A SOCIAL, BEHAVIORAL, & EDUCATION RESEARCH (SBER) CASE STUDY OF EDGES OF RESEARCH/IRB PURVIEW

AN EVALUATION OF AN EARLY INTERVENTION PROGRAM TO AMELIORATE PSYCHOSOCIAL EFFECTS OF TRAUMATIC BRAIN INJURY (TBI) IN COLLEGIATE ATHLETES

By: Lara N. Sloboda and Matt Stafford
with the SBER Subcommittee of Harvard Catalyst’s Regulatory Foundations, Ethics, and Law Program

OVERVIEW

The social, behavioral, and education research (SBER) case studies provide education and guidance on how to identify and mitigate risks associated with SBER. These studies may be used by both IRB administrators and investigators when reviewing and designing research studies that involved SBER components.

Case studies follow a standard format that includes: 1) a fact pattern, 2) regulatory, cultural, and ethical issues, and 3) a risk/benefit analysis and risk management options. This format was created to allow for flexibility in applying the case studies.

By identifying common themes, linking them directly to federal regulations and guidance, and outlining risk mitigation options, the case studies can be used in a variety of ways, which include: 1) as an education tool for training individuals in human subjects research, 2) as a basis for developing reviewer checklists/worksheets, and 3) as a tool in designing research projects.

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CASE STUDY

SCENARIO/FACT PATTERN:

Dr. Spikes, a sports medicine physician at a major research university with division I athletics program has partnered with a psychiatric clinician in the University’s Student Health Services department as well as a researcher in the Neuropsychology and Brain Sciences program to develop a multidisciplinary treatment program to lessen the long-term impact of post-concussion syndrome (PCS) caused by mild Traumatic Brain Injury (TBI). The study team intends to research the positive effects of the program on emotional adjustment, memory, and brain functioning.

Potential participants are those students actively involved in at least one Division I Varsity sport. The researchers intend to recruit participants in to the study based on referral by the coaching staff, team doctors and physicians, or athletic sports trainer. Sports staff will be instructed to provide the names of...
student athletes that suffer a concussion during a sporting event. Upon receipt of a potential participants' name, a member of the research team will contact the participant and set a meeting to conduct an in person prescreen interview which will include demographic items, questions regarding the incident that lead to the concussion, and questions regarding the student athlete's diagnosis. This information will be confirmed through health records from Student Health Services. The prescreen interview will take place within 48 hours of the concussing event. The inclusion criteria for the study include being over the age of 18, having suffered a concussion during a NCAA sporting event and treated at the Sports Medicine clinic or Student Health Services with a diagnosis mild TBI (mTBI) as established by ICD-9 score. Students must be enrolled in college aged and not in their final semester at school. They must also confirm that there is no history of drug abuse or clinical depression. If deemed eligible, the participant will be presented with the consent form.

Researchers have planned four-week controlled aerobic intervention program to reduce ongoing symptoms. The program will include closely monitored physical activity, matched with physical conditioning, coordination exercises, visualization techniques, cognitive behavioral therapy to focus on motivation and anxiety, and medical education. The training will be conducted in 4 weekly group therapy and physical training sessions, coupled with daily monitoring during individual conditioning sessions.

At the beginning of the four-week intervention, participants will complete an in-person data collection session which will include basic memory and attention tasks, emotional quotient questionnaires, and psychosocial questions. The same tasks will be completed after the four-week intervention, and every six months until the participant graduates. To monitor the functional changes in the brain due to PCS, Functional Magnetic Resonance Imaging will be used at study time points to functional changes in the brain’s memory and executive function centers over time. Participants will complete basic working memory tasks. The scanning will help the researchers identify any structural changes in the brain as well as determine whether there is a relationship between symptoms reported pre- and post-intervention and the function of the brain during working memory tasks.

Discussion

Questions/Comments for the researcher:

- Will participants be able to provide the information needed for eligibility with 48 hours of the concussing event?
- If the research team is not referred to a potential participant immediately, will this affect the outcome of the study?
- Will the requirements for enrollment in to the study contradict the potential participants' doctor's orders?
- If participants are only referred by the coaching staff or Health Services, will their personal doctors be made aware of their enrollment in the research?
- Are there any exclusion criteria, including assessing whether an injury is too severe to be eligible?
- What is the justification for collecting health information both through self-report and student health records? Both carry risks (confidentiality around health information, putting the participant in a stressful situation post-concussion). Is there a reason why both are necessary?
• Is the participant able to consent to the study immediately following the concussion? Has the research team a means of identifying whether participants are able to consent, and if not, will the research team involve a Legally Authorized Representative?

• Will the research team be looking into academic performance? Will the time effort needed for the study affect the students’ work load and academic performance?

REGULATORY, ETHICAL, & CULTURAL ISSUES:

46.102 Definitions (in relevant part)

(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) Research subject to regulation, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b) An IRB may use the expedited review procedure to review either or both of the following:

Visit: http://catalyst.harvard.edu/programs/regulatory/sber.html
Email: regulatory@catalyst.harvard.edu

Traumatic Brain Injury in Collegiate Athletes November 2018
(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

**List of categories** (in relevant part):

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

**46.111 Criteria for IRB approval of research.**

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

**46.112 Review by institution.**
Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:
(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject’s legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject’s legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject’s wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Massachusetts Mandated Reporter Laws

Child Abuse

M.G.L. c. 119 § 51A requires that nurses who have reasonable cause to believe that a child is suffering physical or emotional injury resulting from: (i) abuse inflicted which causes harm or substantial risk of harm to the child’s health or welfare, including sexual abuse; (ii) neglect, including malnutrition; (iii) physical dependence upon an addictive drug at birth; or (iv) being a sexually exploited child; or (v) being a human trafficking victim must immediately communicate with the Department of Children & Families (DCF) orally and, within 48 hours, submit a written report to DCF detailing the suspected abuse or neglect.

Any mandated reporter who fails to make required oral and written reports of witnessed or suspected child abuse and/or neglect shall be punished by a fine of up to $1,000. Any mandated reporter who willfully fails to report child abuse and/or neglect that resulted in serious bodily injury or death shall be punished by a fine of up to $5,000 and up to 2½ years in jail, and be reported to the person’s professional licensing authority. Whoever knowingly and willfully files a frivolous report shall be punished by: (i) a fine of not more than $2,000 for the first offense; (ii) imprisonment in a house of correction for not more than 6 months and a fine of not more than $2,000 for the second offense; and (iii) imprisonment in a house of correction for not more than 21/2 years and a fine of not more than $2,000 for the third and subsequent offenses.

Elder Abuse

M.G.L. c. 19A §15 requires that nurses who have reasonable cause to believe that an elderly person is suffering from or has died as a result of abuse to immediately make an oral report and submit a written
report within forty-eight hours. Elder abuse is defined as an act or omission which results in serious physical or emotional injury to an elderly person or financial exploitation of an elderly person; or the failure, inability or resistance of an elderly person to provide for himself or herself one or more of the necessities essential for physical and emotional well-being without which the elderly person would be unable to safely remain in the community. Forms of abuse include physical, sexual, emotional, neglect, financial exploitation, and self-neglect. However, no person is considered to be abused or neglected for the sole reason that such person is being furnished or relies upon treatment in accordance with the tenets and teachings of a church or religious denomination by a duly accredited practitioner thereof.

Mandated reporters who fail to make elder abuse reports when appropriate are subject to a fine up to $1,000. In addition, the law provides mandated reporters with immunity from any civil or criminal liability that otherwise could result from making a report, provided the reporter did not commit the abuse.

Abuse of a Disabled Person

M.G.L. c. 19C, § 10 requires that nurses who have reasonable cause to believe that a disabled person is abused must report the situation to the Disabled Persons Protection Commission (DPPC). Abuse of a disabled person includes acts of physical, sexual, emotional, verbal abuse and omission by a caregiver of a person with a physical disability between the ages of 18 and 59. Abuse of a disabled person under age 18 must be reported as child abuse and if older than 59 as elder abuse (see above). In addition to reporting suspected abuse and neglect, mandated reporters are also required to report to the DPPC all cases in which an individual with a disability has died, regardless of whether or not abuse or neglect is suspected.

Questions for the IRB:

- Does this study qualify for a waiver of documentation of consent and a Health Insurance Portability and Accountability (HIPAA) waiver?
- Who is conducting each aspect of the research? While there is a collaborative study team, who will be conducting the intervention? Does this individual have the training to be able to ensure the safety of the participants?
- Is there any control comparison in the study? The study is a within subjects design, but is there any reason to think that there will be measurable results over such a short duration?
- Are participants being asked to do too much following a brain injury? Are there ways to assess the effectiveness of this intervention in other ways?

Resolution & Discussions:

Risk/Benefit Analysis:

- Based on the details of the study, would the study need to go to full review? Do the research methods fall within the expedited review categories?
- The study methods add increased physical and mental stress for participants in recovery after a traumatic brain injury. The loud noises in the scanner as well as the audiotaped exercises could be a physical risk to participants during their recovery. The stress of the study due to the arduousness of the study requirements and mental exercises is a potential risk, as well as the added stress of the responsibility of being a participant.
- Involvement in the study has the potential to lead to a confirmation bias for the participants. It is possible that knowledge of their deficits would lead to the participants’ having a slower recovery.
- While also a potential benefit to the study, there is a concern that participants may not be able to return to their respective sports due to the results of the study, or the research team’s perception of their recovery. There is a possibility that participants who would normally have cleared their
institutions concussion protocol would be delayed in returning to their sport because of their performance in the research.

• For those athletes with the potential to be professional athletes, it is possible that the role in the research could affect their recruitment prospects.

Mitigation/Management of Risks:

• Risk of confidentiality could be decreased if participants were to self-disclose their concussion as opposed to being referred by the team doctor.

• The research team should create a protocol for assessing ability to consent and have a plan for inclusion of LARs if necessary.

• Research team members should be trained to identify severe signs of post-concussion symptomology so as to discontinue data collection or intervention should participants’ symptoms become too severe.

Alternate Details:

• In order to determine whether participants are eligible to return to sports, athletes will undergo an exertional test including running to determine if symptoms occur. They will also fill out a symptomology index. Only when symptoms are no longer present at baseline or after the exertional test will athletes be allowed to return to their sport.

• The study team determines that some participants will be allowed to return to sport earlier than the school’s concussion protocol usually allows if they agree to being in a concurrent research study, since clinic and coaches agree that the extra monitoring may make it safer to resume athletic activities. The concurrent study includes audio-taping the athletes reading a predetermined script to monitor changes in speech patterns over time. The use of speech patterns will help the researchers identify any micro-changes in word usage which could be indicative of long-term mTBI damage leading to CTE.

Other Events:

• After being allowed to return to sport, a participant suffers another head injury. The research team determines that the participant should be removed from the study protocol because, having suffered two concussions in succession, the participant is no longer comparable to other participants.

• While enrolled in the study, a research participant is arrested for public intoxication and aggravated assault. Individuals known to the participant report that both drinking and aggressive behavior are not typical of this individual. The clinical psychiatrist indicates that the criminal proclivity is likely a side-effect of the concussion.

Reference(s):

45 CFR 46.111-112: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111

45 CFR 46.102: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102

45 CFR 46.116:

45 CFR 46.117:

Massachusetts Mandated Reporter Laws: