Olanzapine for Acute Headaches

NCT03066622

Study Protocol and Statistical Analysis Plan

11 Nov 2016

Staff Only
Project #
PI:
Submission Date(s):

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The following **9 headings/sections highlighted in blue** correspond with the criteria used to evaluate your proposal. All the **questions/requests are highlighted in yellow;** they all must be answered providing sufficient detail for a reviewer to determine whether the review criteria have been met.

****MAIN RESEARCH QUESTIONS, STUDY AIMS, SPECIFIC HYPOTHESES****

1.1 Please clearly state your overall research questions and/or study aims.

Primary Question:

Does oral rapidly dissolving olanzapine provide efficacious analgesia in patients with acute headache of non-organic origin (primary headache) who come to the ED for abortive therapy when compared to current standard of care?

Secondary Aim:

Additionally, the study will aim to see if oral rapidly dissolving olanzapine decreases 1) duration of ED length of stay and 2) need for IV access when compared to the current standard of care.

****1. BACKGROUND & SIGNIFICANCE****

1.2 What is the specific knowledge gap that the project intends to fill? Include a brief review of past research in this area, numbering your citations to relevant literature as well as including them in the reference section #9.1.

It is estimated that there are approximately 5 million visits to US emergency departments annually for evaluation and treatment of headaches, the majority of which are benign and can be classified as primary headaches (migraine, cluster, and tension type headaches).[1,2] The one year incidence of migraine headaches in the United States has been estimated to be 18% for females and 6% for males.[3] The mean cost of an emergency department visit for a migraine headache is $775 which translates into a total national annual cost of $700 million for these visits.[4] Furthermore, the majority of the current abortive therapies used for acute primary headaches in the emergency setting are parenteral medications as patients are commonly presenting for abortive therapy after their home oral medication regimen did not provide adequate analgesia. Some of the commonly used parenteral medications include: Sumatriptan, metoclopramide, prochlorperazine, chlorpromazine, dihydroergotamine, and ketorolac.[5] Droperidol has also been shown to be an effective analgesic in acute migraine headaches;[6] however, a black box warning by the FDA regarding risk for cardiac arrhythmias has led to it falling out of favor for many practitioners. It is worth noting that 4 of the 7 aforementioned medications are classified as dopamine and serotonin receptor antagonists regarding their mechanism of action which correlates with the dopamine theory of migraine headaches first proposed in 1977 by F. Sicuteri. He hypothesized that migraine headaches and their associated symptoms are secondary to a state of dopamine hypersensitivity which would help explain the efficacy seen with dopamine antagonists in treating acute migraine headaches.[6,7,8] Additionally, serotonin receptor antagonists have also been the focus of abortive migraine therapies in the emergency department for some time now. Per the American College of Emergency Physicians' clinical policy on acute headaches in the emergency department:

> *"Serotonin (5-HT) receptors are the main focus of pain management because they are known to modulate neurogenic peptide release and vasoconstrict dilated dural vessels. The goal of therapy is to prevent or abort the neurogenic inflammation that occurs as a result of neuropeptide release. Subtypes of the 5-HT1 receptor are believed to be the most important receptors in the final common pathway of headache. Pharmacologic agents with an affinity for 5-HT receptors are currently the preferred therapy in acute headache management."*[9]

Olanzapine is an atypical antipsychotic with antagonistic properties at both the dopamine and serotonin receptors and has been recently studied as an abortive agent for primary headaches. Olanzapine also has the added benefit of having some antiemetic properties which is beneficial given that nausea is a symptom commonly associated with primary headaches.[10] The olanzapine product information label notes that the mechanism of action of olanzapine is not completely understood. However; it does state that the antipsychotic effects may be related to blockade of dopamine, serotonin, histamine, alpha- 1 adrenergic and muscarinic receptors.[11] In a 2008 study based out of an urban emergency department,

intramuscular olanzapine was found to have similar analgesic efficacy when compared to intramuscular droperidol without any serious adverse events in either arm of the study (n=100).[2] An orally dissolving version of olanzapine is available in the United States and has been found to have a more rapid onset of absorption when compared to standard oral olanzapine.[12] This orally dissolving formulation has not been specifically studied as an initial therapeutic medication for acute primary headaches but has been used with some success as an adjunctive therapy for patients admitted to a migraine clinic in status migrainous.[13] Orally dissolving olanzapine was also noted to have a safe side effect profile in that same study.[13] One of the common goals of abortive medications for primary headaches is administration of the medications as early as possible in the course of the headache.[14] Therefore, it would seem plausible that an oral agent would have the benefit of being able to be administered earlier than parenteral medications given that IV placement or preparation of IM formulations can be time consuming in a busy emergency department. Additionally, if olanzapine has an adequate analgesic effect patients may not require IV placement at any point during their stay. Taking into account the earlier administration and the possibility of reduced need for IV/IM preparations this medication has a high likelihood of improving length of stay and patient flow in the emergency department in patients who present with primary headaches. Additionally, this would decrease the patient discomfort experienced with IM/IM administration of medications and also eliminate the risk of infection and thrombophlebitis that is seen with IV placement. An emergency department can be a noisy and hectic environment and in patients who may be suffering from associated phonophobia and photophobia it is not an ideal environment to spend any prolonged period of time. Therefore, any modality that decreases length of stay would likely be viewed as beneficial by both emergency department administrators as well as emergency department patients.

1.3 What preliminary results do you have that support your proposal?

As mentioned above, medications with dopamine antagonism and anti-emetic properties (droperidol, metoclopramide, prochlorperazine, chlorpromazine) are commonly used as abortive agents for primary headaches in the emergency department in their parenteral forms.[5,6] Intramuscular olanzapine has been shown to have similar analgesic effects in primary headaches when compared to droperidol.[2] However, to our knowledge, the orally dissolving formulation has yet to be studied for this purpose. Orally dissolving olanzapine has been studied as an adjunct to patients in status migrainous and was noted to have a safe side effect profile, but there are no studies looking at the efficacy of treating acute primary headache in an emergency department setting.[13] Based on the aforementioned studies as well as our experience in the emergency department with this medication, we hypothesize that orally dissolving olanzapine will have similar efficacy to other anti-dopaminergic medications in treating acute primary headache without the time requirement and added discomfort of IV/IM administration. Oral olanzapine is used frequently in the emergency department at Regions Hospital with 1664 doses being administered over the last year so practitioners are already familiar with the medication and its dosing. Additionally, IV olanzapine and oral olanzapine had no severe adverse events in two recent studies where they were used as abortive therapies for headaches.[2,13]

1.4 What is the importance of the research to the scientific community?

This study has the possibility of having many positive outcomes that may change the standard of practice for treatment of primary headaches in the emergency department. If effective, this drug would give providers the option of an oral medication that is rapidly dissolving and therefore better tolerated when compared to many other oral medications in patients with nausea and vomiting. The medication can also be administered early in the treatment course of patients presenting with primary headaches as it will not require pretreatment with anti-emetic medications or IV/IM administration. Additionally, it would decrease the discomfort and time required that is typically seen with IV/IM administration of medications which in turn may decrease length of stay in the emergency department and result in higher patient satisfaction scores.

****2. APPROACH****

Some questions in this section do not apply to all study designs; please mark Not Applicable as appropriate

2.1 Describe the study design (e.g., "This is a randomized controlled trial to test the effect of a guided imagery intervention on sleep quality"). Please see this List of Study Designs.

This is a prospective, randomized, convenience sample, feasibility trial to test for non-inferiority of oral rapidly dissolving olanzapine versus current emergency department standard of care in providing symptomatic relief to patients presenting with primary headache.

2.2 How are you identifying eligible subjects or records? (e.g., clinic visit, search of Epic, registry, etc.)

	Not Applicable

CRCC interns will monitor the emergency department track-board in Epic for chief complaint of headache. If the patient has a chief complaint of headache, the intern will consult with the patient's attending physician to confirm the patient's eligibility into the study. If the physician agrees that the patient is a candidate for the study, the intern will proceed with the consent process.

2.3 What is the study population of interest and what are the study inclusion/exclusion criteria?

Inclusion and Exclusion Criteria

Inclusion Criteria	*Exclusion Criteria*
1. Adult patient between 18-65 years of age presenting to the emergency department with acute primary headache 2. Patient approved for inclusion by primary attending physician in the emergency department	1. Age < 18 or > 65 2. Pregnancy 3. Breastfeeding mother 4. Known allergy to olanzapine 5. Known QT prolongation or underlying condition that places patient at risk for QT prolongation 6. Inability to give written consent (intoxication, altered mental status) 7. Headache of organic origin (trauma, infection, previous recent head or neck surgery) 8. Patient already prescribed daily olanzapine on an outpatient basis 9. Patient has been administered olanzapine within the past 24 hours 10. Language barrier 11. Patient has a narcotic restriction care plan in place

2.4 If you are not using the entire population of interest, what is the method for obtaining a subset or sample of this population?

	Not Applicable

As indicated in Section 2.2, patients will be screened based on a chief complaint of headache when they come to the emergency department. All patients with this complaint will be screened and discussed for inclusion into the study with the patient's ED attending physician.

2.5 Will you need to perform "preparation for research" activities prior to consenting subjects for research?

	No
X	Yes
	Not Applicable

If you answered yes above, appropriate preparation for research activities prior to consenting subjects must include the following process to determine inclusion/exclusion criteria:

1) Study staff will work with the PI to determine the methods used in identifying potential subjects for the research. For example, this may include creating an Epic Workbench report of patients who are in the hospital and meet minimum criteria for the research.

2) Study staff may access medical records of all potential subjects' identified (i.e., Workbench) to determine eligibility criteria using information that already exists in the medical record. During this process, no identifiable information may be recorded and any documentation made of a potential subject's information that would disqualify them will be destroyed.

   If an eligible patient is not being cared for by the PI, study staff must approach the patient's provider to determine if it is appropriate to proceed with the consent process.

3) If additional testing needs to be done to see whether a patient meets criteria for entry into the study, the PI or staff will need to consent the patient first.

4) If the preparation activity confirms a patient is a possible subject, PI/staff approaches the patient to begin the consent process.

2.6 Describe the steps in your recruitment process.

	Not Applicable

Interns in the Critical Care Research Center will screen patients with a chief complaint of headache for inclusion into the study. If eligible, the intern will discuss the patient's enrollment into the study with the patient's ED attending physician. If the physician agrees that the patient is an appropriate candidate and agrees to use the study drug vs. standard of care drugs, the CCRC intern will approach the patient to initiate the consent process. Patients and if applicable, family members will be given the opportunity to ask questions and will be given approximately 15 minutes to discuss participation privately. If the patient agrees to participate, the intern will proceed with obtaining signed consent and randomizing the patient to olanzapine or standard of care. Immediately after randomization, the intern will inform the patient's physician and nurse which group the patient was randomized to and will enter the study order in EPIC for the ED pharmacist to prepare the appropriate medication for treatment. If the patient is randomized to standard of care, the treating physician will notify the pharmacist about which medication should be dispensed to the patient.

2.7 Describe any interventions that are used in this study.

	Not Applicable

There will be two arms of the study. One arm will administer oral rapidly dissolving olanzapine 5 mg for analgesia in acute primary headaches. The second arm will involve treatment with the current emergency department standard of care for providing analgesia in acute primary headache. The current standard of care typically includes but is not limited to one of the following medications administered in the IV or IM formulation: Sumatriptan, metoclopramide, prochlorperazine, chlorpromazine, dihydroergotamine, diphenhydramine, and ketorolac.

Please note that in the event the patient is randomized to the oral olanzapine group and does not have pain relief or a reduction in their pain score following administration, the physician may decide to treat the patient with another medication in order to resolve the patient's pain at their discretion. This data is recorded in the data collection database.

It should be noted that IV fluids, Benadryl, and Zofran may be administered in either arm at the provider's discretion as they are not considered analgesics and are not routinely given with the goal of providing pain control. These treatments are standard of care options in the emergency department and will not interfere with the treatment medication.

2.8 Provide a brief, sequential, bullet-point description of the all the data collection activities you will conduct from start to finish (e.g., chart review, patient survey, follow-up visits, data pull from the electronic medical record, etc.) and who will conduct each. Please see our Example of Data Collection Steps.

Training Plan

CCRC Intern Group: All interns will be trained on the study protocol, consent and data collection by the manager of the CCRC. All interns attend a monthly intern dinner with the primary intent of refresher training and training on new protocols. The protocol will be presented at the February intern dinner. Training is followed by a quiz to determine if there is any aspect of the protocol that is not understood prior to implementation of the protocol. Training at the intern dinner also

involves watching a "mock consent." Following training, interns practice the consent until the time that they feel they are ready to be "check-off" by the manger. Interns schedule 1:1 time with the manager to perform their own mock consent. Consent checklists are utilized by the manger to ensure that all aspects of the consent were included in the mock consent process. Once the intern has "passed" the protocol quiz and the consent check-off, they are cleared to consent patients and collect data. The CCRC has used this training process for the past 3 years with 5 other studies in the ED and it works very well to ensuring that the interns are well-trained and meet the expectations of the manger.

ED Staff Physicians: The PI and CCRC manager will present the study via PowerPoint presentation to the ED attending physicians at the monthly staff meeting in February. In the event a physician is not at the staff meeting, the study presentation is posted on the Emergency Department Intranet (EDNET) where they can view the PowerPoint presentation and read about the protocol. The CCRC has a 24/7 research hotline that is well-known to the ED physician group should they have any questions about the study once the study begins.

Screening, Enrollment and Data Collection

Screening: Interns are typically housed in Pod A in the emergency department during their shift. They will use the EPIC ED Manager Trackboard to watch for patients that report a chief complaint of headache. If a patient has a chief complaint of headache, the intern will review the ED chart for the visit to determine if they are eligible for the study. If the patient appears eligible based on a review of the inclusion/exclusion criteria, the intern will approach the patient's emergency department physician to discuss whether or not the physician agrees they are a good candidate for the study. If the physician agrees to the patient participating, the intern will approach the patient for consent. If the physician does not want the patient to be approached for the study, the intern will enter the patient in the screen fail log.

Enrollment and Consent:

1. Intern will approach the patient to discuss the study and assess patient interest. The intern will review the consent form with the patient and be available to answer any questions the patient may have. The patient will be given 20-30 minutes to review the consent form and make a decision regarding participation. If the patient agrees to participate, the intern will obtain informed written consent from the patient and begin enrollment and data collection. If the patient declines consent, the intern will enter the patient in the screen fail log.
2. If the patient has consented, the intern will first inform the patient's physician and RN that the patient has consented. The intern will assign the patient the next ID number and draw the ID randomization envelope from a drawer in the CCRC. The intern will inform the physician, RN, and ED pharmacist which group the patient was randomized to. The intern will then enter the randomization into the study EPIC order set. If the patient is randomized to the "standard of care" arm, the physician will place the order for their drug of choice for the patient and the intern will enter that medication into the notes in the study order set. If the patient is randomized to the "study" arm, the intern will select the medication in the order set and inform the pharmacist who will validate the order in the study EPIC order set. Once the medication is ready, the intern will hand deliver it to the patient's RN for administration to the patient.
3. Following medication administration, the intern will use the data collection form (in RedCap) to begin assessing patient pain scores and any other adverse events. The intern will collect data from the patient regarding pain scores and nausea immediately at the time of drug administration and then 30- and 60- minutes following drug administration. The intern will use the EMR to collect additional information on the data collection form. Prior to ED discharge, the intern will assess patient satisfaction with the study treatment.
4. 48 hours (± 24 hours), the intern on shift will call the patient to perform a brief patient satisfaction and adverse event follow-up questionnaire. This should take approximately 5 minutes to complete. Patient follow-ups are tracked in the RedCap calendar for the study and can be marked as missed or completed in RedCap. In the event the intern is not able to reach the patient, the intern from the next shift will try the call again. In total, three attempts will be made to contact the patient for the 48-hour follow-up. Messages will not be left on the patient's voice mail to protect confidentiality. In the event the patient cannot be reached in 3 attempts, the follow-up data for that patient will be considered to be lost data.
5. All data will be downloaded from RedCap into an Excel spreadsheet for data validation and analysis.

Note: A data collection form has been uploaded with this application for your review. Upon approval, the data collection form will be transferred to RedCap. All data will be entered and stored in the secure HealthPartners RedCap database.

2.9 Provide a timeline for the main study activities. Please see our Example Timeline

- **December 2015 - January 2016** — **IRB application preparation and submission**
- **February 2016** — **IRB review**
- **February 2016** — **CCRC Intern training and consent check-off**

- **March 2016 – March 2017** **Data collection**
- **March – April 2017** **Data verification and analysis prep**
- **April – May 2017** **Statistical analysis**
- **June – July 2017** **Manuscript preparation and submission**

2.10 Describe your plans for ensuring data security

All paper and electronic data will be housed within the Critical Care Research Center either in a locked file cabinet (consent, paper CRFs) or on the shared password-protected drive with access limited to research staff in the CCRC. Data collection will take place via RedCap. Data on RedCap is password-protected and securely stored on the HealthPartners network.

2.11. List the KEY variables that will be collected to support the study aims outlined in item 1.1. KEY variables include those used for:
1) achieving the study aims (outcomes, predictors, potential confounders),

2) identifying the study population (for inclusion/exclusion criteria),

3) describing the study population

Please see an Example of a Completed Table and an Example Data Dictionary.

Variable Name	**Data Source (patient survey, EMR, claims, registry)**	**Purpose (sample identification, description, grouping variable, study endpoint, predictor, covariate)**	**Measurement Scale (binary, continuous)**
Randomization group	Assignment	Independent variable	Binary (orally dissolving olanzapine vs. standard of care)
Pain via Numeric Rating Scale (NRS) at time 0 minutes	Patient survey	Study endpoint	Continuous (0-10)
Nausea at 0 minutes		Descriptive	Binary (yes or no)
Pain via Numeric Rating Scale (NRS) at time 30 minutes	Patient survey	Study endpoint	Continuous (0-10)
Nausea at 30 minutes		Descriptive	Binary (yes or no)
Pain via Numeric Rating Scale (NRS) at time 60 minutes	Patient survey	Study endpoint	Continuous (0-10)
Nausea at 60 minutes		Descriptive	Binary (yes or no)
Pain via Numeric Rating Scale (NRS) at time 90 minutes	Patient survey	Study endpoint	Continuous (0-10)
Nausea at 90 minutes		Descriptive	Binary (yes or no)
Total ED time	EMR time stamping	Descriptive	Continuous (total ED length of stay in minutes)
Patient satisfaction with visit	Patient survey	Descriptive	Continuous (Poor, Below Average, Average, Above Average, Excellent)
Patient satisfaction with	Patient survey	Descriptive	Continuous (Poor, Below

medication			Average, Average, Above Average, Excellent)
Would patient use medication again in future for headache	Patient survey	Descriptive	Binary (yes or no)
Adverse reaction	EMR/Patient survey/Patient call back	Descriptive	Binary (adverse reaction present vs. no adverse reaction)
Need for rescue medications (any different medication administered for analgesic purposes after the initial analgesic medication administration)	EMR	Descriptive	Binary (rescue medication required vs. no rescue medication required)
IV access utilized	EMR	Descriptive	Binary (IV access utilized vs. no IV access utilized)
Demographic Data to include, age, gender, race and ethnicity	EMR	Descriptive	Categorical: Gender, Race, Ethnicity Continuous: Age
Rebound headache	Call back	Descriptive	Binary (yes or no)
Need for return visit	Call back	Descriptive	Binary (yes or no)

2.12 Provide operational definitions of any variables listed above that aren't adequately described by the variable name above, and provide a brief background of any validated measurement scales listed above.

Numeric rating scale (NRS) for pain: Validated in many different studies and commonly used as an objective way of quantifying pain.[15]

2.13 If you are collecting data elements besides those listed in Table 2.10 above, provide a justification for gathering the additional data.

Reminder: For chart review studies, a data collection form must be uploaded with your application listing variables collected and how they are recorded (chart review studies). Provided are links to two example chart review tools: **Word Chart Review Example** and **Excel Chart Review Example**

****3. ANALYSIS****

3.1 Describe the statistical methods that will be used to address the study aims. For each aim, this will usually include:

- Description of the sample used for the particular analysis
- The variables included in the specific analysis and their role in the analysis
- Numeric summaries computed (e.g., mean, standard deviation, proportion, correlation)
- A summary of data exploration and presentation activities (e.g., generating scatter plots, summary tables)
- Description of statistical tests (e.g., independent samples t-test, Mann-Whitney test), and models constructed (e.g., logistic regression)

Please see our Examples of Statistical Methods.

Describe here:

Note: Please reference the area/pages of an established protocol if you are not writing your own analysis plan.

Descriptive statistics (mean, median, standard deviation for continuous variables; frequencies on categorical variables) will be computed on demographic variables as well other key variables such as patient satisfaction visit, patient satisfaction with medication, adverse events, need for rescue medication, etc... .

Primary Question:

Does oral rapidly dissolving olanzapine provide equally efficacious analgesia in patients with acute headache of non-organic origin (primary headache) who come to the ED for abortive therapy when compared to current standard of care?

Primary Analysis Plan:

The primary question will be answered by comparing the average pain scores (measured by the NRS) along the three post drug administration time periods between the patients that were given the oral rapidly dissolving olanzapine and the patients that were given the standard of care. Given that there are two independent groups of patients, a two sample independent t-test will be conducted to determine whether the oral rapidly dissolving olanzapine provide the same kind of relief as the standard of care

Secondary Aim:

Additionally, the study will aim to see if oral rapidly dissolving olanzapine decreases 1) duration of ED stay and 2) need for parenteral access when compared to the current standard of care.

Secondary Analysis Plan:

In the secondary aim will, the duration of ED stay will be determined by conducting a two sample independent t-test on duration of stay among the two groups and the need for IV access will assessed by conducting a chi-square test for association between the IV access and the study groups.

Sample size:

3.2 What is the estimated sample size(s) for the primary study analyses (per group for studies with different arms or comparison groups)?

The total sample size is 124. Each group will be comprised of 62 patients.

3.3 The sample size selected was (check all that apply):

X	Based on data likely to be available during a specific time period (often based on data available in past periods)
	To conduct one or more specific analyses with adequate statistical power
	To achieve a specified level of precision in one or more key estimates
	Other (explain):

3.4 Explain your choice of the sample size selection you listed above:

The sample size was calculated based on a two sample independent t-test for comparing the pain scores between the patients that were given the rapidly dissolving olanzapine for acute headache and the patients who received the standard of care (no difference in pain scores between the two groups versus a difference between the two groups). We are planning a study from independent control and experimental patients with 1 control per experimental patient. We assumed that the pain score variable (NRS) within each patient group was normally distributed with a standard deviation of 1.7. If the true difference in the experimental and control means is 1, we will need to study 46 experimental patients and 46 control patients for a total of 92 to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.80. The Type I error probability associated with this test of this null hypothesis is 0.05.

Given that a follow up survey will be conducted 48 hours after the patient's discharge from the ED and assuming that 75% of the patients will be reachable during this follow up survey, we will collect data on 62 patients per group for a total of 124 patients for the study in order to account for drop out. Therefore, we will need 62 patients in each group in order to achieve statistical significance if any.

3.5 Describe your assumptions concerning data available for analysis (e.g. How many subjects will be randomized, possibly lost to follow-up or a procedure? What do you expect for survey response rates, and how much missing data do you expect?). Include information as it pertains to your study (human or animal).

Based past data on headache diagnostic at the ED within the last six months at Regions Hospital, we anticipate that we will collect enough data during the study period. The power analysis shows that we will need 124 patients to complete this study. Claims data from the emergency department reports that from June-November 2015 (6 months), 673 patients were seen in the emergency department with a chief complaint and primary diagnosis of headache.

Power analysis

NOTE: If you are doing a descriptive study (i.e., aside from computing confidence intervals you are not using statistical tests, inferential statistical testing for group comparisons, or statistical models), please complete 3.6 and skip 3.7-3.8.

If you are conducting statistical tests, using statistical inference to compare groups, or are building statistical models, please skip 3.6 and complete 3.7-3.8. **Please see our Example Power Analysis.**

3.6 Provide a measure of the precision of your estimates for key study endpoints, (e.g., 95% confidence intervals on proportions or means), using actual expected estimates.

N/A

3.7 What level of differences observed in your primary endpoints would be considered clinically or practically significant?

Because this is a non-inferiority study, the power analysis was conducted to show equal efficacy between the groups

3.8 What is the power for your primary analysis (and the set of assumptions underlying it: hypothesis addressed, expected pattern of effects with justification for these expectations, analysis used, variables in the analysis, effect sizes, sample sizes, alpha level, one or two-sided test)?

The sample size was computed based on a power of 80% for the study.

3.9 What are the limitations of the proposed approach and analysis?

One potential limitation is that the results of this study may not be generalizable to other emergency departments given that we are only collecting data at Regions Hospital. Because the patient's attending physician can decide whether or not to allow their patient into the study, there is the potential for selection bias. An additional limitation is due to the pilot nature of this feasibility study. We may not have a large enough sample size which may deter us from seeing statistical efficacy between the drugs.

3.10 Please name the people who completed the analysis section of this application.

Vincent Agboto, Ph.D.

3.11 Please name the people who will summarize data and conduct statistical analysis.

Vincent Agboto, Ph.D.

Sandi Wewerka, MPH

******4. RESEARCH TEAM******

	List what each person will do: Identify study subjects; Data entry; Chart abstraction;	**List each person's experience** Explain each person's previous research experience with the tasks	**Time Estimate** Please estimate the number of

	Statistical analysis; Study recruitment Interview patients; Draft and revise manuscripts	assigned or what other background/experience relates to the task they are assigned.	hours or % effort each person will spend on the study
Bradley Hernandez,	Principal Investigator: Dr. Hernandez will be responsible for study oversight including attendance at monthly study update meetings as well as reviewing the analysis and assisting with manuscript preparation and submission. He will present the study to the ED Physician Attending group prior to the study beginning in order to answer any questions.	Dr. Hernandez is a senior faculty attending physician in the Regions Hospital Emergency Department. He has mentored residents in the past on research protocols and has conducted research in the Regions ED for the past 8 years.	3% in-kind
Bradford Hansen, MD	Co-Investigator: Dr Hansen will assist with all aspects of this study including being available for physician questions about the protocol. He will attend the monthly research progress meetings and assist with the interpretation of the results and manuscript preparation and submission	Dr. Hansen is a G-1 Resident in the Regions Hospital Emergency Department. This study will serve as his resident research project under the direction of Dr. Hernandez. He will also assist in training the interns on screening and data collection.	5% in-kind
Sandi Wewerka, MPH	Co-Investigator: Ms. Wewerka will assist with the day-to-day aspects of the study including oversight for the CCRC interns, data collection and ensuring that the study follows GCP guidelines. She will assist with analysis and manuscript submission.	Ms. Wewerka is the Clinical Research Manager in the CCRC. She has assisted with numerous studies in the Regions Hospital ED and has served as a Co-I and PI on several studies.	3% in-kind
Vincent Agboto, Ph.D.	Statistician: Dr. Agboto will be responsible for the statistical analysis plan and the analysis of the final data set. He will assist with the interpretation of the results and manuscript preparation.	Dr. Agboto is the Director of the CCRC and a Ph.D. trained biostatistician. He has written the analysis plan for several studies in the emergency department and serves as an expert in study design and methodology on an NIH review panel.	3% in-kind
CCRC Interns	The CCRC intern group will be trained in the study protocol and consenting patients under the direction of Ms. Wewerka. They will be responsible for screening, consenting, randomization and data collection.	The CCRC intern group is well-versed in data collection in the Regions Hospital Emergency Department. They are involved in several studies in which they consent patients and conduct protocols for data collection.	15% paid 20% in-kind

****5. DISSEMINATION****

5.1 What are your plans for publication, including target journals?

We plan to publish the results in an Emergency Medicine based journal such as Annals or the Journal of Emergency Medicine. We also hope to present the results of this study at an Emergency Medicine conference, ACEP and/or SAEM.

5.2 What plans do you have to share results or translate results to care delivery at HP or for HP personnel?

The results of the study will be shared with the Emergency Medicine attending physicians, residents, nurses and pharmacists. We will also share the results with the Regions Hospital pharmacy group.

****6. ENVIRONMENT****

6.1 Where will the study be conducted? Why is the proposed location appropriate for study?

The screening, enrollment, consent and data collection will take place in the Regions Hospital Emergency Department. This is the appropriate location because this is where the patients are being treated and evaluated for their headache.

6.2 How will the results of this study impact the health of HealthPartners members and the community? Be specific as to whether and how you see any clinical application as a result of this study.

If the results of this study show clinical efficacy with oral rapidly dissolving olanzapine compared to standard of care, we may be able to reduce the patient's length of stay in the emergency department, reduce pain from an IV stick or IM injection and improve the patient satisfaction scores for their ED visit. Because the olanzapine can be administered orally, patients randomized to this group have the potential for faster pain relief compared to IV or IM medications. If the results are positive, physicians in the emergency department will have an alternative way in which to treat patients presenting with headaches.

6.3 Does the treatment strategy (drug or service) proposed in the study commit HP to covering or continuing to provide the treatment or program support after the study is completed?

No. Even if the results of the study show efficacy with oral olanzapine, physicians are free to choose the best and most appropriate medication for their patients.

****7. OTHER REVIEW****

7.1 Has this study been submitted for other review and/or received approval/rejection previously, including but not limited to: Federal, collaborative agency, previous HealthPartners (rejected), or other funding sources (e.g., nonprofit foundation review)?

X	**No**
	Yes (Provide dates of submission and status of review [approved, pending, or rejected])

7.2 Does this study require review by HealthPartners Radiation Safety Officer?

X	**No**
	Yes Please state that you have spoken to the Radiation Safety Office (651-254-3322) and have their support for this study.

If a research protocol is to involve the use of ionizing or non-ionizing radiation, the principal investigator (PI) should contact the Institutional Radiation Safety Officer (RSO) for Regions Hospital and HealthPartners clinics.
Regions Radiation Safety Office: 651-254-3322.
Frank E. Zink, Ph.D., Radiation Safety Officer for X-Ray Use

****8. DATA ACCESS REQUEST****

These questions must be completed if you are accessing HP/Regions data or if you study involves a HealthPartners Institute programmer. You will need to work with an Institute programmer to complete this form. Please contact Ann Hanson (952-967-5263) or Teri Defor (952-967-7304) for assistance.

If you are not proposing the access HP/Regions data (e.g. Animal Study), you may check "N/A" below.

8.1 What is the name of the programmer helped you complete this section?

N/A. This is a prospective study that will not require a programmer.

8.2 Will you need to add a programmer to your study team?

X	**No**
	Yes

8.3 Considering your inclusion/exclusion criteria described in 2.3, what specific data will you need?

8.4 What years of data are needed?

N/A – this is a prospective study that will collect data in the Regions Hospital ED from March-December 2016.

8.5 Will any of the study data be shared or transferred to others within HealthPartners?

No. The study data will only be shared with research personnel listed on this application.

8.6 Will any study data be shared or transferred to others outside of HealthPartners?

X	**No**
	Yes - mark which method you will use to share study data: [ ] E-transfer [ ] Secure website/portal [ ] Other secure, encrypted method. Describe below.

8.7 Data Sources (please mark all known data sources)

Mark (X)	Data Source	Mark (X)	Data Source
	EWIS – Claims Data		Registries (chronic condition, disease)
	RDW (Research Data Mart) – historical medical, dental, state death data		Inpatient Case Management data (i.e., Care Guide, Care Partner)
	Claims/Mumps/Cache		Paper Medical Chart
X	EPIC (Electronic Medical Record)		Provider's own source (own patient's chart, provider or department/hospital registry)
	EDR (Electronic Dental Record)		Geriatric department data (i.e., transitional, long term care database)
	EDR Reporting		Data directly from contracted clinics

	New Subject Survey		VDW (Virtual Data Warehouse)
	MEDIPAC System (Regions Billing System)		Consolidated Network Provider (CPN)
	Physician Services Department Data		Health Behavior Group Data (e.g., 10,000 steps, HRA)
	MN State Death Data		MN State Birth Data
	Misys/Sunquest (Lab production system)		Clarity (Epic Reporting Database)
	Other (Please describe):		

8.8 Exclusion Lists: Institute programmers are required to review and apply the following privacy requirements to study patients and their wishes regarding access to medical record information.

Mark X	Exclusion List
	HealthPartners Institute Exclusion List which excludes persons from all medical research. This should be used for all studies. Applies to all data used internally and externally.
	Gramm-Leach-Biley Opt-Out List: (if known; sometimes this can be determined after a study starts). Applies to identifiable data being sent externally.
	Consent for Treatment-Payment-Operations (TPO) Opt-Out List: (if known; sometimes this can be determined after a study starts). Applies to identifiable data being sent externally.

8.9 Data Elements (Please mark all elements that will be used/ accessed during the study):

Mark (X)	Data Elements
X	Name
	Address
X	Telephone Number (any)
	Fax Number
	Certificate/license number (i.e., DEA number, professional license number)
	Email address
	Device identifier or serial number
	URL or IP address (web addresses)
	Full face photos, biometric identifiers, or other images
	Health Plan beneficiary number (or family contract number)
X	Date of Birth
	Vehicle identification or serial number
X	Medical Record number (or any personal record identifier)

8.10 Data Content (Please mark all content areas that apply to your study

Mark (X)	Data Content
X	Demographic: age and gender
	Health Plan enrollment information (i.e., dates, coverage)
X	Diagnoses - Medical
X	Procedures - Medical

	Mortality Data
	Lab Results
X	Prescriptions/ Medications
	Dates of Service (treatment)
	Facility or Provider Identifier / Characteristics (e.g., specialty, FTE, Clinic)
	Birth Certificate Data
	Pathology / Tissue Type
	Financial data
X	Provider notes
	Vitals – height, weight, BP, etc
	Social history – tobacco use, etc.
X	Other Clinical data: imaging results to rule out "other" reason for headache
X	Other: please describe: pain scores,

****9. REFERENCES****

9.1 Please list below or attach a list of numbered references to support your literature review in section 1 above.

1. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med. 2002;39(3):215-22.
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4. Insinga RP, Ng-mak DS, Hanson ME. Costs associated with outpatient, emergency room and inpatient care for migraine in the USA. Cephalalgia. 2011;31(15):1570-5.
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8. Charbit AR, Akerman S, Goadsby PJ. Dopamine: what's new in migraine?. Curr Opin Neurol. 2010;23(3):275-81.
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10. Tan L, Liu J, Liu X, et al. Clinical research of Olanzapine for prevention of chemotherapy-induced nausea and vomiting. J Exp Clin Cancer Res. 2009;28(1):131.
11. Olanzapine [package insert]. Indianapolis, IN: Eli Lilly & Co; 2009,2015.
12. Montgomery W, Treuer T, Karagianis J, Ascher-svanum H, Harrison G. Orally disintegrating olanzapine review: effectiveness, patient preference, adherence, and other properties. Patient Prefer Adherence. 2012;6:109-25.
13. Mogollón J, Serrano A, Padrón de Freitez A, Uzcátegui E, Baptista T. Olanzapine as an add-on treatment in migraine status: A randomized double-blind, placebo-controlled, pilot study. Eur J Psychiat. 2012;26(4):260-265.
14. Matchar DB, Young WB, Rosenberg JA, et al. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacological management of acute attacks. American Academy of Neurology. Accessed January 10, 2016.
15. Ferreira-valente MA, Pais-ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011;152(10):2399-404.