TWIST: Treatment With Sumatriptan for TBI Headache
(Sumatriptan as Treatment for Moderate to Severe Post-Traumatic Headache)

Protocol Version 6.1
Principal Investigator: Jeanne Hoffman, PhD

Funded by National Institute on Disability, Independent Living and Rehabilitation Research
H133A120028

ClinicalTrials.gov Identifier: NCT01854385

Investigators:
Jeanne M. Hoffman, Ph.D.
Sylvia Lucas, M.D., Ph.D.
Sureyya S. Dikmen, Ph.D.
Nancy Temkin, Ph.D.
Jennifer Zumsteg, M.D.

Natalia Murinova, M.D. – Data Safety Monitor

Leslie Kempthorne, B.S. – Project Coordinator
Jason Barber, M.S. – Systems Analyst
Erica Wasmund – Research Assistant
Taylor Obata, B.A. – Research Assistant

Table of Contents	Page Number

I. Need and Target Population:

The Significance of the Problem of Headache after TBI*:* Since there are over 1 million people who sustain a TBI in the US each year[1] and headache is one of the most frequent complaints after even mild TBI or concussion, PTH is an extremely common problem. Observational studies have demonstrated that the most common physical symptom following TBI in civilian and military groups is headache which is often persistent. Although some PTHs resolve soon after the initial injury, a substantial number of persons complain of headache that persists.[21, 28, 29] In fact, our work in the last 5 years has indicated that approximately 70% of persons with TBI complain of headache in the year following their injury,[19] though only about 17% have had a prior history of headache before injury.

Military figures also support the common occurrence of PTH. Almost 20% of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) veterans are thought to have experienced a traumatic brain injury.[3, 30] Headache stands out as the salient physical symptom that is specific to mild TBI where most other symptoms of TBI overlap with symptoms of post-traumatic stress, acting as a marker of TBI.[31] Headache is also a frequent residual symptom for those service members with moderate to severe TBI.[21] For soldiers receiving care in a headache clinic after return from deployment, almost half met criteria for mild TBI.[32]

II. Beneficial Impact on Target Population

Why is treatment of PTH important*?* In general, beyond the work that we have conducted (see Figure 2 below), little research has been directed at the functional impact of chronic PTH. Cohen et al[33] found that headache, including PTH, was a significant cause of unit attrition in

deployed military personnel, but did not specifically examine PTH separate from all other headache causes.

III. Review of the Current Literature

From the general headache literature, we know that chronic headache takes a major toll on productivity. Some investigations of quality of life in migraines reveal significant adverse effects on the ability to participate in daily activities.[34] In a random-dialing survey study, almost 10% of people missed work because of a headache and 31% felt that their work effectiveness was reduced.[35] Students report significant decreases in study productivity with the occurrence of headaches, migraine more so than tension-type.[36] A 1999 study estimated that there was an economic cost of $13 billion a year in the U.S. for missed work days and decreased work productivity due to headache.[37] A recent review article on disability in chronic daily headache notes that studies have documented a pervasive negative effect on work and household duties, as well as impairments in social and familial duties, cognitive functioning, and psychological health.[22] We also know that painful conditions in general can result in sleep disturbance and depression, both of which can adversely affect cognition. It is likely that these effects would be at least as severe in persons after TBI who may be dealing with additional cognitive or behavioral challenges. For patients with TBI such functional impact may slow rehabilitation efforts and successful re-entry into employment and other areas of productive activity.

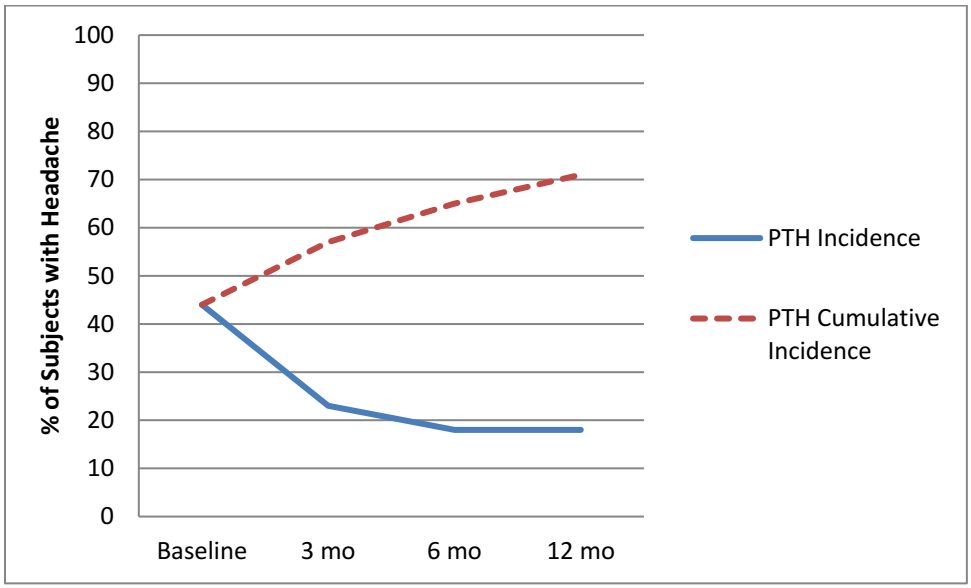
IV. Preliminary Data

Prior work on PTH at the UWTBIMS: In the prior cycle, we led a multicenter study, which prospectively followed a cohort of 452 persons enrolled into the TBI Model Systems at 7

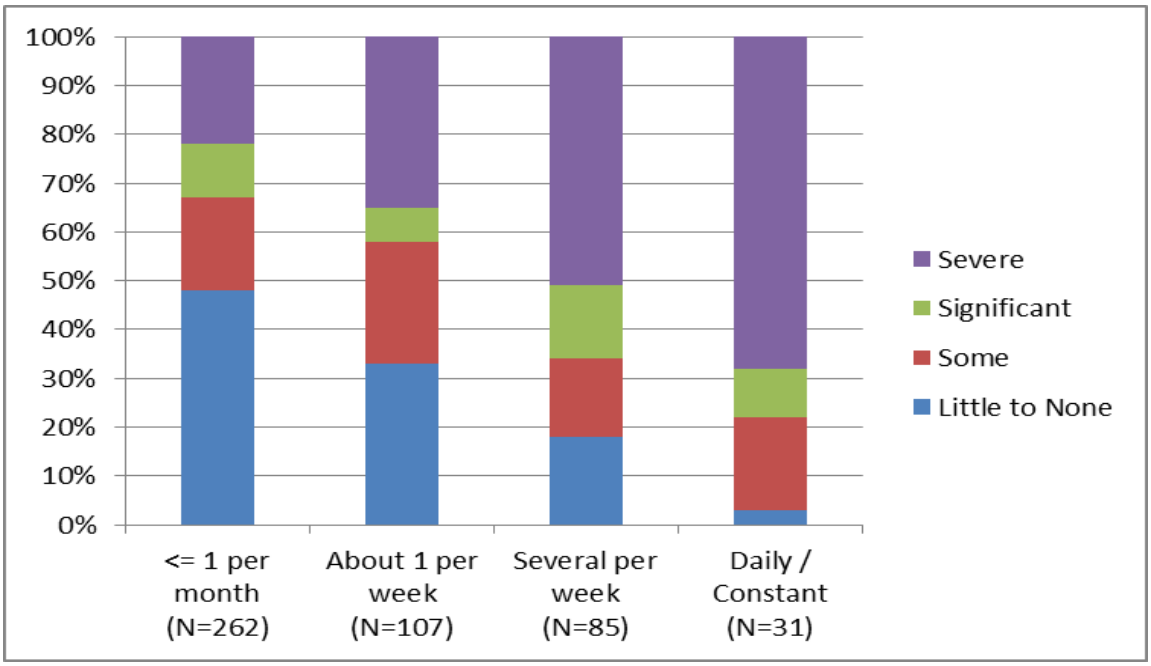
centers over 16 months. Each subject was assessed in-person at baseline for current and persisting headache, headache history, headache characteristics, risk factors for headache occurrence, and effect of headache on normal function. Subjects were interviewed by research staff via telephone at 3, 6, and 12 months after injury with a headache survey including frequency, severity, and characteristics.

The prevalence of PTH was high with over 40% of participants reporting headache at every time point measured (3, 6, and 12 months) after injury, indicating that PTH is a very common and persistent problem for those with brain injury. An astonishing cumulative 71% of the cohort reported PTH at some point during the first year after injury (see Figure 1). Two factors were found to be significantly related to the occurrence of PTH, prior history of headache and female gender. In this study, we found that 22-29% of the sample reported frequent headaches (multiple times per week/daily). This stands in contrast to what is reported for the non-brain injured general population in which 4-5% report chronic daily headache (greater than 15 days per month).[38-40]

Figure 1. Incidence and cumulative incidence of headache across 1 year after TBI.



Recently, we reported the preliminary results of the second natural history study of PTH after mild TBI.[41] We enrolled 220 persons admitted to the hospital for observation or for other injuries with mild TBI based on ACRM criteria. Baseline prevalence of headache prior to injury was 17%. However, prevalence at 3 months was 73%, at 6 months 79%, and at 12 months 67%, even higher rates than for those with moderate-severe TBI. The majority of these headaches appeared to have characteristics of migraine or probable migraine headache. At 12 months, 25% had headaches that occurred several times a week. Impaired function (inability to engage in daily activities including work, school, household, or social activities) due to headaches was reported even by those with lesser frequency of headaches as seen in Figure 2 which is consistent with reports from those with moderate to severe TBI. More than 50% of reported headaches at 6 and 12 months after injury were rated as having significant or severe impact on functioning in those with moderate to severe TBI. **Figure 2. Headache Impact by Frequency**



There have been opposing points of view regarding the association of head injury severity and incidence of headaches where some believe that headaches occur primarily in mild injuries and others disagree.[17, 18, 21] Our research indicates that headaches are common in all severities of TBI although the prevalence is higher in mild TBI.[42]

PTH falls into the category of secondary headache. The International Headache Society (IHS) defines a secondary headache as one that occurs de novo with another disorder recognized to be capable of causing it, e.g., traumatic brain injury causing a PTH.[43] The IHS acknowledges that the clinical characteristics of secondary headaches are poorly described in the scientific literature and therefore, does not use clinical characteristics of these headaches as part of their definition. In fact, the IHS classification of post-traumatic headache is defined by the latency of headache following injury, duration of the headache, and severity of the brain injury preceding the headache. According to this definition, an acute PTH must occur within 7 days of injury. After 3 months, an acute PTH is considered to be a chronic PTH. The time

element that is included by the IHS in the definition of PTH, that is, that the headache must have an onset within the first week after injury, likely leads to an underestimation of PTH.[19, 42] Our work as well as that of Theeler et al[44] has found that up to one-third of PTHs can first be recognized outside this window of time, therefore PTH may manifest in much the same way that post-traumatic epilepsy presents, occurring months to years after injury.[45]

In our research using classification criteria designed for the primary headache disorders, we found PTH to be characterized most frequently as migraine or probable migraine, followed by tension-type headaches, and cervicogenic headaches.[25] It is also recognized that trauma to the head can result in worsening of a previous headache syndrome. We recently published an article that provides characterization of PTH in our cohort of individuals enrolled into the TBI Model System with moderate to severe TBI.[25] Our study revealed that of those reporting headache, 63% met criteria for migraine and probable migraine using primary headache classification criteria for this cohort of prospectively studied individuals. Tension type headache accounted for 21% and cervicogenic headache for only 10%. Consistent with the general headache literature, females were more likely to have migraine headache and to have reported migraine headache prior to injury. Those with migraine headache also reported higher frequency of headaches compared to those with other headache types.

Virtually all early reports of PTH have relied on populations with mild TBI and post-concussion syndrome disorders. Many of the studies report on self-referred populations. Lew et al[16] in 2006 reviewed all articles published in English on post-traumatic headaches in a 15 year period (145 in total) and found only 5 articles reporting studies that addressed the characteristics and types of headaches, and 10 articles on the treatment of PTH (2 single case reports, 3 case

series, 5 retrospective or uncontrolled prospective studies). Pooled data from these 5 studies indicated that for those with headaches, tension-type headaches were most common occurring in 33.6% of headache sufferers. Migraines occurred in 28.6% of the headache patients. More recent examination of characterization of PTH has come from studies conducted on military populations with similar results to our study.[44, 46] In contrast to earlier research on PTH,[18, 47, 48] results from military populations suggest that characterization of PTH is consistent with higher rates of migraine type headache, over tension or cervicogenic.[32, 49-52]

What is the current approach to treatment of PTH?: Currently, the literature on treatment of PTH suggests following guidelines for treating headache using general population studies on those with primary headache disorders.[46, 53-55] However, all these recommendations also note the lack of randomized controlled trials in individuals with TBI and cite concerns in treatment trials of headache in a brain-injured population for the potential for more adverse effects from medication. In our survey of rehabilitation physicians and headache specialists, we found that physicians had difficulty utilizing headache type to drive treatment choice. Therefore, more data on defining characteristics of PTH and effective treatment of PTH is necessary. While physical therapy and counseling were among the most frequent choices of treatment among this group, the effectiveness of these treatments in this population is not known.[26]

With no Class I randomized, prospective, blinded treatment trials of PTH, some clinicians have used migraine-specific therapy for PTH based on anecdotal evidence of success. Erickson et al conducted a retrospective review of PTH treatment in a clinic-based population of active duty soldiers, and found that the “triptans”, a class of migraine-specific medications, were effective in those suffering from moderate to severe PTH, both blast and non-blast related.[56]

Most, but not all, of these headaches had migraine characteristics. A breakdown of reported effectiveness did not specifically correlate headache characteristics with drug responsiveness. The rationale for treatment with migraine specific therapy is that though primary headache disorders may be due to an inherited disorder of transmission resulting in episodic brain dysfunction and PTH is thought to have a structural basis or potentially treatable cause relating to an injury, both may have a similar response to migraine-specific treatment based on a similar phenotype. Therefore, in moderate to severe PTH meeting classification criteria for migraine or probable migraine, the use of triptans has been thought to be a reasonable course of action. However, no research has been conducted on triptans in PTH to determine whether there may be different side effect profiles from primary migraine treatment or whether the medication can be taken appropriately (for example, that is has greater efficacy when taken at headache onset) by individuals with TBI.

Why triptans? Pharmacological features of triptans and the concept of the physiological "common pathway": Migraine specific medications include the "triptans" which are serotonin 5-HT 1B/1D agonists that work to inhibit inflammatory peptide release (e.g., calcitonin gene-related peptide, CGRP, a potent vasodilator) in the meninges through the serotonin 1D receptor. Blocking release decreases a "pain signal" being generated from peripheral trigeminal nerves to the trigeminal nucleus caudalis which is thought to modulate or generate migraine. Triptans also bind to receptors on the meningeal artery endothelium via serotonin 1B (5-HT 1B) receptors causing vasoconstriction of vessels dilated by CGRP or other inflammatory peptides.

Based on evidence of multiple Class I studies, triptans are recommended for treatment of migraine at any level of pain. Sumatriptan was the first triptan approved by the FDA for treatment of migraine in 1993. It has been the most prescribed triptan and the gold standard against which all other triptans have been compared. It has proven efficacy and tolerability for the treatment of primary migraine. It comes in several oral doses (25 mg, 50 mg and 100 mg) and the 100 mg dose has been evaluated against placebo in 19 randomized, double-blind, placebo-controlled clinical trials of migraine.

There is evidence to show that if a single subject has a variety of headache types which include migraine (mixed headache disorder), then sumatriptan is effective for all headache phenotypes in that subject as compared to treatment of those individuals with headache disorders that do not include migraine (primarily mild-moderate, non-disabling headache). In this group of only non-migraine headache, sumatriptan is no more effective than placebo.[57] This argues for a common underlying mechanism of different headache "types" in those who having a moderate to severe headache which fits the definition of "migraine" or probable migraine despite differing headache types at different times (mixed headaches), all of which are responsive to 5-HT 1B/1D agonists. Given anecdotal response to the triptans in PTH described in one observational study by Erickson[56] and potential physiologic similarities between primary headache disorders and PTH, resulting in similar headache phenotypes, there may be a final common path with response to migraine medication in primary migraine and PTH which would provide clinicians with tools to effectively treat these headaches which have a significant impact on function following brain injury.

Indirect evidence for this common pathway comes from similarities between TBI and migraine in biochemical changes found in the brain. Increased extracellular potassium and intracellular sodium, calcium and chloride have been reported.[58] Both migraine and PTH show excessive release of excitatory amines such as glutamate and aspartate. Intracellular and total brain magnesium has been found to decline in mild TBI and is thought to be low during and between migraine attacks. There is a change in the calcium/magnesium ratio in both conditions and nitric oxide, while potentially leading to tissue injury through free radical formation following TBI, is thought to be involved in migraine, as it is a potent vasodilator at the vascular endothelium.[58] These similarities between neurochemical changes in TBI and migraine suggest a shared mechanism of headache occurrence by way of a "final common path."[59] Since the migraine pathway is thought to involve activation of the trigeminovascular system and the release of inflammatory neuropeptides, causing neurogenic inflammation which is blocked by sumatriptan, it is plausible that direct physical force from TBI can cause the biochemical changes discussed above also activating the trigeminovascular system and causing neurogenic inflammation and therefore, responding to treatment with a drug so far only approved to treat the moderate to severe headaches known as migraine.

V. Specific Aims of Study: The ultimate aim of this Phase II open-label study is to test the research methods and approach necessary to successfully carry out a Phase III study for the treatment of post-traumatic headache (PTH). During this study, we will

1. Determine the feasibility of using a headache diary accessed via smart phone application, the web, or paper/pencil to record accurate headache data in a group of

individuals with mild (with adequate documentation or in the opinion of study physician), moderate and severe TBI, and their caregivers as indicated.

2. Evaluate the approximate effect size of sumatriptan on pain severity, duration, and recurrence of headaches in persons with moderate to severe PTH in order to establish the necessary sample size for a Phase III study.
3. Assess the side effect profile of sumatriptan in a brain-injured population as well as the safety of sumatriptan in subjects with TBI.
4. Evaluate the ability of persons with TBI, and their caregivers as indicated, to successfully use abortive headache medications and comply with treatment.
5. Examine the relationship between PTH and cognitive, emotional, and other self-report measures to determine important factors to include in a Phase III study.

VI. Overview of Study Design

This phase II evaluation of sumatriptan as a treatment for PTH will examine the methods and approach necessary to take the next step to a phase III trial. The sample will include 40 individuals with mild (with adequate documentation or in the opinion of study physician), moderate and severe TBI who will be recruited primarily from patients within UWTBIMS and from outpatient clinics and brain injury related organizations to be followed over 3 months. We plan to enroll individuals with moderate to severe headache who experience at least two and up to a maximum of fifteen moderate to severe headaches per month. **Severity will be rated using a 4 point pain scale (0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache).** Headache classification will be confirmed by clinician interview.

Table 1. Summary of Protocol for Proposed Study of Sumatriptan for PTH

Pre-Screening	**Visit 1** (Day 1)	**Days 1-29**	**Visit 2** (Day 30)	**Days 31-89**	**Visit 3** (Day 90)
Inclusion/ Exclusion Criteria	Consent Headache questionnaire All subjects trained in use of headache diary	Daily headache diary Weekly telephone calls Daily headache diary reminders (phone, text, email)	Evaluate headache diary for eligibility (pre-visit) Baseline assessment (if meets headache diary eligibility) History, clinical headache interview and physical examination Dispense drug if eligible	Daily headache diary Study drug use per instruction Weekly telephone calls	Follow up Assessment Drug count

Population

A. Inclusion criteria:

A subject will be eligible for enrollment into this study if all of the following criteria are met:

- Age 16-65. The higher age limit is set to 65 to reduce likelihood of health issues which may be a contraindication to the use of sumatriptan and to meet recommendations by the International Headache Society.[62]
- Diagnosis of mild (with adequate documentation or in the opinion of study physician), moderate or severe TBI occurring at least 2 weeks but not greater than 60 months before enrollment. Two weeks was chosen to include only those subjects who are having headache beyond their acute injury and 60 months was chosen to ensure that the headache may reasonably be connected to the TBI.
- Subject has at least two and up to a maximum of fifteen total moderate to severe headache days per month. Subject report of meeting this criterion will result in the subject entering the first month of the study. However, this frequency must be documented in headache diary to enter the treatment phase of the study.
- Headaches are classified as moderate to severe (2 or 3 on the 4 point pain scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache). As above, headache severity must be documented in the month-long headache diary prior to entry into the treatment phase.
- Subject obtains a score of 25 or greater on the Mini Mental Status Examination[63] or has a caregiver to monitor implementation of study procedures including the headache diary and medication regimen.

- Subject is able and willing to give written informed consent for participation in screening activities and to participate fully in the study if eligible. For those subjects who score below 25 on the Mini Mental Status Examination, there must be a caregiver willing to also be consented for participation in the study.
- Female subjects of childbearing potential must have a negative pregnancy test at enrollment, and agree to remain abstinent or use acceptable methods of birth control (i.e., hormonal contraceptives, intrauterine device, diaphragm with spermicide, cervical cap or sponge, condoms, or partner has had a vasectomy). Sumatriptan has been assigned to pregnancy category C by the FDA. Animal studies have revealed evidence of decreased fetal body weight, embryo lethality, and cervicothoracic vascular defects. There are no controlled data in human pregnancy and therefore, sumatriptan should only be given during pregnancy when benefit outweighs risk.

B. Exclusion criteria:

A subject will not be eligible to participate in this study if any of the following criteria apply:

- History of ischemic heart disease (angina pectoris, history of myocardial infarction, silent ischemia, Prinzmetal's angina/coronary vasospasm, ischemic bowel disease, or peripheral vascular disease) based on self-report or history of basilar or hemiplegic migraine.
- Uncontrolled hypertension at initial visit (sitting systolic pressure > 140 mm Hg, diastolic pressure > 90 mm Hg).
- Impaired renal or liver function by medical history.
- Subject has taken an MAO inhibitor within 2 weeks of screening because these drugs and sumatriptan use the same metabolic pathway.

- Subject has hypersensitivity reactions or other intolerance to sumatriptan or any other 5-HT 1B/1D-receptor agonists.
- If subjects have medication overuse headache in the opinion of the investigator (if using medication to treat acute headache on more than 15 days per month).
- Inability to speak or read English which would limit ability to interact with examiners and complete headache diary and other questionnaires during this study.

C. Sample Size

- This is a single arm, unblinded study and is being undertaken to test necessary study instruments and procedures, establish feasibility and determine side effects in a population with moderate to severe TBI in preparation for a subsequent Phase III study. Therefore, we are using forty subjects as a reasonable sample size to meet these aims.

VII. Overview of Study Procedures

A. Recruitment

Description of the recruitment process: Subjects enrolling in the UWTBIMS will be provided information regarding the study and asked for permission to call them post discharge from the hospital (and at least two weeks out from their injury) for screening. Additionally, subjects enrolled in the UWTBIMS over the 60 months prior to the study start date will **be called for screening** if they had indicated on their prior consent form interest in being contacted for future studies. **If there is interest in study participation, then a pre-screening survey for inclusion/exclusion criteria will be given**. Also, subjects will be recruited from outside the TBI MS, including outpatient headache and TBI clinics, and be advertised through related organizations such as the Washington Brain Injury Alliance. There will also be advertising on our own TBI MS website. Study information emails using study brochure will be sent out to UW providers on a monthly basis to aid with recruitment. A provider may respond with the name and medical record number of a potential subject whom the provider has spoken to about the study and given verbal permission for the coordinator to contact for screening.

Subjects will be encouraged to bring a family member or caregiver with them to any screening or research appointments. Participants who are under 18 will be required to bring a parent or guardian with them to their research appointments. As part of the process to evaluate participants' ability to comply with the use of the headache diaries and study drug, these family members/caregivers will be interviewed about the amount of assistance needed

by the subject and any discrepancies in subjects' reports. In our prior study, while family member/caregivers were not able to give details of headache characteristics, we did find that they were able to report accurately the occurrence of headaches when compared to subjects' reports.

B. Data Collection and Measures

Data collection will occur at enrollment, and at each clinic visit. Table 2 provides a summary of the measures that are collected at each step in the study. Figure 3 outlines all activity over throughout the duration of the study. A full description of each measure and the reason for its use follows the table. (Table 2: List of measures.)

Table 2. List of measures

Assessment	**Timeline**		
	Pre-Treatment Visit (Clinic Visit 1)	**Treatment Visit (Clinic Visit 2)**	**Outcome Assessment (Clinic Visit 3)**
INITIAL SCREENING MEASURES			
Mini Mental State Examination[63]	X		
Demographic Questionnaire	X		
Headache History Questionnaire	X		X (since study start)
Headache Diary	X (to be kept for 1 month)		
Medical History and Physical Examination	X		
Weekly Compliance Phone Calls	X	X	
Pregnancy Test (if needed)		X	
COGNITIVE MEASURES			
Cognitive Assessment *1. Rey Auditory Verbal Learning Test (RAVLT)[64] *2.Trail Making Test (TMT)[65] *3.Wechsler Adult Intelligence Scale – IV (WAIS-IV), Processing Speed Index[66]		X X X	
SELF REPORT AND EMOTIONAL HEALTH MEASURES			

*Physician Health Questionnaire-9 (PHQ-9)[67]		X	X
General Anxiety Disorders 7 (GAD-7)[68]		X	X
Analog Pain Scale[69]		X	X
Insomnia Severity Index[70]		X	X
Brief Pain Overview[71]		X	X
*EuroQol[72]		X	X
*Satisfaction with Life Scale (SWLS)[73]		X	X
*Rivermead Post Concussion Symptom Questionnaire (RPQ)[74]		X	X
OUTCOME MEASURES			
Headache Diary		X (kept throughout treatment period)	X
Headache Impact Test 6 (HIT-6)[75]		X	X
Compliance measures (Headache diary completion percentage, medication counts		X	X
Reduction in number of headaches and pain relief		X	X
Number and type of adverse events		X	X

*indicates measures which are part of the Common Data Elements for TBI

Measures were chosen to best assess domains of interest for this project. Where applicable, measures were chosen that are part of the Common Data Elements for TBI recommended as a result of a scientific initiative led by several sponsoring federal agencies (NINDS, NIDRR, VA, DCOE, and DVBIC) and the results of which were published in a special edition of Archives of Physical Medicine and Rehabilitation (2010, Volume 91 (11)) and which have been recently updated for Rehabilitation of Moderate to Severe TBI (TBI Version 2.0 CDE Review Package, http://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards). The purpose of using Common Data Elements is to allow comparisons between studies, ease scientific communication, and accelerate accumulation of scientific knowledge. Three of the content experts involved in the CDE initiatives are investigators on the proposed study (Dikmen, Temkin and Bell). The headache questionnaire has been used in our prior natural history studies

and is available for review in Appendix A along with the proposed flow chart for the headache diary.

C. Primary Outcome Measure: Resolution of headache 2 hours after drug is taken.

D. Secondary Outcome Measures:

a. *Physician Health Questionnaire-9 (PHQ-9)67,

b. General Anxiety Disorders 7 (GAD-7)68,

c. * Analog Pain Scale69,

d. Insomnia Severity Index70,

e. *Brief Pain Overview (BPO)71,

f. *EuroQol72, *Satisfaction with Life Scale (SWLS)73,

g. *Rivermead Post Concussion Symptom Questionnaire (RPQ)74,

h. Headache Impact Test 6 (HIT-6)75,

i. compliance measures (headache diary completion percentage,

j. medication counts, reduction in number of headaches and pain relief, number and type of adverse events.

k. Injury type and severity, medication use, and accompanying disorders.

l. Data on cognitive status to ascertain appropriateness for participation and to further characterize the population with respect to ability to use headache diary.

   i. Mini Mental State Examination63,

   ii. Rey Auditory Verbal Learning Test (RAVLT)64,

   iii. Trail Making Test (TMT)65,

   iv. Wechsler Adult Intelligence Scale – IV (WAIS-IV)

v. Processing Speed Index66.

E. Rationale/Explanation for Measure Selection:

Headache relief, frequency and severity are the most frequently used measures of medication efficacy in headache research. The headache survey and HIT-6 will further characterize the headache syndrome and functional impacts of headache. The headache survey will gather information on several factors that will be used to comprehensively describe PTH and its treatment including International Classification of Headache Disorders, 2nd edition (ICHD) criteria (type of headache by characteristics such as location, duration, severity, associated symptoms).76 This measure was developed by our group and used for the multi-site study on the natural history of headache after TBI funded by NIDRR through the TBI Model Systems5 program and a second single site field-initiated study funded by NIDRR to examine the natural history of headache in individuals with mild TBI.

The **Mini Mental State Examination**[63] will be administered at the screening visit. Any score greater than or equal to 25 points (out of 30) indicates a sufficient cognitive level likely to enable a subject to participate without support. A lower score would indicate that the support of a caregiver would likely be necessary for successful adherence to the study protocol.

The other cognitive measures (Rey Auditory Verbal Learning , Trail Making Test, WAIS IV Digit Symbol, and WAIS IV Symbol Search) will be given at the clinic visit on Clinic Visit 2 to characterize the population.

The RPQ is a well-validated measure of post-TBI symptoms/severity and is used to measure other symptoms that may impact headache. Other measures were selected to capture

the areas of functioning expected to be impacted by headache and to change as a function of treatment. The EuroQoL and Satisfaction with Life Scale (SWLS) are intended to examine not only functional independence in various activities of everyday life, but also satisfaction with that quality of life. The PHQ-9, GAD-7, BPO, Analog Pain Scale and ISI measures will allow for evaluation of frequently co-occurring disorders (pain, sleep disorders, and depression) and broader response to the intervention.

A negative pregnancy test will be required for any female of child-bearing years.

F. Headache Diary: As there are no biomarkers for headache or headache severity, headache diaries are used to concurrently record the characteristics, frequency, and severity of headaches and the response to treatment and have been successfully used in a variety of populations, including children.[77] We will ask the subject to fill out a headache diary each day during the study to rate the frequency and severity of headache, simple headache characterization, and response to study drug. This diary will be available on a smart phone application, via a secure internet survey or on paper, depending on the fit for the participant. The paper-based diary is rated at a 3rd grade reading level. The research assistant will practice filling out the diary with the subject prior to discharge from the hospital and will review on the weekly telephone calls. [See Attachment 19 for headache diary content]

VIII. Enrollment and Visits (See Table 2, Figure 3)

Enrollment: Subjects enrolling in the UWTBIMS will be provided information regarding the study and will be asked for **permission to call them post discharge from the hospital for screening.** Additionally, subjects enrolled in the UWTBIMS over the 60 months prior to the study start date will be called for screening if they had indicated on their prior consent form interest in being contacted for future studies. **If there is interest in study participation, then a pre-screening survey for inclusion/exclusion criteria will be given**. Additionally, subjects will be recruited from outside the TBI MS, including outpatient headache and TBI clinics, and be advertised through related organizations such as the Brain Injury Alliance.

Subjects will be encouraged to bring a family member or caregiver with them to any screening or research appointments. Again, participants under 18 will be required to bring a parent or guardian with them to their study visits. As part of the process to evaluate participants' ability to comply with the use of the headache diaries and study drug, these family members/caregivers will be interviewed about the amount of assistance needed by the subject and any discrepancies in subjects' reports. In our prior study, while family member/caregivers were not able to give details of headache characteristics, we did find that they were able to report accurately the occurrence of headaches when compared to subjects' reports.

Description of obtaining informed consent: Subject Informed Consent will be obtained after pre-screening and prior to any collection of any study data. Subjects will be emailed or given a copy of an ICF (Informed Consent Form) prior to their baseline clinic visit. This will allow extra

time to review study procedures, however it is not required for them to review the consent form before meeting with research staff. All interested participants will be consented in a private conference room or exam room by the study coordinator or research assistant. Each page of the ICF will be reviewed with the subjects. For those subjects scoring <25 on the MMSE, an authorized proxy will be consented and we will document the assent of the subject. Subjects will be given ample time to ask if anything is unclear about the study and what is expected of them as participants in the study. The subjects will be encouraged to ask questions about the study. Once all questions are answered, subjects and proxies will be asked to voluntarily sign and date the ICF. The person conducting the Informed Consent discussion will sign and date the consent form. The original ICF will be filed in a study binder stored separately from subject's study ID.

Pre-treatment Visit *(Visit 1)**:*** Subjects who complete informed consent and meet the inclusion criteria (with no exclusion criteria) will be asked to complete 30 days of headache diary questions. This will document the number of headaches, headache severity, headache days and description of their headache and associated symptoms. This will assist in determining compliance and ability to complete this portion of the study, and ensure that the frequency of headaches is sufficient to include into study intervention (See Attachment 9 Study Sequence Flow Sheet). Research staff will meet with the subject (and caregiver) to provide training on headache diary utilization and will contact them on a daily and/or weekly basis to answer questions and maximize accuracy and compliance with the diary, depending on the subject's preference. Proper utilization of a headache diary and success of data input by the subject and caregiver will be evaluated following weekly interviews with the research assistant. The

headache diary will be available in multiple forms. We will have iPod Touch devices loaded with a headache diary application that will allow for direct entry of responses onto a security protected survey site and will include reminders for daily completion as well as prompts for efficacy of drug treatment used. However for those who prefer, a computer accessed web-based headache diary (otherwise similar to the iPod version) and a paper version with identical questions will be available. For those who choose the alternate forms of diary, a clip-on timer will be provided for recording of headache duration and reminders may be sent as text messages or emails based on subject preference.

Treatment Visit (*Visit 2*):

Medical History and Physical Examination. A medical history will be obtained at the first visit to review inclusion and exclusion criteria and to elicit a thorough review of systems so that adverse events will be identifiable if they occur. Physical examination at the second visit will also ensure that cardiovascular status is compatible with sumatriptan use and will document current status to allow for identification of potential adverse events. Finally, standard primary headache classification criteria will be reviewed with each patient to determine whether they meet criteria for migraine or probable migraine. The headache diary will be reviewed before the treatment visit is scheduled, and patients who disqualify based on the classification of their headaches will not be scheduled to come in for Visit 2, as this would be an undue and unnecessary burden given they will not be continuing with the study. .

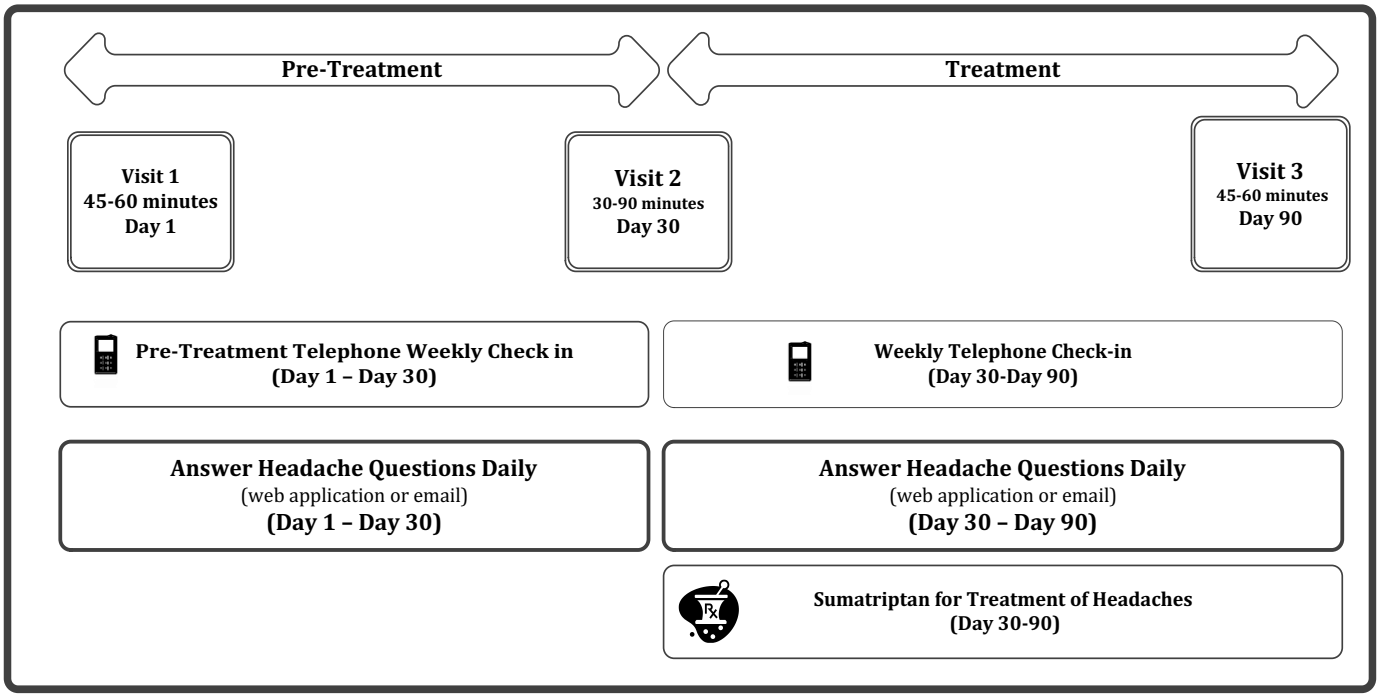
Data Collection at Treatment Visit *(Visit 2)***:** Headache histories will be assessed after 30 days (+/- 3 days), and subjects that have experienced between 4-15 headaches will be included in the medication intervention with sumatriptan. Subjects who qualify for the sumatriptan intervention will receive several assessments, given medication, usage instructions, and scheduled for weekly phone calls for weeks 5-11. (See Table 2). Individuals whose headaches do not meet criteria for migraine or probable migraine, based on data from headache diaries, will have their participation in the study end and will not participate in Visit 2. This is due to the lack of evidence that sumatriptan is effective for the treatment of non-migraine types of headache.

Weekly Telephone Follow-Up Calls: Research staff will call each participant weekly to check on compliance with drug diary use during the first month of the study (Weekly calls 1-3) to check on compliance in diary usage. For weekly calls in weeks 5-11 (for the intervention participants), research staff will inquire about study drug usage, and query for adverse events. Use of rescue medications for headache will be recorded. In the case of minor adverse effects which are bothersome to the patient, the dosage will be decreased to a ½ pill per use.

Follow up Visit (Visit 3). This will be the final visit for the subjects. Vital signs will be obtained. Drug containers and headache diaries will be collected from all subjects. Measures administered on this visit will include:

1) **Interim medical history form** (new diagnoses, changes in medications)
2) **Headache Survey**
3) **Headache Impact Test (HIT-6)** – Questions about headaches and how much they affect patient's life.
4) **Satisfaction with Life Scale (SWLS)** – Questions about how satisfied patient is will life.
5) **Rivermead Post-Concussion Symptoms Questionnaire (RPQ)** – Questions about the 16 most common symptoms after concussion.
6) **Patient Health Questionnaire (PHQ-9)** – Questions about symptoms of depression.
7) **Brief Pain Overview (BPO), Analog Pain Scale** - Questions asking about pain.
8) **Insomnia Sleep Index (ISI)** – Questions about sleeping habits.
9) **Euroqol** – Questions about quality of life.
10) **Brief Symptom Inventory** – Questions about other symptoms.

Figure 3: Subject Participation Summary



Subject Instruction: During the Visit 1, research staff will explain headache diary and demonstrate usage to ensure patient (and caregiver if present) understand. Instructions will include how and when to take the study medication. Their pain will be assessed 2 hours following use of sumatriptan, this will include:

1. pain presence
2. severity throughout the first 24 hours after use of the study drug
3. whether there was a need for 2nd dosage of sumatriptan
4. Whether there was any use of any rescue medications
5. Whether there was recurrence of pain.

Written and verbal instructions will be given on which drugs to avoid during the study, acceptable drugs to use for rescue therapy, and what to do in the case of an adverse event.

IX. Treatment with Sumatriptan Procedures

Use of sumatriptan and rescue drug: Two packages of nine (9) sumatriptan 100- mg. pills (18 pills total for 2 months of treatment) will be dispensed to each subject on Day 30 once they have gone through baseline assessment. On average, this will treat a minimum of 5 headaches or a maximum of 9 headaches per month. Subjects will be instructed to take the sumatriptan at the onset of headache pain. If subjects are not pain free at 2 hours after the first dose of study medication, they will be allowed to take one additional pill, but will be limited to 2 pills in a 24 hour period. Subjects will be instructed to take no more than 9 pills in a 30 day period based on research which suggests that additional dosages may increase the risk of medication-overuse headache. A list of appropriate medications will be provided that they can use if they: 1) continue to have headache pain 2 hours after their second dose of study drug, or 2) they have used their 30 day supply of study drug within the month. All subjects will be contacted by telephone on a weekly basis to review their headache diaries, assess potential adverse events, review compliance with use of the study drug, assess other treatments being utilized, and answer any questions. After 60 days, all subjects will be given an outcome assessment. The measures included in this assessment are shown in Table 2.

Compliance: Compliance will be assessed during the weekly telephone follow-up calls to subjects and caregivers and we will have subjects return their medication packs and any unused medication at Visit 3. Any lack of compliance to the study protocol will be recorded on case

report forms for that subject. Subjects will be encouraged to improve compliance and the research staff will assist the subject and/or caregiver in problem solving compliance issues, including suggesting to subjects that staff contact them either via email, telephone or text with daily reminders to complete their headache entry.

Medication administration: The study drug will be distributed in blister packs. Subjects will be instructed to decrease the dose by 50% (cut the tablet in half) if side effects occur after the first dose. They will also be required to contact the research staff to report the side effects. If the side effects continue to be intolerable, that subject will be discontinued from the intervention portion of the study but will be asked to continue keeping their headache diary.

Rationale for Dosage Selection and Medication Administration Procedures: The recommended initial dosage of Sumatriptan is 100 mg[76] and this is the most commonly prescribed dose in primary care as well as neurology or headache specialty clinics. In a meta-analysis of 53 clinical trials involving sumatriptan,[77] 100 mg of Sumatriptan resulted in 29% of patients becoming pain free at 2 hours (moderate to severe pain to no pain) vs. placebo. This is a much more rigorous end-point than the pain relief response which showed a 59% headache relief response (moderate to severe to mild or no pain) vs. placebo. Rescue medications will include acetaminophen, ibuprofen, or other analgesic as prescribed by the subject's own physician; detailed instructions will be provided to the subjects.

A. **Subject Discontinuation:** Subjects may be discontinued from the study drug by their request or if the subject experiences an adverse effect sufficient to warrant withdrawal

from the study drug. In the case of discontinuation of study drug, the reason will be recorded and the subject will be asked to continue to monitor their headaches with use of the headache diary and to participate in a final assessment.

Compensation: Subjects will be given $25 upon completion of each of the three clinic visits (total $75). This compensation is to defray the cost of phone use, transportation/parking cost, and any meals and to compensate subjects for their time. Subjects will also have their parking costs validated.

X. Data Analysis

Study Sample Size and Rationale: This is a single arm, unblinded study and is being undertaken to test necessary study instruments and procedures, establish feasibility and determine side effects in a population with mild (with adequate documentation or in the opinion of study staff) moderate, or severe TBI in preparation for a subsequent Phase III study. Therefore, we are using forty subjects as a reasonable sample size to meet these aims.

Case Availability: We anticipate no difficulty in recruiting 40 subjects to participate. Given our natural history study,[19] we expect at least 48% of TBIMS subjects to have headaches that qualify in terms of both frequency (4 to 15 headaches per month) and severity (rating of 2 or 3 on the 4 point scale), (26% had qualifying headaches at 3 months, another 10% who did not qualify at 3 months had qualifying headaches at 6 months and another 12% who had not qualified previously had qualifying headaches at 12 months). The UWTBIMS expects to

recruit at least 45 patients per year. Those entered in the first 3.5 years of the upcoming cycle (45*3.5=158 TBIMS participants) will be eligible for the headache study. Additionally, because eligible subjects can be between 3 and 60 months post-injury at recruitment, we will be able to contact the UWTBIMS subjects enrolled in the previous 60 months who indicated interest in being contacted for future studies.

Data Analysis: Data analysis for the feasibility and safety aims will be primarily descriptive. We will calculate the percent of subjects who used the diary successfully, percent who stopped taking sumatriptan because of side effects, percent who experienced each adverse event, and percent who were able to maintain compliance with treatment. We will present a confidence interval for each estimate. To get preliminary data on efficacy of sumatriptan, we will compare headache control before and after the participants start taking sumatriptan. We will calculate the percent of headaches that had complete resolution (pain free at 2 hours) for each person, during the initial (pre-intervention) month when they used their regular treatment and during the two months (intervention) when they treated headaches with sumatriptan and compare them using a paired t-test. We will also examine different definitions of headache relief (pain free by 30 minutes, no more than mild pain (score <=1) by 30 minutes, no more than mild pain by 2 hours) to see if another outcome measure may have advantages for a future Phase III study. We will descriptively examine any differences in compliance, side effects, and feasibility based on cognitive functioning, as well as by other self-report and emotional health measures. Changes in these measures from pre to post

treatment will also be examined to determine whether there is any change that occurs with treatment and which may be important variables to include in a Phase III study.

XI. Data Management

Assessment data and some headache diary data will be collected on paper forms and entered locally into a specially-designed Access database that incorporates data quality checks. Device and web-based headache diaries will be entered directly into a Catalyst survey site (located on a secure, password protected server). All files will be password protected to ensure only authorized personnel can view or change them. Data will be uploaded to the Biostatistics Unit monthly. Data are stored on a University of Washington secure server that is backed up nightly. More sophisticated checks than can be implemented at the time of entry will be run monthly, generating queries for the staff to evaluate and correct if necessary. Neuropsychological tests will be double checked and double scored. Reports monitoring the progress of the study will be generated monthly to help the investigators identify areas such as enrollment or follow-up rates that might need specific attention. Analyses will be performed using SPSS or SAS.

A. *Identifiers and confidentiality***:** Data will be identified by study number and coded initials (MS replacing true initials NT), not universal identifiers such as name or hospital number. Study number, rather than name will be on data collection forms (other than the form that gathers contact information). Study files will be kept in a locked cabinet or stored in a locked room. Computer files will be encrypted and password protected.

Identified information such as phone numbers needed to contact the participant and consent forms will be kept in separate files from the study data.

B. Study staff will have access to study records as will representatives of the human protection offices and representatives of the funding agency. The study will not intentionally collect any data that would need to be shared with state or local authorities. If the subject responds to questionnaire items or volunteers information about intent to harm themselves or others, we have a standard IRB approved protocol that will be enacted to manage such disclosures to ensure subject or others safety.

C. If the subject reveals suicidal ideation on the PHQ-9, one of the clinician investigators will be notified immediately to evaluate the subject. If the investigator is convinced that active suicidal ideation or plan is NOT present, we will resume evaluation and participation in the study. If the provider is concerned that the subject has active suicidal ideation and/or plan, we will use suicide management protocols that have are approved by our Institutional Review Board and include specific algorithms to assess risk, use of local Crisis Clinic numbers and 24/7 back-up by MD or PhD staff who can conduct more comprehensive assessments, and make referrals as needed, including escorting the subject to the emergency department.

D. *Disposition of data*: Hard copy data will be stored in locked file cabinets or locked rooms while the study is ongoing. When the study is complete, the data will be sent to a secure archive like that used for medical records. Washington state law requires clinical trial data be retained for 25 years. At the end of that time, the data will be destroyed. Electronic data will be encrypted and stored on secure University of Washington servers.

At the end of the study, each investigator will get a copy of the de-identified data. At the end of the study, all local copies of the encrypted contact information files will be destroyed.

E. *Sharing study results*: As this will be an open-label study, each subject will be able to personally decide whether sumatriptan was helpful to them. We will offer to send a letter summarizing the study to the subjects' primary health care provider to allow for further prescriptions if the subject desires. While the study drug may be of benefit to an individual subject, the main sharing of study results will be with the general public and medical community which may benefit from our study outcome. Further information on information sharing is contained in Section D, Plan of Dissemination Activities.

F. *Laboratory evaluations*: This study will not collect any specimens nor do any laboratory evaluations other than a pregnancy test in female subjects at randomization, and those results will be immediately communicated to the subjects.

XII. Plan of Evaluation

The research team, under the direction of Dr. Hoffman, has outlined a plan that provides for periodic evaluation of the progress towards study outcomes, quality of data collection and entry, and dissemination with clear assignment of responsibilities for these tasks. Performance measures were chosen for their relevance in achieving the specific aims of the study and in assessing the impact on the stakeholders for this study (including researchers, health care providers, and most importantly, consumers).

Review of performance will be conducted through: (1) review of staff performance by Dr. Hoffman, (2) review of human participants' protection measures by the IRB, (3) review of overall performance and responsiveness to consumer concerns by the UW TBI Model System consumer advisory panel, and (4) review of scientific rigor of publications and presentations outside reviewers. The PI, co-investigators, and study staff will meet weekly to assess study progress and quality assurance. Research staff will receive ongoing supervision and feedback in these meetings from Dr. Hoffman and Ms. Glorieux. Data completeness, timeliness, and quality will be tracked by Ms. Glorieux in conjunction with Dr. Hoffman.

XIII. Objective and Quantifiable Performance Measures

Project outcomes for which performance measures have been developed are: (1) Pre-Enrollment Activities, (2) Post-Enrollment Activities, and (3) Data Analysis / Dissemination (See Table 4 for complete listing of performance measures). There will be substantial pre-enrollment activities that will be addressed including completion of the manual of procedures, obtaining full IRB approval, database construction and testing, research staff training, equipment certification, pharmacy set-up, and subject binder/headache diary application completion. Post-enrollment activities include subject recruitment and retention, completion of all data collection, monitoring of data safety and data audit and clean-up. Data analysis and dissemination will consist of primary and secondary reports (presentation and publications) from the study, and design and submission of a Phase 3 trial (if the results so indicate).

XIV. Safety and Adverse Events

Pill counts will be conducted at each visit and a current medication list will be obtained for study physician review. Daytime queries by the subject will be triaged by the research assistant. For nighttime or weekend queries, the subject will have access to a 24 hour paging operator to contact a physician in case of question relating to the study medication. Dr. Natalia Murinova, a neurologist with expertise in headache treatment, has agreed to be the Safety Monitor. She will receive a quarterly report of all Adverse Events and will be contacted by the study team within 24 hours of any Serious Adverse Event to review with the study physician. Any serious adverse event will be reported to the Human Subjects Division as well immediately.

A. Definitions

a. **Unanticipated Problems Involving Risk to Subjects or Others:** Any incident, experience, or outcome that meets all of the following criteria:

b. **Unexpected in nature, severity, or frequency** (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

c. **Related or possibly related to participation in the research** (i.e. 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)

d. **Suggests that the research places subjects or others at greater risk of harm** (including physical, psychological, economic, or social harm).

e. 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

Adverse events are classified as serious or non-serious.

f. **Serious Adverse Event:** A ***serious adverse event*** 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

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious should be regarded as ***non- serious adverse events***.

g. Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last study clinic visit.

h. Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

i. Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the Data Safety Monitor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

j. Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

k. Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

1. Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
2. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

B. Recording of Adverse Events

At each contact with the subject, the study staff must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been

determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study, action taken, and outcome.

C. Evaluating Adverse Events

Assessment should include the intensity (severity) of the event and the relationship to Study Agent(s)/Intervention(s).

Severity of AEs will be graded by the Investigator using the following criteria as guidelines:

1. Mild: Nuisance, barely noticeable.
2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
3. Severe: Symptoms significantly interfere with daily activities or sleep.

The relationship of the AE to the study drug should be specified by the Investigator, using the following definitions:

- ***Not Related***: Concomitant illness, accident or event with no reasonable association with treatment.
- ***Unlikely***: The reaction has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

- ***Possibly Related***: The reaction follows a reasonably temporal sequence from administration of the drug and follows a known response pattern to the suspected drug; the reaction could have been produced by the study drug or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.
- ***Probably Related***: The reaction follows a reasonable temporal sequence from administration of study drug; is confirmed by discontinuation of the study drug or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state.
- ***Definitely Related***: The reaction follows a reasonable temporal sequence from administration of study medication; that follows a known or expected response pattern to the study medication; and that is confirmed by improvement on stopping or reducing the dosage of the study medication, and reappearance of the reaction on repeated exposure.

D. Reporting of Serious Adverse Events and Unanticipated Problems

1. Investigator Obligations

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be promptly reported are those that are:

- serious and related to study participation;
- serious and unexpected; and
- any other unanticipated problem involving risks to subjects or others

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

2. Notifying the Principal Investigator

Any study-related unanticipated problem posing risk of harm to subjects or others that are not Adverse Events should be reported on the "*Unanticipated Problems Form*". Any type of serious adverse event, must be reported to the Principal Investigator or designee within 1 business day of the event. To report such events, a "*Serious Adverse Event Form*" must be completed and delivered to the Principal Investigator or designee within 1 business day.

3. Notifying the Local IRB

Within the following 48 hours, the investigators must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Dr. Hoffman or her designee is responsible for safety reporting to the UW IRB and complying with their reporting requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the study file.

4. Notifying the Data Safety Monitor

Unanticipated problems posing risks to subjects or others and serious adverse events associated with the research will be forwarded to the Data Safety Monitor of the study within 24 hours.

5. Stopping Rules

There are no planned interim or futility analyses. The Data Safety Monitor may recommend stopping for safety.

6. Independent Data Safety Monitor

The Data Safety Monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report. At a minimum the Data Safety Monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The Data Safety Monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator.

XV. Ethical Considerations/Protection of Human Subjects

Ethical Conduct of the Study

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Institutional Review Board (IRB)

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.

Subject Information and Informed Consent

This study will be conducted in compliance with Title 45 Part 46 of the CFR pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects will give their written consent to participate in the study. Subjects will be provided information about the purpose of the study, participation/termination conditions, risks, and potential benefits. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families. Consent forms describing in detail the Study Agent(s)/Intervention(s) study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Sample Characteristics that Raise Special Concerns

We do not anticipate that sufficient cognitive impairment will exist in any of the participants to the level that would impair the ability to give consent for participation. However, those with more significant cognitive impairment will be identified at screening and will have a caregiver to monitor them on a daily basis.

XVI. Risk/Benefit Assessment

Possible risk:

- Some people may experience side effects to sumatriptan including sensations such as chest tightness, tingling, muscle tightness. These are usually mild and transient, and rarely require urgent care.
- Although rare, some people may experience allergic or hypersensitivity reactions to sumatriptan and may need to contact a physician.
- Excessive use of sumatriptan can cause overuse headaches.
- Sumatriptan is contraindicated in pregnant women and people with ischemic cardiac, cerebrovascular or peripheral vascular disease because of its vasoconstrictive effects mediated by weak 5HT-2 binding. Some subjects may have subclinical disease.
- Subjects may be asked personal questions regarding such topics as depression and insomnia, and may be asked whether they have thoughts of death or suicide. This may cause some emotional discomfort.
- There is a risk that this private information about them may be disclosed.
- Unexpected detection of a potential diagnosis such as major depression may carry with it the risk of emotional distress.

Risk management and emergency response:

A study or on-call physician will be available 24/7 in case of side effects or adverse events related to the study drug. The consent form will indicate the name and contact numbers of the study physicians. There will also be a business card sized contact card with phone numbers given to subjects when study medication is given. Depending on the event, the physician may

direct the subject to call 911 or go to an emergency department. If the reaction is a typical side effect of the medication, the physician may instruct the patient to continue or to stop taking the study drug. If the reaction is sufficiently severe, the research coordinator will be notified and the patient will be discontinued from taking further study medication.

Subjects will be given 2 packages of 9 tablets of study drug at Day 30, each package to be opened at the start of that month. This amount is not expected to cause medication overuse (rebound) headaches. Subjects will be instructed not to take non-study sumatriptan, or any other triptan, for headache or any other reason while on study medication. A list of alternative medications will be provided to take if needed for rescue. Potential subjects will be excluded if they are on medication which has a high clinical probability of drug interaction. Subjects will be provided with a list of drugs they should not take during the study.

All serious adverse events will be sent to Dr. Natalie Murinova, the safety monitor, within 2 business days. The safety monitor will evaluate how the event was handled by the study and make recommendations to the Principal Investigator on how procedures can be improved to further enhance patient safety. The safety monitor will have only safety-related responsibilities within the study.

Subjects will be interviewed in private settings, will be counseled that they may refuse to answer any question, and will be reassured that the information they provide is confidential.

We will take all the usual steps to protect the confidentiality of their personal information, including but not limited to dissociating identifying information from research data; using unique alpha-number coding systems that permit linkages to identifying data only via files that are stored separately; storage of data on password protected servers or computers; storage of paper data forms in locked files within locked rooms with access limited to approved research staff; storage of audiotapes on a secure server with highly restricted password access and periodic download to permanent storage in locked facilities. All investigators and research staff are required to undergo HIPAA training and to sign a confidentiality agreement under the authority of the Human Subjects Division of the University of Washington.

When a diagnosable condition such as major depression is detected, we will assess for potential suicidality. If the patient does not indicate current suicidal ideation, we will discuss immediately with the psychologist (Dr. Hoffman) or physician (Drs. Bell and Lucas) and an appropriate referral will be made. In the case of suicidality, we will use suicide management protocols that have are approved by our Institutional Review Board and include specific algorithms to assess risk, use of local Crisis Clinic numbers and 24/7 back-up by MD or PhD staff who can conduct more comprehensive assessments and make referrals as needed. (See Appendix for Emergent Problem Protocol).

Potential benefit of the study: Study participants may benefit from improvement in headache pain, associated symptoms and a decrease in disability following the use of study drug. Weekly telephone calls and the utilization of a headache diary may provide greater insight into their headaches. Potential societal benefits include decreased work loss and increased productivity,

decrease in loss of social interactions, and improvement in quality of life following the use of study drug.

XVII. Study Finances

Funding Source

This study is financed through a grant from the National Institute on Disability and Rehabilitation Research.

Conflict of Interest

All Study Principal Investigators and Key Personnel identified on the Study must file an initial COI disclosure with the University of Washington Office of Research by completing a form that captures disclosures of financial support and interests in several categories, including interests of a spouse or other immediate family member relative to the study; the aim is to provide the broadest and most comprehensive disclosure possible, while still respecting the Individual's right to privacy. Subsequent COI disclosures must be filed annually until the end of the study, at the conclusion of the study, and one year following the end of the study.

Subject Stipends or Payments

The subjects will be reimbursed $25.00 per clinic visit to honor their time and defray any costs.

XVIII. Overall Project Evaluation

Overall study data completeness, timeliness, and quality will be monitored by Leslie Kempthorne in conjunction with Jeanne Hoffman, PhD. Automated data reports will be generated monthly, displaying information relevant to the milestones described in the previous section. For example, cumulative subject accrual rates, subject retention rates, inter-rater reliability, and data accuracy reports will be generated routinely to monitor progress toward

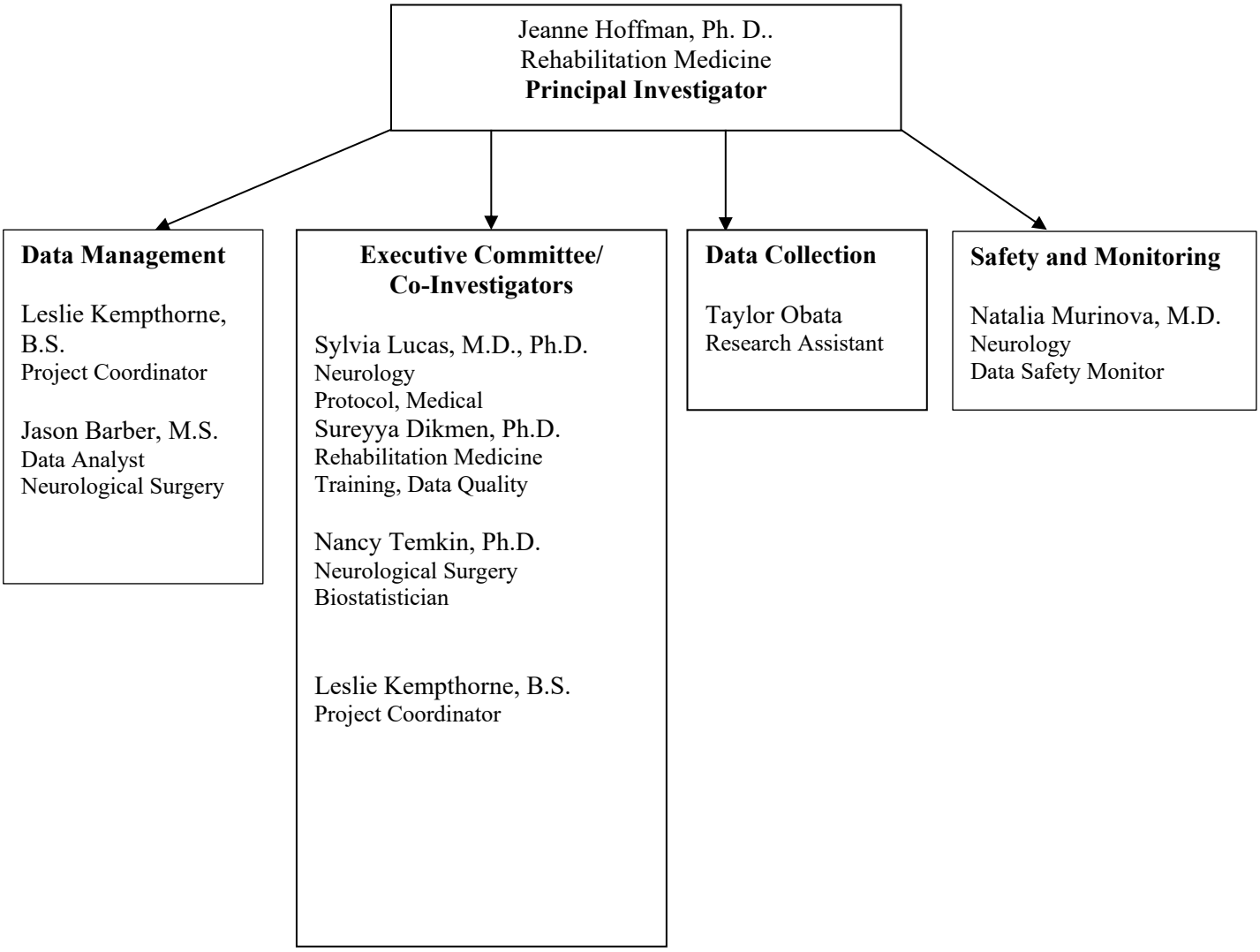
goals. Progress toward study milestone will be discussed at the project meetings. Quarterly reports will be filed with the NIDRR project officer. Quarterly safety reports will be submitted to Dr. Murinova.

If problems arise or tasks are not progressing as planned, Dr. Hoffman will work with the research team to devise an action plan. Plans will be put in writing with a timeline to correct the problem. Research Project Coordinator, Leslie Kempthorne, will track and follow-up on these plans. Any significant problems that would affect overall project outcomes will be reviewed with the NIDRR project officer to obtain additional assistance in developing an action plan.

Table 4. Performance measures

Performance Area	Goal	Review Schedule	Evaluation Method	Accountability*
Pre Enrollment Activities				
Manual of Procedures	3-2013	Y1: Q2	Ready for IRB	**Hoffman**
IRB Submission	3-2013	Y1: Q2	IRB approval	**Hoffman,** Glorieux
Database complete	4-2013	Y1: Q3	Trial data entry	**Barber**
Pharmacy set-up	4-2013	Y1: Q3	Protocol	**Glorieux**
Research Assistant trained	5-2013	Y1: Q3	Observation of test administration and scoring	**Dikmen**
Study Binders and Patient Instruction Material	4-2013			**Lucas**, Glorieux
Post-Enrollment Activities				
Enrollment per month	2 per month	Begin Y1: Q3, Monthly	Enrollment report	**Hoffman**
Completion of baseline assessments	95%	Monthly	Review by PI, Data Report	**Glorieux**, Hoffman
Completion of clinic visits/FU assessments	95%	Monthly	Review by PI, Data Report	**Glorieux,** Hoffman
Completion of telephone FU calls	95%	Quarterly	Review by PI, Data Report	**Glorieux**, Hoffman
Data Safety Monitoring	100%	Quarterly and as needed	Review by PI, Quarterly report to Medical Monitor	**Hoffman**, Murinova
Data audit	95% agreement	Quarterly	Rescoring and coding of 5% of assessments	**Hoffman**, Temkin, Barber
Data Analysis/Dissemination				
Complete primary report of study	1-2017		Submission of manuscript for review	**Hoffman,** et al
Design multi-center RCT	May 2017		Submission of grant proposal	**Hoffman,** et al

Figure 4: Project Staff Flow Chart



TIMELINE

Table 5: Anticipated Timeline for Sumatriptan Study

	Y1				Y2				Y3				Y4				Y5			
Pre-Enrollment Activities																				
IRB Approval																				
Completion of Manual of Procedures																				
Headache Diary Application Development																				
Pharmacy Set-up																				
Staff Training																				
Enrollment Activities																				
Enrollment																				
Intervention																				
Outcome Assessment																				
Post-Enrollment Activities																				
Data Clean Up																				
Data Analysis																				
Primary Publication																				
Phase III Study Application																				

References

1. Faul M, Xu L, Wald M, Coronado V. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.

2. Thurman D, Alverson C, Dunn K, Guerrero J, Sniezek J. Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil 1999;14(6):602-15.

3. Tanelian T, Jaycox L. Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery. Santa Monica, CA: Rand Corporation; 2008.

4. Warden D. Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil 2006;21(5):398-402.

5. Council WSTBI. Traumatic Brain Injury: A Life Altering Impact 2011 [cited 2012 July 27]. Available from: URL: http://www.tbiwashington.org/tbi_wa/facts.shtml.

6. Finkelstein E, Corso P, Miller T. The Incidence and Economic Burden of Injuries in the United States. New York: Oxford University Press; 2006.

7. Thompson HJ, Weir S, Rivara FP, Wang J, Sullivan SD, Salkever D et al. Utilization and costs of health care after geriatric traumatic brain injury. J Neurotrauma 2012;29(10):1864-71.

8. Taylor BC, Hagel EM, Carlson KF, Cifu DX, Cutting A, Bidelspach DE et al. Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran V.A. users. Med Care 2012;50(4):342-6.

9. Fann JR, Burington B, Leonetti A, Jaffe K, Katon WJ, Thompson RS. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry 2004;61(1):53-61.

10. Deb S, Lyons I, Koutzoukis C, Ali I, McCarthy G. Rate of psychiatric illness 1 year after traumatic brain injury. Am J Psychiatry 1999;156(3):374-8.

11. Annegers J, Grabow J, Kurland L, al. e. The incidence, causes and secular trends of head trauma in Olmstead County, Minnesota. Neurology 1980;30:912-9.

12. Chamelian L, Feinstein A. The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci 2006;18(1):33-8.

13. Suter P. Rehabilitation and management of visual dysfunction following traumatic brain injury. In: Ashley M, editor. Traumatic Brain Injury: Rehabilitation Treatment and Case Management. Boca Raton: CRC Press; 2004. p 209-49.

14. Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. Arch Neurol 1997;54(9):1131-40.

15. Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC et al. Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 2004;21(6):685-96.

16. Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: a focused review. Am J Phys Med Rehabil 2006;85(7):619-27.

17. Couch JR, Bearss C. Chronic daily headache in the posttrauma syndrome: relation to extent of head injury. Headache 2001;41(6):559-64.

18. Haas DC. Chronic post-traumatic headaches classified and compared with natural headaches. Cephalalgia 1996;16(7):486-93.

19. Hoffman J, Lucas S, Dikmen S, Braden C, Brown A, Brunner R et al. Natural History of Headache Following Traumatic Brain Injury. Journal of Neurotrauma 2011;28:1-8.

20. van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. J Neurol Neurosurg Psychiatry 1999;66(2):207-13.

21. Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. Arch Phys Med Rehabil 2005;86(9):1793-800.

22. D'Amico D, Grazzi L, Usai S, Raggi A, Leonardi M, Bussone G. Disability in chronic daily headache: state of the art and future directions. Neurol Sci 2011;32 Suppl 1:S71-6.

23. Dueland AN, Leira R, Burke TA, Hillyer EV, Bolge S. The impact of migraine on work, family, and leisure among young women -- a multinational study. Curr Med Res Opin 2004;20(10):1595-604.

24. Frontera WR, Fuhrer MJ, Jette AM, Chan L, Cooper RA, Duncan PW et al. Rehabilitation Medicine Summit: Building Research Capacity--executive summary. Assist Technol 2006;18(1):2-14.

25. Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. Characterization of headache after traumatic brain injury. Cephalalgia 2012;32(8):600-6.

26. Bell K, Hoffman J, Brown A, Lucas S, Dikmen S. Physician perception of post-traumatic headache and practice patterns. American Academy of Physical Medicine and Rehabilitation. Seattle, WA; 2010.

27. Theeler BJ, Erickson JC. Post-traumatic headaches: Time for a revised classification? Cephalalgia 2012;32(8):589-91.

28. Baandrup L, Jensen R. Chronic post-traumatic headache--a clinical analysis in relation to the International Headache Classification 2nd Edition. Cephalalgia 2004;25(2):132-8.

29. Packard RC. Posttraumatic headache: permanency and relationship to legal settlement. Headache 1992;32(10):496-500.

30. Meyer K, Helmick K, Doncevic S, Park R. Severe and penetrating traumatic brain injury in the context of war. J Trauma Nurs 2008;15(4):185-9; quiz 90-1.

31. Hoge C, McGurk D, Thomas J, Cox A, Engel C, Castro C. Mild traumatic brain injury in U.S. soldiers returning from Iraq. New England Journal of Medicine 2008;358(5):453-63.

32. Theeler B, Erickson J. Mild head trauma and chronic headaches in returning US soldiers. Headache 2009;49(4):529-34.

33. Cohen SP, Plunkett AR, Wilkinson I, Nguyen C, Kurihara C, Flagg A et al. Headaches during war: analysis of presentation, treatment, and factors associated with outcome. Cephalalgia 2012;32(2):94-108.

34. Dahlof CG, Solomon GD. The burden of migraine to the individual sufferer: a review. Eur J Neurol 1998;5(6):525-33.

35. Schwartz BS, Stewart WF, Lipton RB. Lost workdays and decreased work effectiveness associated with headache in the workplace. J Occup Environ Med 1997;39(4):320-7.

36. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. Neurology 2006;67(2):246-51.

37. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Arch Intern Med 1999;159(8):813-8.

38. Castillo J, Muñoz P, Guitera V, Pascual J. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. Headache 1999;39(3):190-6.

39. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. Headache 1998;38(7):497-506.

40. Silberstein S, Lipton R. Overview of diagnosis and treatment of migraine. Neurology 1994;44(10 Suppl 7):S6-16.

41. Lucas S, Hoffman J, Bell K, Dikmen S. Natural history of headache in the first year after mild traumatic brain injury. American Academy of Neurology. New Orleans, LA; 2012.

42. Hoffman J, Lucas S, Bell K, Dikmen S. Prevalence of Headache Following Mild Traumatic Brain Injury. American Congress of Rehabilitation Medicine. Atlanta, GA; 2011.

43. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.

44. Theeler B, Flynn F, Erickson J. Headaches After Concussion in US Soldiers Returning From Iraq or Afghanistan. Headache 2010;Jun 10. [Epub ahead of print].

45. Evans RW. Post-traumatic headaches. Neurol Clin 2004;22(1):237-49, viii.

46. Theeler BJ, Erickson JC. Posttraumatic headache in military personnel and veterans of the iraq and afghanistan conflicts. Curr Treat Options Neurol 2012;14(1):36-49.

47. Baandrup L, Jensen R. Chronic post-traumatic headache--a clinical analysis in relation to the International Headache Classification 2nd Edition. Cephalalgia 2004;25(2):132-8.

48. Lieba-Samal D, Platzer P, Seidel S, Klaschterka P, Knopf A, Wöber C. Characteristics of acute posttraumatic headache following mild head injury. Cephalalgia 2011.

49. Afari N, Harder LH, Madra NJ, Heppner PS, Moeller-Bertram T, King C et al. PTSD, combat injury, and headache in Veterans Returning from Iraq/Afghanistan. Headache 2009;49(9):1267-76.

50. Patil VK, St Andre JR, Crisan E, Smith BM, Evans CT, Steiner ML et al. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. Headache 2011;51(7):1112-21.

51. Theeler BJ, Flynn FG, Erickson JC. Chronic daily headache in U.S. soldiers after concussion. Headache 2012;52(5):732-8.

52. Theeler B, Mercer R, Erickson J. Prevalence and impact of migraine among US Army soldiers deployed in support of Operation Iraqi Freedom. Headache 2008;48(6):876-82.

53. Lucas S. Headache management in concussion and mild traumatic brain injury. PM R 2011;3(10 Suppl 2):S406-12.

54. Vargas BB, Dodick DW. Posttraumatic headache. Curr Opin Neurol 2012;25(3):284-9.

55. Watanabe T, Bell K, Walker W, Schomer K. Systematic Review of Interventions for Post Traumatic Headache. PM&R 2012;4:129-40.

56. Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: an observational study. Headache 2011;51(6):932-44.

57. Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: results of the Spectrum Study. Headache 2000;40(10):792-7.

58. Packard RC, Ham LP. Pathogenesis of posttraumatic headache and migraine: a common headache pathway? Headache 1997;37(3):142-52.

59. Packard RC. Epidemiology and pathogenesis of posttraumatic headache. J Head Trauma Rehabil 1999;14(1):9-21.

60. Sherman KB, Goldberg M, Bell KR. Traumatic brain injury and pain. Phys Med Rehabil Clin N Am 2006;17(2):473-90, viii.

61. Kozminski M. Combat-related posttraumatic headache: diagnosis, mechanisms of injury, and challenges to treatment. J Am Osteopath Assoc 2010;110(9):514-9.

62. Saxena P, Tfelt-Hansen P. Triptans, 5HT 1B/1D Agonists In the Acute Treatment of Migraine. In: Olesen J, Tfelt-Hansen P, Welch K, Goadsby P, Ramadan N, editors. Headache. 3rd ed.: Lippincott Williams & Wilkins; 2005. p 469-503.

63. Folstein M, Folstein S, McHugh P. "Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12:189.

64. Strauss E, Sherman E, Spreen O. Rey-Osterrieth Auditory Verbal Learning Test. Compendium of Neuropsychological Tests. New York: Oxford University Press; 1990. p 776-807.

65. Reitan R. Validity of trail making test as an indicator of organic brain damage. Perceptual Motor Skills 1958;8:271-6.

66. Wechsler D. Wechsler Adult Intelligence Scale IV. San Antonio, TX: Harcourt Assessment, Inc; 2008.

67. Kroenke K, Spitzer R, Williams J. The PHQ-9: Validity of a brief depression symptom severity measure. Journal of General Internal Medicine 2001;16:606-13.

68. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder. Archives of Internal Medicine 2006;166:1092-7.

69. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). Behav Res Ther 1996;34(8):669-73.

70. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297-307.

71. Ware JE, Kosinski M, Keller SD. SF-12: How to score the SF-12 Physical and Mental Health Summary Scales. 2 ed. Boston: The Health Institute, New England Medical Center; 1995.

72. Williams A. EuroQol - A new facility for the measurement of health-related quality-of-life. Health Policy 1990;16(3):199-208.

73. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. Journal of personality assessment 1985;49(1):71-5.

74. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol 1995;242(9):587-92.

75. Kosinski M, Bayliss M, Bjorner J, Ware JJ, Garber W, Batenhorst A et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 2003;12(8):963-74.

76. Winner P, Landy S, Richardson M, Ames M. Early intervention in migraine with sumatriptan tablets 50 mg versus 100 mg: a pooled analysis of data from six clinical trials. Clin Ther 2005;27(11):1785-94.

77. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358(9294):1668-

78. Mitrushina M, Boone K, Razani J, D'Elia L. Handbook of Normative Data for Neuropsychological Assessment. Second ed. New York: Oxford University Press; 2005.

79. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York: Oxford University Press; 2006.

80. Ouellet MD, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. Sleep Med 2006;7(6):486-97.

81. Jennum P, Jensen R. Sleep and headache. Sleep Med Rev 2002;6(6):471-9.

82. Bell K, Temkin N, Esselman P, Doctor J, Bombardier C, Fraser R et al. The effect of a scheduled telephone intervention on outcome after moderate to severe TBI: A randomized trial. Arch Phys Med Rehabil 2005;86:851-6.

83. Jakola AS, Müller K, Larsen M, Waterloo K, Romner B, Ingebrigtsen T. Five-year outcome after mild head injury: a prospective controlled study. Acta Neurol Scand 2007;115(6):398-402.

84. Ingebrigtsen T, Romner B, Marup-Jensen S, Dons M, Lundqvist C, Bellner J et al. The clinical value of serum S-100 protein measurements in minor head injury: a Scandinavian multicentre study. Brain Inj 2000;14(12):1047-55.

85. Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. Neurology 2008;70(12):948-55.

86. Smits M, Dippel DW, Houston GC, Wielopolski PA, Koudstaal PJ, Hunink MG et al. Postconcussion syndrome after minor head injury: brain activation of working memory and attention. Hum Brain Mapp 2009;30(9):2789-803.

87. Crawford S, Wenden FJ, Wade DT. The Rivermead head injury follow up questionnaire: a study of a new rating scale and other measures to evaluate outcome after head injury. J Neurol Neurosurg Psychiatry 1996;60(5):510-4.

88. Ware JE, Jr., Bjorner JB, Kosinski M. Practical implications of item response theory and computerized adaptive testing: a brief summary of ongoing studies of widely used headache impact scales. Med Care 2000;38(9 Suppl):II73-82.

89. Pryse-Phillips W. Evaluating migraine disability: the headache impact test instrument in context. Can J Neurol Sci 2002;29 Suppl 2:S11-5.

90. Fann J, Hart T, Schomer K. Treatment for depression after traumatic brain injury: a systematic review. J Neurotrauma 2009;26(12):2383-402.

91. Shenouda C, Hendrickson P, Davenport K, Barber J, Bell KR. The effects of concussion legislation one year later-what have we learned: a descriptive pilot survey of youth soccer player associates. PM R 2012;4(6):427-35.

92. Sheffield JV, Young A, Goldstein EA, Logerfo JP. The public hospital mission at Seattle's Harborview Medical Center: high-quality care for the underserved and excellence in medical education. Acad Med 2006;81(10):886-90.