The Children's Hospital *of* Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title: **HIT HEADS Trial: Head Injury Treatment with Healthy and Advanced Dietary Supplements: A randomized, placebo-controlled, double-blinded, therapeutic exploratory clinical trial of dietary supplements in the treatment of concussion**

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You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you do decide to take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child, please note that the word "you" refers to your child.

Why are you being asked to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with a concussion within the past three days. There are several inclusion and exclusion criteria for this study which will be reviewed with you by a study team member. If you do not meet these criteria you will not be allowed to continue with this study.

What is the purpose of this research study?

The purpose of this research study is to study the effects of dietary supplements on the recovery from a concussion injury. A concussion is a type of traumatic brain injury (TBI), caused by a bump, blow, or jolt to the head that can change the way your brain normally works. It is common to experience symptoms after concussion such as having difficulty thinking clearly, feeling slowed down, or having difficulty concentrating or remembering new information. Some people also have symptoms like headache, feeling off balance, irritability and difficulty sleeping. Recent research in mice has shown that taking these dietary supplements after a concussion injury can reduce the amount of time to recover from a concussion injury. The purpose of this study is to measure the recovery

of patients after a concussion injury, and to see whether dietary supplements may speed the recovery.

The study drug, which is often used as a dietary supplement, has been used in over 100 scientific studies over the past several decades to treat thousands of patients with a multitude of medical conditions. They are generally regarded as safe and well tolerated. The US Food and Drug Administration (FDA) has given their approval for these supplements to be studied in people with concussions. However, the study drug being used in this study is not approved by the FDA. The use of the study drug is considered "investigational."

How many people will take part?

About 70 subjects will take part in this study.

What is involved in the study?

As a participant in this study, you will be asked to drink 20 ounces or 2.5 cups of a flavored liquid twice per day for 21 days. Not everyone will receive the study drug. Some people will get a drink called a "placebo" which looks and tastes the same as the drink with the study drug but doesn't contain the drug in it. There are four different concentrations of the study drug being evaluated, thus you have a four out of five chance of getting a beverage that includes some concentration of the study drug, and a one in five chance of getting a beverage that is essentially flavored water. Whether you receive the study drug or the flavored water will be decided at random.

There are no dietary restrictions while participating in this trial. However, you cannot take any dietary supplements (e.g. protein powder, whey powder, amino acids, etc.) during the 3 weeks of this study.

In addition to the drink, you will be asked to take around 10-15 minutes each day to complete a web-based program to measure how your brain is recovering from the concussion along with a web-based questionnaire to understand how you are feeling. Specifically, we will measure brain functions like processing speed, attention and memory, ask about symptoms like headache and tiredness, and ask about how much physical and brain-related activity you have done each day. To understand how your sleep has been affected by the concussion, you will wear a motion monitor on your wrist during the study. Lastly, to measure how your balance has been affected by the concussion, you may undergo balance testing three times during the study.

How long will you be in this study?

If you agree to take part, your participation will last for 22 days. You will be required to complete a web-based program every day for the duration of the study that will take about 10-15 minutes. There will be two additional in-person visits where you may have the option to complete dynamic balance testing. You will also be required to return the motion monitor and used, partially used, or empty dietary supplement bottles after the study is done on day 22.

What are the study procedures?

The study involves the following tests and procedures.

Interview: A team member will ask you about any prior concussions or traumatic brain injuries you have had and what the outcomes were. The team member will gather details about your current concussion including the time of the concussion, the way that you were injured, whether you were wearing any protective equipment, and the mechanism of your concussion (i.e. head to head, foot to head, head to ground, head to object, blow to body, etc.).

Physical Examination: You will have your weight and height measured.

Pregnancy Test: All post-menarchal women will be asked to take a urine pregnancy test before starting this study. For children: the results will be shared with you and not with your parent(s). We strongly encourage you to share the results with your parents. If you are found to be pregnant, you will not be able to continue participation in the study.

Administration of the study drug or placebo: You will be asked to drink 20 ounces, which is equal to 2.5 cups or 590 milliliters of a flavored liquid twice per day for 21 days. There are four different concentrations of the study drug that are being tested in this study, in addition to a placebo that is essentially flavored water. All concentrations of the study drug, as well as the placebo, will look and taste the same. Whether you receive the study drug or placebo will be decided at random. Each bottle must be finished in no more than 60 minutes. The recommended time between the two daily beverages is 6 hours, however, the minimum time between beverages is 2 hours. You should not consume more than 2 of the beverages supplied by this study in a 24-hour period. If a beverage is missed and you do not have time to drink another beverage the same day, then you should skip the beverage and begin your regular schedule again the following day.

Axon Sports Computerized Cognitive Assessment Tool (CCAT): You will be asked to spend 8-10 minutes on tests designed to measure your brain function. These tests, called the CCAT, consist of 4 computerized tests which measure processing speed, attention, learning, and working memory. All of the tests involve a card-playing game. You will be shown a picture of a playing card and asked to answer a question about the card. For each test you will respond by pressing the 'YES' or 'NO' buttons on a computer keyboard. Different tests are created by changing the question. The entire CCAT takes 8-10 minutes to complete and can be accessed from any computer with internet access. We request that you choose a computer that is in a quiet, calm environment. You will complete a single short practice session with the study coordinator so you will have the chance to practice the tests and ask any questions. The CCAT will be completed daily during the trial.

Clinical Symptom Checklist: You will also be asked to take 1 or 2 minutes each day to complete a symptoms checklist via the study website. The checklist will be given twice, first to ask how long the symptoms affect you each day, and second to understand how bad the symptoms are. The symptoms are: headache, nausea,

balance problems, sleeping more than usual, drowsiness, fatigue, feeling "slowed down", feeling like "in a fog", and difficulty concentrating.

Physical and Cognitive Activity Assessment: You will be asked to spend no more than 1 minute each day to tell us, via the study website, about your level of physical activity and brain activity.

Sleep Assessment and Motion: You will be required to wear a motion monitor on your wrist for the duration of the study. The motion monitor is a small non-invasive, wristwatch sized activity monitor. The monitor will be worn at all times on your non-dominant wrist, with the exception of bathing or swimming. You will be instructed to push a button on the device each time you go to bed, get out of bed, take the watch off or put the watch back on, and for any unusual events that occur. The device may also be removed if it is not permitted in an academic or athletic situation. You will also take1-2 minutes each day to complete a questionnaire on your sleep via the study website.

Computerized Dynamic Balance Testing *(Optional)*: Computerized dynamic balance testing will be used to measure your ability to balance. Testing is performed by standing on a computerized support surface to measure how well you sustain upright stance while the support surface and/or visual surround moves in response to your own postural movements. The evaluation takes about 15 minutes and can be conducted when you enroll, and on days 7 and 14 of the study. If you enroll on a Saturday or Sunday, you will have the option to complete the balance testing on a week day.

Supplement Accountability Assessment: You will need to take the study dietary supplement by mouth twice a day for 21 days. You will be asked daily on the study website to indicate whether or not you have taken the supplement. Additionally, a small concentration of deuterium oxide or heavy water will be added to each bottle. This compound is not dangerous to your health in any way. Your urine will be collected at the beginning of the study and then weekly to measure the concentration of this compound to determine how much of the study drug you have been taking. Throughout the study you will be also asked to report if you think that anything bad has happened as a result of the study drug or the study.

The study physicians will not be responsible for the medical management of your concussion or your routine medical care. They are available to answer general questions about concussion or concussion management.

Visit Schedule

The table below provides a brief description of the purpose and duration of each part of the study.

Visit	Purpose	Main Procedures	Duration
Visit 1, Day 0	Screening	Informed consent Review inclusion/exclusion criteria Urine pregnancy test (post-menarchal females only)	15 minutes
Visit 1, Day 0	Orientation Start Study Drug	Orientation to study & study website Demographics & concussion history Baseline compliance urine test Computerized balance testing (optional)* Distribute actigraphy sleep monitor Distribute study drug	2 hours
Days 0-21	Daily assessments via study website	Computerized cognitive testing Clinical symptom checklists Cognitive & physical activity assessments Sleep assessment	15 minutes
Visit 2, Day 5-9	Routine Visit	Computerized balance testing *(Optional)* Compliance urine test	20 minutes
Visit 3, Day 12-16	Routine Visit	Computerized balance testing *(Optional)* Compliance urine test	20 minutes
Visit 4, Day 22-24	End of Study	Return used and unused drug bottles Return actigraphy monitor	10 minutes

* - If enrollment occurs on a Saturday or Sunday, balance testing will be conducted the following Monday or Tuesday.

What are the risks of this study?

Taking part in a research study involves inconveniences and risks. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

While in this study, you are at risk for the following side effects:

Risks associated with study dietary supplements:

- Gastrointestinal symptoms such as an upset stomach, abdominal distention or bloating, diarrhea, or constipation.
- Allergic reactions (e.g. rash, runny nose, watery eyes, or itching).
- If you have maple syrup urine disease or family history of maple syrup urine disease should not participate in this study as the supplement can potentially be dangerous for individuals with this condition.

Risks associated with interview:

- There are no physical risks with the medical interview but you might experience momentary embarrassment or discomfort. You do not have to answer any questions that make you too uncomfortable.
- There are no risks to the physical exam. Only your height and weight will be measured. You will not be required to remove your clothes.

Risks associated with Axon Sports CCAT:

- Performing the CCAT may make your concussion symptoms worse. If this occurs, you may stop the program. This will not result in your removal from the study. We request that you attempt the CCAT each day.

Risks associated with Clinical Symptoms Checklist and Physical and Cognitive Activity Assessments:

- Performing the clinical symptom checklists and the physical and cognitive activity assessments may make your concussion symptoms worse temporarily.

Risks associated with the Sleep and Motion Assessments:

- Some individuals with sensitive skin may have irritation of their skin from the motion monitor strap. You will be permitted to wear the motion monitor over long sleeves or a wristband. You can remove the motion monitor at any time if it becomes uncomfortable or painful to wear.

Risks associated with Computerized Dynamic Balance Testing

- Balance testing may temporarily exacerbate your concussion symptoms, particularly feeling dizzy, being off balance or disoriented. Since you are harnessed into the testing device, the risk of falling is minimal.

Reproductive Risks

For female subjects: If you are pregnant or nursing, you will not be allowed to participate in this study. You should not become pregnant while in this study. You will need to take safety measures to prevent pregnancy (such as not having sexual intercourse, or using a medically accepted form of contraception such as condoms or birth control pills) during the study. If you have questions about how to avoid pregnancy, talk to your doctor or the researcher and they will provide you with information on contraceptive choices. You should contact the study investigator at once if you become pregnant during this research study.

Are there any benefits to taking part in this study?

You might benefit by having symptoms of your concussion affect you less severely and or resolve more quickly. However, we cannot guarantee or promise that you will receive any direct benefit by participating in this study. The knowledge gained from this research may help doctors understand how the brain recovers from concussion injury, treat other individuals with concussions or traumatic brain injuries, and may help develop further treatments for concussion.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record. Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study. You will need to follow the study doctor's instructions, complete your web-based assessments daily, and take the study dietary supplement as directed.

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP or Penn. If you decide not take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

Can the study doctor take you out of the study early?

The study doctor may take you off of the study if:

- Your condition worsens.
- The study is stopped.
- The dietary supplement is no longer available.
- You cannot meet all the requirements of the study.
- New information suggests taking part in the study may not be in your best interest.

What choices do you have other than this study?

There are options for you other than this study including:

- Not participating in this study.
- You may discuss other options available to you with your doctor.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information about your medical history, as well as cognitive and symptom assessments. Laboratory test results will appear in your medical record. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized personnel at CHOP or Penn;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the U.S. Department of Health and Human Services and the Office for Human Research Protections;
- Groups monitoring the safety of this study, including the Medical Monitor;
- The database management team at the Penn Clinical Research Computing Unit will know your date of birth, but no other identifying information;
- Axon Sports will know your date of birth, but no other identifying information

  The Food and Drug Administration.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study. Your permission to use and share the information and data from this study will continue until the research study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you inform the investigator in writing.

Dr. Sage Myers
The Children's Hospital of Philadelphia
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In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Additional Information

A medical monitor, an independent physician who is an expert in clinical trials, will be reviewing the data from this research throughout the study. You will be informed if

changes to the study are needed to protect your health. You will be told about any new information that could affect your willingness to stay in the study, such as new risks, benefits or alternative treatments.

One of the Investigators on this study, Dr. Akiva Cohen, is the author of a "provisional application for patent" (35 U.S.C. §111(b)) pertaining to the study agent. Dr. Cohen may gain financial benefit from this technology if it is successful.

Financial Information

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

Will there be any additional costs?

The Dana Foundation is providing financial support for this study and the following research procedures, study medication, and study visits:

- Cost of parking
- Cost of study medication
- Urine pregnancy test (post-menarchal females only)
- Cost of study assessments including Axon Sports CCAT, Actigraphy, and Computerized Dynamic Posturography

Will you be paid for taking part in this study?

- You will be paid as an incentive for participation in this study. At time of visit 1, you will receive $20.You will also receive $1 for each day that you complete all study procedures (drink 2 drinks and complete online assessment), with an additional bonus of $2 if you complete 3 days in a row and $5 if you complete 7 days in a row. You will be provided $10 for each in person assessment (for a possible total of $30 for 3 visits). In total, if all study procedures are completed fully, you could be paid $100. All payments will be given via gift card. If you receive payment using a bankcard, the bank will have access to identifiable information. The bank will not have access to any medical information.
- If you drive to and park at CHOP for any visits, you will also receive a parking voucher.

Who is funding this research study?

The Dana Foundation is providing funding for this study.

Please ask Dr. Myers if you have any questions about how this study is funded.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. Myers at 267-426-7939. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-5902830.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research. No funds have been set aside to compensate you in the event of injury.

You and your insurance company will be billed for the costs of any care or injuries.

If you think you have been injured from taking part in this study, call Dr. Myers at 267-426-7939. She can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date:

By signing this form, you are indicating that you have had your questions answered and agree to take part in this research study. If your child is participating, you are indicating that you are legally authorized to consent to your child's participation. You are also agreeing to let CHOP and Penn use and share your health information or your child's health information as explained above. If you don't agree to the collection, use and sharing of your health information or your child's health information, your child cannot participate in this study. **NOTE:** *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject	
Signature of Subject (18 years or older)	Date
Name of Authorized Representative (if different than subject)	Relation to subject: ☐ Parent ☐ Legal Guardian
Signature of Authorized Representative	Date

Child Assent to Take Part in this Research Study

For children capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

_____

Person Obtaining Assent

_____ _____

Signature of Person Obtaining Assent Date

This study has been explained to me and I agree to take part.

_____ _____

Signature of Subject (optional) Date