A PILOT STUDY OF A NOVEL HELMET DESIGN IN PATIENTS WITH SEIZURES

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Study Summary

Title	A Pilot Study of the Safety of a Novel Helmet Design in Patients with Seizures
Short Title	Inflatable Helmet for Seizures
IRB Number	824620
Methodology	Open Label Pilot Study
Study Duration	1 year
Study Center(s)	Single Center: University of Pennsylvania
Objectives	Part 1: • To determine reliability in helmet deployment, as evidenced by deployment of the helmet during 4 staged falls with normal controls or dummies Part 2: Primary: • To determine safety of the use of the Hövding Helmet in seizures, as evidenced by the deployment of the helmet only during seizures and qualitative patient reporting. • To conduct an initial limited study in humans to confirm the design and operating specifications before beginning an extensive clinical trial. Performance of this device in this limited study serves to establish the parameters for a larger clinical study. Secondary: • To compare rates and types of head injuries and post concussive syndrome in seizures where the helmet deployed versus seizures where the helmet did not deploy.
Number of Subjects	Part 1: 4 Part 2: 40
Main Inclusion and Exclusion Criteria	Part 1: Healthy controls Part 2: Patients who experience at least one seizure every 6 months who do not wear static solid helmets.
Investigational Product	Hövding Inflatable Helmet
Duration of administration (if applicable)	Part 1: 1 day Part 2: 6 months

Reference therapy	Static solid helmet
Statistical Methodology	Part 1: the number of times that the helmet deploys in normal controls falling from standing. Part 2: the number of days that subjects assigned to wear the helmet wore the helmet. We will compare the rates of injury and post concussive syndromes in patients where the helmet inflated during a seizure related fall to seizure related falls where the helmet did not inflate.
Safety Evaluations	Medical Record Review, Rivermead Post Concussive Scale, Qualitative Subject Report
Data and Safety Monitoring Plan	The Sponsor will appoint a qualified Monitor to review and evaluate study data and activities. The details of monitoring are included in the Data and Safety Monitoring Plan.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1 Introduction

Patients with epilepsy often sustain head injuries from the falls that occur during their seizures. While neurologists often advise patients with difficult to control seizures to wear helmets at all times to prevent injuries, patients nearly universally refuse because of social stigma and impracticality. A new, less obtrusive, inflatable helmet has been designed by Hövding Inc. that may encourage increased helmet use; and therefore, potentially result in decreased head injuries caused by seizures.

The primary goal of this study is to estimate effect size and trial outcome instruments to design a study of the safety of a new helmet designed by Hövding Inc. for use in patients with risk of head injury from seizures. The target population with be patients with poorly controlled seizures. Subjects will wear the helmet, fill out a seizure calendar and describe how the helmet reacted during a seizure and during its use in everyday life.

1.1 Background and Relevant Literature

Epilepsy is a common chronic neurological condition defined by recurrent seizures that frequently lead to falls; the original description of epilepsy translated to "The Falling-Down Disease.[1]" The CDC estimates that 2.3 million adults in the United States have Epilepsy, with 150,000 people developing the condition each year[2,3]. The total indirect and direct cost of Epilepsy in the United States is estimated to be $15.5 billion. Recent studies have concluded that the rates of severe head injuries, lacerations, dislocations, fractures, and drowning in Epileptic patients are higher than their non-Epileptic counterparts[4,5,6,7]. The risk is increased for children and as well as adults[8,9]. One study reported that injuries were reported in as many as 15% of epilepsy patients evaluated in an emergency room setting for a seizure[10]. This population of patients is also specifically susceptible to head injuries during their seizures. In a recent study that followed 247 Epilepsy patients over 10 years. 16% of patients had seizure related injuries, 79% of which were cranial soft tissue lacerations or contusions[11]. However, these injuries can be severe and result in traumatic brain injury, skull fractures, and intracranial bleeding.

Helmets are effective in reducing the injuries from serious falls and accidents. A meta-analysis of motorcycle helmets, for example, suggest that they reduce head injuries 69% (OR 0.31, 95% CI 0.25 to 0.38)[12]. Moreover, improvements in motorcycle helmet design significantly different (reduced?) rates of facial injury and skull fractures[13]. However, the same attention has not been paid to the helmets used in Epilepsy patients. In one study, 33 institutionalized young patients with drug resistant Epilepsy were provided with helmets to wear. 59 injuries were recorded during the trial, over half of which were scalp and facial bruising, with 48% of those required medical attention. The helmet provided was not in use in 41% of these injuries; and even so, there were not significant differences in rates of laceration, bruising, or the need to seek medical attention at the time of injury in the group wearing helmets versus the group who were not wearing the helmets. This study not only demonstrates the difficulties with static helmet compliance even in a controlled setting but also calls into question whether or not standard static helmets themselves are optimized to prevent injuries during seizures.

Patients with frequent or difficult to control seizures, are often recommended to wear a helmet at all times. Unfortunately, this can result in significant social stigma. The use of static helmets may be a reasonable goal for patients with significant cognitive disability, but is often not acceptable in cognitively normal patients who view them as socially unacceptable and impractical. Consequently, they can accumulate seizure related head injuries and the financial costs resulting from subsequent emergency room visits and hospitalizations.

1.2 Name and Description of the Investigational Product

In 2012, a Swedish company named Hövding began to manufacture a new type of inflatable bicycle helmet. The helmet is designed as a collar with a deployable airbag that inflates when a sensor detects

rapid changes in acceleration. When the rider encounters a crash, the airbag deploys and wraps the back and sides of the users head in inflated nylon fabric which then slowly deflates after deploying. Its design is meant to be unobtrusive and fashion conscious to encourage greater compliance among the cyclist population; it is tested to a higher pounds per square inch standard than the current industry requirements for conventional bicycle helmets. This technology could be adapted to serve as a potential safety device for patients with drug resistant epilepsy (DRE), and patients might use such a device because of its novel, less obtrusive and more fashion conscious design. We believe that use of these helmets by individuals with DRE would reduce the number and severity of head injuries incurred by the DRE population.

1.1.1 Nonclinical Data

The Hövding helmet is currently commercially marketed in Europe. It is CE (Conformité Européenne) marked after undergoing an extensive process for approval by Science Partner Technical Research Institute of Sweden. CE marking is required for a cycle helmet to be able to be sold in Europe and certifies that the helmet complies with the requirements endorsed by the EU Directive for personal protection equipment.

Complete protection in the event of an accident and functioning during normal use are basic criteria for CE marking. For this helmet, “normal use” is defined as wearing the helmet correctly while cycling. All types of helmets have to provide protection for the head in the form of shock absorption and force distribution in an accident to obtain CE marking. The helmet must also be designed so as to cause no unnecessary risks, i.e. there must be no sharp edges, etc. which could injure the wearer. The environmental tolerance criteria for helmets dictate that they must be able to withstand moisture and work in heat and cold and when subjected to the sun’s ultraviolet light.

As with many other new types of products launched on the market, for Hövding there was no standard for testing airbag cycle helmets. This meant that SP, which was commissioned to CE mark Hövding, had to develop a new test method in accordance with the requirements of the Personal Protective Equipment Directive, that was adapted for airbag cycle helmets. When the test method had been developed, it was accredited and approved by SWEDAC (the Swedish Board for Accreditation and Conformity Assessment). The test method for Hövding consists partly of tests that are the same as those for traditional cycle helmets, such as an impact test on a flat surface and on a curbstone, and tests relating to the features of an airbag helmet that are unique and that differ from those of traditional cycle helmets. For example, tests are performed to ensure that Hövding inflates when it should, doesn’t inflate when it shouldn't and the durability of the airbag fabric[1].

The Hövding helmet is not an approved medical device in the European Union or the United States.

1.1.2 Clinical Data to Date

To date, there is no available clinical research data on the Hövding Inflatable Helmet.

2 Study Objectives

The overall objective is to conduct a pilot study of the use of the Hövding helmet in patients with risk of head injury as a result of seizures to help plan a larger study to determine the safety and efficacy of the helmet for this indication. Ultimately, we hope to demonstrate that its use decreases the rate or severity of head injuries due to seizures that occur from standing. This study will help confirm the assumed safety of this device for use in patients with seizures, estimate the effect size, and pilot the use of novel patient-administered outcome instruments and a previously validated post concussive syndrome scale. We will compare injury types and rates in 5 seizures from standing when the helmet deployed and 5 seizures from standing when the helmet did not deploy.

2.1 Part 1 Objectives

2.1.1 Primary Objective

- Reliability in helmet deployment, as evidenced by the deployment of the helmet during 4 staged falls with normal controls or dummies.

2.2 Part 2 Objectives

2.2.1 Primary Objective

- Safety of the use of the Hövding Helmet in seizures, as evidenced by the deployment of the helmet only during seizures and qualitative patient reporting.
- To conduct an initial limited study in humans to confirm the design and operating specifications before beginning an extensive clinical trial.

2.2.2 Secondary Objective

- Rates and types of head injuries and post concussive syndrome in seizures where the helmet deployed versus seizures where the helmet did not deploy.

3 Investigational Plan

3.1 General Design

We propose to investigate the safety of the Hövding helmet device in patients with DRE. While the Hövding helmet is commercially marketed in Europe, it has not been specifically used in a defined epilepsy population. Our project would aim to analyze the safety of the use of the device during 5 seizures from a standing position. For Part 1 of this pilot study, the study team will test helmets on 4 normal controls (or dummies) and have subjects fall directly over onto their sides on a padded floor and record whether or not the helmet deploys. Assuming that the helmet deploys in at least 3/4 of the 4 falls in this scenario as we believe it will, we would proceed to the next phase of the trial.

For Part 2, we propose to enroll 40 patients from our DRE population who suffer frequent seizures who have a history of at least one head injury associated with a seizure. Head injuries may be of any severity and include contusions, lacerations, concussions, skull or jaw fractures or intracranial bleeding. The patients are already identified and their seizure frequency is documented in a database maintained at the University of Pennsylvania. We will also accept referrals from outside providers and review their records of seizure type, frequency, EEG data, age, and pregnancy status to see if their patients qualify for the study.

For the first 10 patients enrolled, patients with seizures occurring more than once monthly will receive helmets, while others will not. After 10 patients are enrolled, the average seizure frequency across all patients enrolled to date will be calculated. Each additional patient's seizure frequency will be compared to that average, and a helmet dispensed if their seizure frequency is higher than average. The average frequency will be recalculated after each additional patient is enrolled. This will continue until 20 helmets are distributed in total.

Patients who are assigned to wear the helmet would be instructed to wear the devices for up to 6 months. During this period, patients will be asked to fill out a daily seizure calendar to help document the frequency of seizures and seizure types. When the patient has a seizure, they will be asked to fill out a questionnaire to help document the circumstances of the seizure and if any injuries occurred. If the patient seeks medical attention, their medical records will be reviewed afterwards. If a head injury is sustained, they will be asked to fill out the Rivermead Post Concussive scale 48 hours after their seizure in order to quantify their head injuries.[2] When the helmet deploys, the subject will be asked to fill out an additional questionnaire detailing the circumstances of its deployment. After the helmet deploys, we will ask subjects to return their helmets to the University of Pennsylvania for Sponsor assessment. Then we will follow these same patients until they have another fall, or until the 6 month time point is reached. We will collect the same data on this second fall, except that the patient will not have the helmet. We will compare circumstances, injuries, and post concussive scales in 5 seizures where the helmet deploys to 5 seizures where the helmet did not deploy.

3.1.1 Part 1: Helmet Deployment in Controls

3.1.1.1 Screening Phase

For Part 1 of this pilot study, the study team will recruit 4 normal controls (or dummies) using flyers placed around the University of Pennsylvania. The study team will obtain informed consent, and review inclusion/exclusion criteria to confirm eligibility.

3.1.1.2 Study Intervention Phase

After the study team obtains informed consent and eligibility is confirmed, normal control participants (defined as non-pregnant participants without epilepsy or other diagnosis that may result in falls) will be given helmets and asked to fall straight over onto their right or left side onto a padded surface. Falls will be witnessed and video recorded by the study team. If the participant significantly attempts to break their fall and the helmet does not deploy, they may be asked to fall again. If the helmet inflates in 3 out of 4 falls, we will proceed with Part 2. If the helmet does not inflate in at least 3/4 falls, we will stop the study.

3.1.2 Part 2: Helmet Deployment During Seizures

3.1.2.1 Visit 1: Screening Phase

40 subjects with high seizure frequencies (greater than one seizure every 2 months and at least 1 seizure every 6 months that could result in a fall) will be recruited. The primary method of recruiting subjects for this study will be reviewing the epilepsy database at the University of Pennsylvania and communicating with attending neurologists about whether it is appropriate to introduce the study to potential subjects. We will offer participation in the trial as part of their standard of care visits in the neurology office. We expect that 40 subjects will be sufficient in this preliminary study to determine safety and to suggest efficacy. Written consent will be obtained prior to any study procedures being conducted.
At visit 1, the following procedures will be performed:

- Subjects will Sign Informed Consent prior to any study activities
- Medical History
- Demographics
- Physical Exam including height, weight, and neck circumference
- Urine Pregnancy Test (if female of childbearing potential)
- Dispense Seizure Calendar
- Dispense Seizure Questionnaire
- Dispense Helmet Deployment Questionnaire (if subject is assigned to wear a helmet)
- Dispense Rivermead Post Concussive Scale
- Subjects with a history of 3 or more seizures per month will receive Hövding Inflatable Helmets at this time, and may skip visit 2.
- Subjects with less than 3 seizures per month will not be given a helmet, and may be asked to return for visit 2.

3.1.2.2 Visit 2: Optional

If all 20 helmets have not been distributed to subjects with a history of 3 or more seizures per month at visit 1, subjects with less than 3 seizures per month may be asked to return for visit 2, during which their seizure frequency will be compared to other enrolled subjects who have not yet received helmets. Of patients with a lower seizure frequency, following every 4 subjects enrolled, if 20 helmets have not been assigned using the above parameter, the study group will calculate which patient has the highest seizure frequency of the enrollees, and that person with will be given a helmet. After 40 patients are enrolled, those with the highest seizure frequencies will be given helmets until 20 helmets are distributed in total. Participants with the highest seizure frequency will be given helmets and Helmet Deployment Questionnaires at this time. Those who do not receive helmets will be assigned to the control (no helmet) group, as they would not normally wear a helmet in their daily lives. Participants will not be restricted from wearing a static helmet if they decide they would like to start wearing one. Hence, standard of care will not be restricted. If participant

decided to wear a static solid helmet, they would be withdrawn from the study and replaced with another participant who met inclusion criteria.

3.1.2.3 Study Intervention Phase

- Subjects assigned to wear the helmet will be asked to wear the Hövding Helmet during their daily lives with the following exceptions: swimming, bathing, driving or riding in a car, participating in activities with frequent changes in velocity such as sports, or handling children or infants.
- All 40 Subjects will complete a Seizure Calendar that will detail which how often and what type of seizures they are having, the 20 who have been assigned to wear helmets will also record the number days that they wear the helmet.
- All 40 Subjects will complete a Seizure Questionnaire, which will be self-administered after the subject has a seizure to detail the circumstances of the seizure and any injuries sustained.
- The 20 Subjects who are assigned to wear a helmet will complete a Helmet Deployment Questionnaire, which will be self-administered after the Helmet deploys to detail the circumstances of its deployment
- All 40 Subjects will complete a Rivermead Post concussive scale which will be self-administered 48 hours after their seizure if they sustain a head injury during a seizure or if the helmet deploys during a seizure, regardless of head injury.
- The study team will make monthly contact with each subject, to ask about seizure frequency, helmet deployment, and any other relevant information.
- If any subject seeks medical care for injuries during the trial, the study team will make every effort to obtain related medical records.
- Subjects will be instructed to contact the study team after a helmet has been deployed to schedule a follow-up visit.

3.1.2.4 Follow Up Phase

After a helmet has been deployed, or at the end of the study regardless of deployment, subjects will be asked to return for a follow-up visit. At this visit, the following study procedures will be performed:

- Medical History review
- Adverse Device Events review
- Helmet collection
- Seizure Calendar collection
- Seizure Questionnaire collection
- Helmet Deployment Questionnaire collection (if subject is assigned to wear a helmet)
- Rivermead Post Concussive Scale collection

After the follow-up visit, subjects assigned to wear the helmet will continue to be followed until the study team is able to capture another seizure resulting in fall, this time without the use of the helmet. The seizure calendar will still be filled out during this time point, and the same questionnaires (with the exception of the Helmet Deployment Questionnaire) will be filled out after the event, and collected at the last follow up visit, which will take place after the event, or at the 6 month time point.

3.2 Study Endpoints

3.2.1 Part 1 Endpoints

3.2.1.1 Primary Study Endpoints

The primary endpoint will be the rate of helmet deployment during staged falls.

3.2.2 Part 2 Endpoints

3.2.2.1 Primary Study Endpoints

- Differences in Rivermead Post Concussive Scale, Seizure Questionnaire, Helmet Deployment Questionnaire, injury-related medical records, and qualitative subject report between subjects

whose helmets deployed during a seizure, and subjects whose helmets deployed during a non-seizure situation.

3.2.2.2 Secondary Study Endpoints

- Differences in Rivermead Post Concussive Scale, Seizure Questionnaire, injury-related medical records, and qualitative subject report between subjects whose helmets deployed during a seizure, and subjects whose helmets did not deploy (or controls).

4 Study Population and Duration of Participation

4.1 Part 1

4.1.1 Inclusion Criteria

1. Age 18-60 at the time of enrollment.
2. Have neck circumference between 34 and 42 cm.
3. Can understand and provide written informed consent.
4. Must be competent to follow all study procedures.
5. Able to read, speak, and understand English.

4.1.2 Exclusion Criteria

1. Subject is currently pregnant

4.2 Part 2

4.2.1 Inclusion Criteria

1. Have at least one seizure every 6 months that might result in a fall (Generalized Tonic Clonic Seizure, Atonic Seizure, and/or Complex Partial Seizure resulting in a fall).
2. Has a seizure frequency of at least once per 2 months.
3. Not have a practice of wearing a static helmet for protection during seizures prior to the study
4. Be between ages 18-65 at the time of enrollment.
5. Have neck circumference between 34 and 45 cm
6. Must live in a home with electrical power supply.
7. If female and of childbearing potential, has negative pregnancy test at the beginning of the study and willing to use appropriate birth control for the duration of the study.
8. Can understand and sign written informed consent.
9. Must be competent to follow all study procedures.
10. Able to read, speak, and understand English.

4.2.2 Exclusion Criteria

1. Subject currently has an intracranial device or vagus nerve stimulator.
2. Patient already wears a helmet for seizure safety.
3. Subject is pregnant, planning to become pregnant during the study, or is unwilling to use an appropriate form of birth control during the study.

4.3 Subject Recruitment

4.3.1 Part 1

We will distribute flyers around the Hospital of the University of Pennsylvania to recruit normal controls.

4.3.2 Part 2

Our primary method of recruiting subjects for this study will be reviewing the epilepsy database at the University of Pennsylvania, screening incoming clinic schedules, and referrals from attending neurologists. We will offer participation in the trial in addition to patients' standard of

care visits in the neurology office. We propose to recruit 40 patients with Drug Resistant Epilepsy (DRE) who suffer from at least one seizure every 6 months that could be expected to result in a fall. Drug Resistant Epilepsy will be defined as patients who have tried 2 or more antiepileptic medications and still having a seizure. Seizures that could be expected to result in a fall include generalized tonic-clonic seizures, drop seizure of any type, or a complex partial seizure with a fall. Prior history of head injury was removed as a criteria as well. We expect that 40 subjects will be sufficient in this preliminary study to determine safety and to suggest efficacy.

4.4 Duration of Study Participation

For Part 1, each subject's participation will last one day. Participation is complete when the subject falls. Subjects may be asked to repeat the fall if necessary. For Part 2, participation for enrolled subjects could last up to six months.

4.5 Total Number of Subjects

4.5.1 Part 1

Recruitment will end when 4 subjects are enrolled.

4.5.2 Part 2

Recruitment will end when approximately 40 subjects are enrolled. It is expected that approximately 40 subjects will be enrolled, and 20 assigned to wear the helmet, in order to document 5 evaluable seizures during helmet wear.

4.6 Vulnerable Populations:

N/A

5 Study Intervention

5.1 Description

The Hövding inflatable helmet is designed for cyclists as a collar with a deployable airbag that inflates when a sensor detects rapid changes in acceleration. When the cyclist encounters a crash, the airbag deploys and wraps the back and sides of the users head in inflated nylon fabric which then slowly deflates after deploying. Its design is meant to be unobtrusive and fashion conscious to encourage greater compliance among the cyclist population; it is tested to a higher pounds per square inch standard than the current industry requirements for conventional bicycle helmets in the EU. Part 1 of this study, where normal controls (or dummies) are asked to fall from standing onto a padded surface while wearing the helmet, will address whether a fall outside of the context of cycling is sufficient for airbag deployment. If so, we will being part 2 of the study.

5.2 Intervention Regimen

For part 2, for the first 10 patients enrolled, patients with seizures occurring more than once monthly will receive helmets, while others will not. After 10 patients are enrolled, the average seizure frequency across all patients enrolled to date will be calculated. Each additional patient's seizure frequency will be compared to that average, and a helmet dispensed if their seizure frequency is higher than average. The average frequency will be recalculated after each additional patient is enrolled until 20 helmets are distributed in total.

Patients who are assigned to wear the helmet would be instructed to wear the devices for up to 6 months. During this period, patients will be asked to fill out a daily seizure calendar to help document the frequency of seizures and seizure types. When the patient has a seizure, they will be asked to fill out a questionnaire to help document the circumstances of the seizure and if any injuries occurred. If the patient seeks medical attention, their medical records will be reviewed afterwards. If a head injury is sustained (as

indicated by responses to the seizure questionnaire, responses to the helmet deployment questionnaire, and/or medical record review), they will be asked to fill out the Rivermead Post Concussive scale 48 hours after their seizure in order to quantify their head injuries[16]. When the helmet deploys, the subject will be asked to fill out an additional questionnaire detailing the circumstances of its deployment. After the helmet deploys, we will ask subjects to return their helmets to the University of Pennsylvania for Sponsor assessment. After the follow-up visit, subjects assigned to wear the helmet will continue to be followed until the study team is able to capture another seizure resulting in fall, this time without the use of the helmet. The seizure calendar will still be filled out during this time point, and the same questionnaires (with the exception of the Helmet Deployment Questionnaire) will be filled out after the event, and collected at the last follow up visit, which will take place after the event, or at the 6 month time point. We will compare circumstances, injuries, and post concussive scales in 5 seizures where the helmet deploys to 5 seizures where the helmet did not deploy.

6 Study Procedures

6.1 Part 1

Table 1: Schedule of Part 1 Study Procedures

	Visit 1
Informed Consent	X
Review Inclusion/Exclusion Criteria	X
Demographics/Medical History	X
Physical Examination	X
Pregnancy Test (if applicable)	X
Subject Training	X
Fall with helmet	X
Adverse Device Effect (ADE) / Unanticipated ADE/ / Unanticipated Problems Assessments	X

6.1.1 Screening/Intervention

6.1.1.1 Visit 1

- Informed Consent
- Review Inclusion/Exclusion
- Demographics/Medical History
- Physical Exam
- Pregnancy Test – only applicable if subject is female and of childbearing potential
- Subject training
- Fall – subjects will be asked to fall on their sides onto a padded floor without breaking the fall with arms. If subject braces themselves and the helmet does not deploy, they may be asked to repeat the fall in the same controlled environment.

6.2 Part 2

Table 2: Schedule of Part 2 Study Procedures

Study Phase	**Screening**		**Intervention**	**Follow-up 1**	**Follow-up 2**
Visit	**1**	**2** (if applicable)	**X**		**6 months**
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				

Demographics/Medical History	X				
Physical and Neurological Examination	X				
Pregnancy Test (if applicable)	X	X[a]	X[a]		
Subject Training	X	X			
Assignment to treatment group	X[b]	X[c]			
Dispense Helmet	X	X			
Seizure Calendar	X[d]	X[d]	X	X[de]	X[e]
Seizure Survey	X[d]	X[d]	X	X[de]	X[e]
Helmet Deployment Survey	X[d]	X[d]	X	X[e]	
Rivermead Post Concussive Scale	X[d]	X[d]	X	X[de]	X[e]
Monthly Contact			X		
Collect Helmet				X[f]	X[f]
Adverse Device Effect (ADE) / Unanticipated ADE/ Unanticipated Problems Assessments			X	X	X

[a] *Subsequent urine pregnancy tests may be administered at the investigator's discretion if there is reason to believe the subject may be pregnant.*
[b] *subjects with 3 or more seizures per month will be given a helmet at visit 1 and may skip visit 2.*
[c] *subjects with less than 3 seizures per month will be asked to return for visit 2, at which it will be determined if they will receive a helmet. Following every 4 subjects enrolled, if 20 helmets have not been assigned to patients with 3 or more seizures, the study group will calculate which patient has the highest seizure frequency of the enrollees, and that person with will be given a helmet. After 40 patients are enrolled, those with the highest seizure frequencies will be given helmets until 20 helmets are distributed in total.*
[d] *dispensing*
[e] *collection*
[f] *if applicable*

6.2.1 Screening

6.2.1.1 Visit 1

- Informed Consent
- Review Inclusion/Exclusion
- Demographics/Medical History
- Physical Exam
- Pregnancy Test – only applicable if subject is female and of childbearing potential

6.2.1.2 Visit 2

(May be combined with visit 1 if subject has 3 or more seizures per month)

- Subject training
- Dispense Helmet

6.2.2 Study Intervention Phase

- Seizure Calendar - daily
- Seizure Questionnaire – self-administered after a seizure
- Helmet Deployment Questionnaire – self-administered after helmet deployment
- Rivermead Post-Concussive Scale – self-administered 48 hours after a seizure if the subject sustains a head injury during a seizure or if the helmet deploys during a seizure
- If subject seeks medical care for injuries during the trial, the study staff will collect any information available, including medical records.
- Study staff will contact subjects monthly

6.2.3 Follow Up Phase of the Study

6.2.3.1 End of Study Visit

After a helmet has been deployed, or at the end of the study regardless of deployment, subjects will be asked to return for a follow-up visit. At this visit, the following study procedures will be performed:

- Medical History review
- Adverse Events review
- Helmet collection
- Seizure Calendar collection
- Seizure Questionnaire collection
- Helmet Deployment Questionnaire collection (if subject is assigned to wear a helmet)
- Rivermead Post Concussive Scale collection

6.3 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, ADEs, or due to a change in medical status that would make the subject ineligible, such as pregnancy. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product, diaries, and questionnaires, and to follow up regarding adverse events.

6.3.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate will have one final visit to collect investigational product, diaries, and questionnaires, and to follow up regarding adverse events.

6.4 Early Termination Visits

Subjects who withdraw consent to participate will have one final visit to collect investigational product, diaries, and questionnaires, and to follow up regarding adverse events.

7 Study Evaluations and Measurements

7.1 Demographics/Medical History

Study staff will collect baseline demographics and medical history at screening visit. A medical history will be reviewed and recorded at the Screening visit. Epilepsy history including etiology, seizure type(s), description, duration, and resulting falls will be documented.

7.2 Physical and Neurological Exam

The principal investigator or designated sub-investigator (MD or NP) will perform a baseline physical and neurological exam and document findings in the subject's file. The systems to be reviewed will be left to the Investigator's judgment.

7.3 Pregnancy Testing

A urine pregnancy test will be performed for female subjects of childbearing potential. Subsequent urine pregnancy tests may be administered at the investigator's discretion if there is reason to believe the subject may be pregnant. Pregnant subjects will be removed from the study.

7.4 Subject Training

Subjects in the helmet group will be trained on proper use of the Hövding Inflatable Helmet and will be provided with an information packet.

7.5 Seizure Calendar

At the first screening visit, all subjects will be given copies of a seizure calendar. On a daily basis, the subject is to complete this calendar, which will capture self-reported seizures and helmet wearing, as well as seizure-free or helmet-free days. At the second screening visit, if necessary, this seizure calendar will be reviewed

7.6 Seizure Questionnaire

At the screening visit, all subjects will be given copies of the seizure questionnaire to be filled out after the subject has a seizure. This questionnaire will capture information such as whether or not the subject was wearing the helmet, whether or not the helmet deployed, the position the subject was in during the seizure, what happened during the seizure, and whether the subject was injured or needed medical attention.

7.7 Helmet Deployment Questionnaire

At the screening visit, subjects in the helmet group will be given copies of the helmet deployment questionnaire to be filled out after the helmet deploys (either during a seizure or otherwise). This questionnaire will capture information such as whether a seizure caused the helmet to deploy, what the subject was doing at the time, whether any injuries were obtained, and whether any medical care was needed or obtained.

7.8 Rivermead Post-Concussive Scale

At the screening visit, all subjects will be given copies of the Rivermead Post-Concussive Scale to be filled out 48 hours after a seizure if the subject sustains a head injury during a seizure or if the helmet deploys during a seizure. This questionnaire will capture information regarding cognitive, somatic, and emotional symptoms associated with post-concussion syndrome.

7.9 Injury-related Medical Record Collection

If subjects seek medical care for injuries during the trial, the study staff will collect any information available, including medical records. Medical records from the University of Pennsylvania will be collected via the electronic medical record. The study staff will make all efforts to obtain related records from all other sites not affiliated with the University of Pennsylvania with the subject's permission.

7.10 Monthly Contact

Study staff will establish contact with subjects monthly via phone or email to ask about seizure frequency, falls, and time spent wearing the helmet. Staff will document the communication in subject files.

8 Statistical Plan

8.1 Part 1 Endpoint

The primary endpoint will be the rate of helmet deployment during staged falls.

8.1.1 Part 2 Endpoints

8.1.1.1 Primary Study Endpoints

- Differences in Rivermead Post Concussive Scale, Seizure Questionnaire, Helmet Deployment Questionnaire, injury-related medical records, and qualitative subject report between subjects whose helmets deployed during a seizure, and subjects whose helmets deployed during a non-seizure situation.

8.1.1.2 Secondary Study Endpoints

- Differences in Rivermead Post Concussive Scale, Seizure Questionnaire, injury-related medical records, and qualitative subject report between subjects whose helmets deployed during a seizure, and subjects whose helmets did not deploy (or controls).

8.2 Sample Size and Power Determination

N/A

8.3 Statistical Methods

Part 2:

- Will use Student's T test to compare rates of injury and post concussive syndrome in falls where the helmet inflated versus falls where the helmet did not inflate.
- Proportion of days that patients assigned to wear the helmet wear the helmet

8.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.3.2 Efficacy Analysis

8.3.2.1 Part 1

- Number of times the helmet deploys in normal controls (or dummies) falling from a standing position.

8.3.2.2 Part 2

- Number of days that subjects in the helmet group actually wore the helmet
- Compare the fraction of the time the device deployed during a seizure that resulted in a fall
- Compare the number of times the helmet deployed in a seizure vs. non-seizure event
- Compare seizures that trigger helmet deployment to those that do not trigger helmet deployment

8.3.3 Safety Analysis

All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse device effects (ADE) for the overall study safety analysis.

8.3.3.1 Part 2

- N/A

8.3.3.2 Part 2

- Compare the rates of injury and post concussive syndromes in patients where the helmet inflated during a seizure related fall to seizure related falls where the helmet did not inflate.

8.4 Subject Population(s) for Analysis

- All-randomized population: Any subjects in the study, regardless of whether they were assigned to wear the helmet, will be used for any analysis comparing helmet wear vs. no helmet wear.
- All-treated population: Any subjects assigned to wear the helmet will be used for analysis of helmet deployment in seizure vs. non-seizure situations. This population will also be used for analysis of seizures that trigger helmet deployment vs. seizures that do not trigger helmet deployment, as well as the analysis of seizures during helmet wear vs. seizures during non-helmet wear.

9 Adverse Device Effects and Adverse Events

9.1 Definitions

9.1.1 Adverse Device Effects

An **adverse device effect (ADE)** is any untoward medical occurrence associated with the use of a device in humans.

9.1.2 Unanticipated adverse device effects (UADEs)

An unanticipated adverse device effect is any ADE that meets at least 1 of the following 3 criteria:

1. Any **serious adverse effect** on health or safety caused by or associated with a device,

   In this case, serious adverse effect is defined as any ADE that is:
   - fatal
   - life-threatening
   - requires or prolongs hospital stay
   - results in persistent or significant disability or incapacity
   - a congenital anomaly or birth defect
   - another important medical event

   All ADEs that do not meet any of the criteria for serious should be regarded as **non-serious ADEs**.

2. Not previously identified in nature, severity, or degree of incidence in the application,
3. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.1.3 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.4 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.1.5 Expectedness

AEs/ADEs must be assessed as to whether they were expected to occur or were unexpected, meaning not anticipated based on current knowledge found in the protocol or product label.

Expected/Anticipated: an AE/ADE known to be associated with the intervention or condition under study.

Unexpected/Unanticipated: an AE/ADE for which the ***nature***, ***frequency***, or ***severity*** is not consistent with information about the condition under study or intervention in the protocol, consent form, or product label.

9.2 Recording of Adverse Device Effects and Adverse Events

The study investigator is ultimately responsible for the recording and reporting of AEs, ADEs, and unanticipated problems related to the research, which occur during the study. The study team will collect AE and ADE information from the start of the study (after consent is signed) until the last follow up visit.

At each contact with the subject, a member of the study team will seek information on AEs and ADEs by specific questioning and, as appropriate, by examination. Information on all AEs and ADEs will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. These AEs and ADEs will be recorded on paper source documents and reviewed by the Principal Investigator and Sponsor designated pharmacovigilance lead (Medical Director).

All AEs and ADEs occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. SAEs and UADEs that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAEs and UADEs that occur after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 AE/ADE Assessment

The Sponsor-Investigator will determine relationship classification (definitely related, probably related, possibly related, unlikely or unrelated), expectedness (expected or unexpected), and seriousness (serious or non-serious as defined per protocol) of all AEs and ADEs. The relationship of each event will be followed up on until it has been determined that the event is definitely related or definitely not related to the device or participation on the study.

9.4 *Investigator Reporting*

9.4.1 Reporting to the FDA

Federal Regulation 21 CFR 812.150 dictates mandatory reporting requirements for all IDE and abbreviated IDE studies to the FDA and the IRB. The regulations describe both expedited and annual reporting requirements. Events that do not warrant expedited reporting will be reported at the time of the IDE Annual Report submission to the FDA. Events that require expedited reporting will be reported to the FDA using **Form FDA3500A**.

Reportable Safety Events		
What Event is Reported	**To Whom is Event Reported**	**When is Event Reported**
Possibly, Probably, or Definitely Related, Unanticipated, & Fatal	Penn IRB	Within **3 days** of initial receipt of information
	FDA	Within **10 days** of initial receipt of information
Possibly, Probably, or Definitely Related, Unanticipated, & Serious (Non-Fatal)	Penn IRB	Within **10 days** of initial receipt of information
	FDA	

Possibly, Probably, or Definitely Related, Unanticipated, & Non-Serious	Penn IRB	Within **10 days** of initial receipt of information
	FDA	Annually
Possibly, Probably, or Definitely Related, Anticipated, & Serious or Non-Serious	Penn IRB	At continuing review
	FDA	Annually
Unlikely or Definitely not related, Anticipated, & Serious or Non-Serious	Penn IRB	N/A
	FDA	Annually
Unlikely or Definitely not related, Unanticipated, & Serious or Non-Serious	Penn IRB	N/A
	FDA	Annually

Other Reportable Events		
What Event is Reported	**To Whom is Event Reported**	**When is Event Reported**
Unapproved protocol deviation to assure protection of human subjects	Penn IRB	Within **5 days** of initial receipt of information
	FDA	
Use of device without obtaining informed consent	Penn IRB	Within **5 days** of initial receipt of information
	FDA	
Withdrawal of IRB approval	FDA	Within **5 days** of initial receipt of information
Withdrawal of FDA approval	IRB	Within **5 days** of initial receipt of information
Change in risk by IRB	FDA	Within **5 days** of initial receipt of information
Request by the manufacturer to recall, repair, or dispose device	Penn IRB	Within **30 days** of request
	FDA	

9.4.2 Other Reporting *to the* Penn IRB

Federal Regulations 21CFR §56.108(b)(1) and 45 CFR 46.103(b)(5) require the IRB to "follow written procedures for ensuring prompt reporting to the IRB…any unanticipated problems involving risk to human subjects or others."

The Office of Human Research Protections (OHRP) considers Unanticipated Problems involving risks to subjects or others, in general, to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

All such reportable events will be reported to the IRB per IRB policy.

Other Reportable Events to the IRB	
New information showing increased risk to subjects	

Protocol deviation that places subjects at risk or has the potential to occur again	Within **10 days** of initial receipt of information
Any serious and continuing non-compliance	
Breach of confidentiality	
Incarceration of subject	

9.4.3 Follow-up reports

If an SAE/UADE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB and the FDA. The investigator is responsible for ensuring that all SAE/UADEs are followed until either resolved or stable.

9.5 Stopping Rules

In Part 1, if 3/4 of the helmets do not inflate due to a fall from standing in normal controls or dummies, the study will not move on to Part 2.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Paper source documents created by the study team will be used to record all subject data. This data will be organized and stored in patient binders located in the locked Clinical Research Office at the Penn Epilepsy Center, Hospital of the University of Pennsylvania, 3400 Spruce Street, 2 Silverstein, Philadelphia, PA 19104. All CRFs will contain de-identified data, and all medical record printouts will de-identified before being stored in subject binders.

A password-protected excel spreadsheet that links patients with de-identified data will be stored on the UPHS Neurology shared drive and will only be accessible to the appropriate study staff.

10.3 Records Retention

All study records will be stored for 7 years, and every effort will be made to maintain subject confidentiality. Study records and personal information may be given out if required by law. Records will not be labeled with names or other identifying information. Instead, they will be identified with a code. The list matching names to codes will be stored separately, password protected, and only available to appropriate study staff.

11 Study Monitoring, Auditing, and Inspecting

11.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents

(e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. clinical research office, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Risks

12.1.1 Part 1

Risk may include possible injury from the fall, however, serious injury is not expected as they will be falling on a padded surface. Another possible risk is injury from the helmet deployment. It is possible that participants may have other adverse device effects that we cannot predict.

12.1.2 Part 2

This study will confirm the design and operating specifications before beginning an extensive clinical trial. Performance of this device in this limited study serves to establish the parameters for a larger clinical study. This will be the first trial of this helmet in patients with drug resistant epilepsy and frequent seizures. It is possible that subjects may have other adverse device effects that we cannot predict.

Risks and adverse device effects that could reasonably be expected to occur include:

- The helmet deploys in a situation not related to a seizure: This risk is possible as the helmet has previously been designed to work in cycling. Activities that have rapid accelerations and decelerations such as running, jumping, or playing sports could potentially increase the chances of the helmet deploying.
- The helmet does not deploy during a seizure: As stated above, the helmet has not been previously optimized for use in this setting and, as such, may not deploy during a seizure.
- Abrasions to the back of the neck when the helmet deploys
- Suffocation: Considered to be very rare as when the helmet deploys, it leaves the face and mouth open and the helmet gradually deflates. No reports of suffocation or near suffocation have been reported despite its commercial availability in Europe over the past 3 years.
- Injury to those around the subject when the helmet deploys, if when deploying the subject is near other people
- Temporary hearing impairment after helmet deployment
- Discomfort from wearing the helmet collar

The risk of falling is not actually an increase in risk from the usual state of participants and there is no increased risk of fall or injury resulting from fall with study participation.

12.2 Benefits

12.2.1 Part 1

Subjects may not receive any personal benefit from being in this study. We hope the information learned in this portion of the study will provide reasonable justification for continuance of the study and to benefit the larger goal of adapting this technology as a safety device.

12.2.2 Part 2

Subjects may not receive any personal benefits from being in this study. A possible benefit is that the Hövding helmet may prevent a head injury during a seizure; however, the study device is experimental and this cannot be guaranteed. We hope the information learned from this study will benefit other people with similar conditions in the future.

12.3 Risk Benefit Assessment

12.3.1 Part 1

The benefits of this study outweigh the risks in that information obtained will help determine the appropriateness of a larger study and will contribute to the design and testing of a device that may help prevent head injuries in patients with seizures. There is only limited personal risk but also no personal benefit to participating in this portion of the trial.

12.3.2 Part 2

The benefits of this study are favorable in comparison to the risks. For those subjects who are assigned to wear the helmet, given that nearly no patients wear any type of protective head equipment for protection because of their seizures, we believe that the use of any potentially protective device confers a potential benefit. This study will not recruit subjects who already wear helmets. It is our hope that the risks of this study will be minimized with the close follow-up and communication throughout the study. For subjects who are not assigned to wear the helmet, they will have the same risks of head injury as if they were not participating in the study at all. The benefit will be further validation of the study tools and a greater understanding of the risk of head injury in patients with seizures.

12.4 Informed Consent Process / HIPAA Authorization

At visit 1, the PI or the Study Coordinator will discuss the study with the subject. Consent for the study will be obtained by the PI, designee, or the sub-investigator(s). Persons who are unable to read English are not allowed to consent for themselves to participate in this study. Subjects will receive an IRB-approved consent/HIPAA authorization form to read in person. At the same time, the PI, designee, or Study Coordinator will read over the form out loud to the subject. They will be allowed as much time as they need to re-read the consent form. It will be stressed to the subjects that this is voluntary and in no way will it impact their medical care. Someone other than their direct provider will administer the consent process so that they will not feel any coercion. The subject will then be asked if they have any questions or concerns. If there are questions or concerns, these will be addressed promptly. If the subject has full understanding of the study description and is agreeable to the study procedures, they will be asked to sign the consent form. A copy of the consent form will be given to the subject. The original consent documents will be placed in the subject's study binder and be securely stored at the study site.

13 Study Finances

13.1 Funding Source

This study is financed through a grant from the Epilepsy Foundation.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Subjects in Part 1 will not be compensated. Subjects in Part 2 will be compensated $25 upon completion of the screening visit, and $25 upon completion of each follow-up visit.

14 Publication Plan

The Principal Investigator holds the primary responsibility for publication of the results of the study. Approval must be first obtained from the primary responsible party before any information can be used or passed on to a third party.

15 References

1. "Hövding - Airbag for Cyclists." Hövding.com. 1 Jan. 2014. Web. 21 Aug. 2014.
2. King NS, Crawford S, Wenden FJ, Moss NEG, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. J Neurol. 1995;242:587–592