Please see Quad Chart on following page.

Comprehensive study of acute effects and recovery after concussion

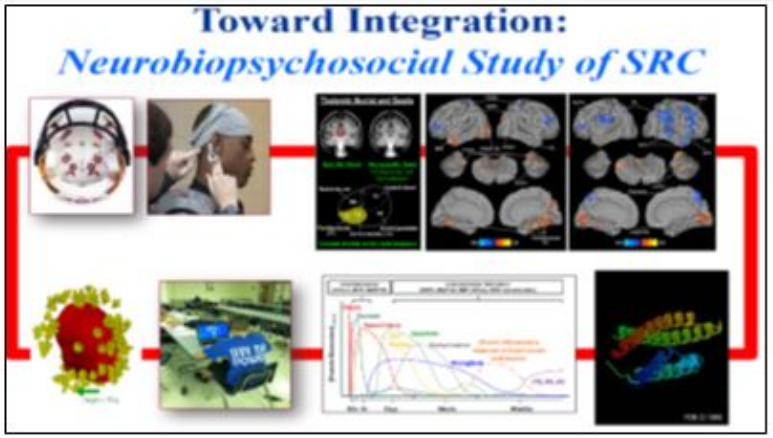
Log No: 13114003
Award No: W81XWH-14-1-0561
PI: Michael McCrea, PhD, ABPP **Org:** The Medical College of Wisconsin, Inc. **Award Amount:** $6.15M

Study Aims

In a prospective study of high school and low level collegiate athletes :
•Conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI.
• Collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion.
• Instrument high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors.
• Conduct genetic testing in our pre-exposure baseline assessments of athletes.

Approach

This study enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and outcome variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).



This study will investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective in a common injured sample and single study design.

Timeline and Cost

Activities CY	14	15	16	17	18
Project Contracting & Regulatory					
Operationalize Protocol					
Data Collection					
Data Management, Analysis & Dissemination					
Estimated Budget ($M)	**$0.5**	**$1.91**	**$1.99**	**$1.45**	**$0.3**

Updated: 10/28/2016

Goals/Milestones

Major Task: **Project Contracting & Regulatory**
- CPR and Amendments submitted to MCW IRB & HRPO

Major Task: **Operationalize Protocol**
- Ongoing protocol refinement within each core area as needed

Major Task: **Data Collection**
- Enrollment: To date, 865 athletes enrolled at baseline
- Accrual: 62 concussed athletes and 54 controls in post injury protocol
- Accrual ahead of schedule, to allow oversampling, controlling for slight attrition and powering multi-dimensional analysis

Major Task: **Data Management, Analysis & Dissemination**
- Continued progress of data pipeline for each core area
- 2015-16 baseline clinical data submitted to FITBIR

Comments/Challenges/Issues/Concerns
- Project toward achieving study aims on course, on schedule

Budget Expenditure to Date
Projected Expenditure: $ 3.95M *Actual Expenditure*: $ 2.85M
Burn-rate to equalize based on timing of project expenses

9. APPENDICES:

Table 2. Study Technical Objectives and Specific Aims

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).

ADVANCED NEUROIMAGING BIOMARKERS:	***Technical Objective***: To conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI. ***Specific Aims***: 1. Characterize the physiological effects of acute mTBI on brain structure and function. 2. Determine how the natural time course of neurophysiological recovery after mTBI compares to the time course of clinical recovery. 3. Determine the window of neurophysiological vulnerability after mTBI, during which the brain is at risk of secondary or cumulative injury.
BLOOD BIOMARKERS:	***Technical Objective***: To collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion. ***Specific Aims***: 1. Measure the direct effects of acute mTBI on brain biology. 2. Correlate the sensitivity and specificity of brain biomarkers with other measures of the effects of mTBI (symptom recovery, cognitive testing, balance assessment, neuroimaging). 3. Determine how the time course of biological recovery after mTBI compares to the time course of clinical recovery.
HEAD IMPACT SENSORS:	***Technical Objective***: To dually-equip high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors. ***Specific Aims***: 1. Cross validate multiple head impact sensors systems used in mTBI research. 2. Measure the relationship between biomechanical metrics of head impact location and magnitude (e.g., rotational acceleration) and measures of clinical and physiological effects of acute mTBI. 3. Determine the minimum biomechanical threshold sufficient to cause mTBI. 4. Determine the clinical effects of subconcussive head impact exposure from contact and collision sports on neurocognitive function through comparison to a noncontact sport control group not exposed to repetitive head impacts.
GENETIC TESTING:	***Technical Objective*:** To conduct genetic testing in our pre-exposure baseline assessments of athletes. ***Specific Aims*:** 1. Determine the influence of genetics on risk of mTBI. 2. Determine genetic influence on acute recovery and outcome after mTBI. 3. Enable longitudinal study of the influence of genetics on long-term outcome after mTBI in a well characterized cohort of injured and control subjects.