

Online Supplement 1

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eAppendix 1. Original Study Protocol

A Preliminary Double-Blind Randomized Controlled Trial of Single Dose Lorazepam as an Adjuvant to Haloperidol for Agitated Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

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A. Study Objectives

Primary objective:

1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on the intensity of agitation (Richmond Agitation Sedation Scale) over 8 hours.

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.

B. Background and Significance

B.1. Delirium is the most frequent neuro-psychiatric complication in patients with advanced cancer.(Centeno *et al.* 2004, Fang *et al.* 2008) It is characterized by acute confusion, altered level of consciousness, restlessness, decreased attention and cognition, and perception abnormalities that tend to fluctuate over the course of the day.(Bush and Bruera 2009)

Delirium is associated with increased morbidity, mortality,(Caraceni *et al.* 2000) and interference with pain and other symptom assessment and control in patients with cancer.(Delgado-Guay *et al.* 2008) In patients with advanced cancer, delirium poses an additional burden of symptom distress, as the consequent awareness and attention deficits impede communication with their families and hinder participation in treatment decisions, counseling, and symptom assessment.(Breitbart and Alici 2008) A large proportion of patients who recovered from delirium and their caregivers recalled their experience as distressing.(Breitbart *et al.* 2002, Bruera *et al.* 2009)

B.2. The Current management of delirium involves (1) identifying and removal of any potentially reversible causes, and (2) pharmacologic and non-pharmacologic interventions to palliate this syndrome. Non-pharmacological measures such as environmental control and aids for orientation are recommended. Pharmacologic measures include neuroleptics (e.g. haloperidol, chlorpromazine, olanzapine and quetiapine) and benzodiazepines.(Breitbart and Strout 2000)

Table 1 highlights the randomized controlled trials supporting the use of neuroleptics. Few studies examined delirium in cancer patients, and only one in the palliative care setting.(Candy *et al.* 2012) Many important questions regarding the management of delirium have not been answered. What neuroleptic dose is therapeutic? Is combination of medications more effective than a single agent?

The role of other agents such as benzodiazepines in the management of delirium has not been well characterized. Lorazepam binds to stereospecific benzodiazepine receptors on postsynaptic GABA neurons in the limbic system, reticular formation and other CNS regions. This increases the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions, hyperpolarization (a less excitable state) and stabilization. This contributes to the sedative and amnesic effects of benzodiazepines. A landmark randomized controlled trial compared haloperidol (N=11), chlorpromazine (N=13) and lorazepam (N=6) for the management of delirium in human immunodeficiency virus (HIV) patients.(Breitbart *et al.* 1996) No improvement in symptoms was found in the lorazepam group, and these patients all

developed treatment limiting adverse effects. Some clinicians are concerned that lorazepam can cause excessive sedation and worsen delirium. However, this study used rapidly escalating doses of lorazepam and without neuroleptics. The National Comprehensive Cancer Network (NCCN) Palliative Care guideline supports the use of benzodiazepines in patients with agitated delirium not controlled by neuroleptics. However, no study to date has specifically examined the adjuvant use of benzodiazepine vs. neuroleptic alone for agitation in delirium. The goal of this proof-of-concept study is to understand the effect of lorazepam as an adjuvant to haloperidol on delirium. This study is not intended to result in FDA approval of lorazepam for a new indication.

Table 1. Randomized controlled trials in delirium

| Study | Setting | Design | Outcome |
|---|----------|---------------------|---------|
| Breitbart 1996 (Breitbart <i>et al.</i> 1996) | HIV | DB-RCT H/C/L; N=30 | H~C>L |
| Hu 2004 (Hu <i>et al.</i> 2004) | Med | OL-RCT H/O/X; N=175 | H=O>X |
| Han 2004 (Han and Kim 2004) | Med | DB-RCT H/R; N=28 | H~R |
| Kim 2010 (Kim <i>et al.</i> 2010) | Med | DB-RCT O/R; N=32 | O~R |
| Tahir 2010 (Tahir <i>et al.</i> 2010) | Med/Surg | DB-RCT Q/P; N=42 | Q~P |
| Grover 2011 (Grover <i>et al.</i> 2011) | Med/Surg | SB-RCT H/O/R; N=74 | H~O~R |
| Skrobik 2004 (Skrobik <i>et al.</i> 2004) | ICU | DB-RCT O/H; N=73 | O~H |
| Pandharipande 2007 (Pandharipande <i>et al.</i> 2007) | ICU | DB-RCT D/L; N=106 | D>L |
| Riker 2009 (Riker <i>et al.</i> 2009) | ICU | DB-RCT D/M; N=375 | D>M |
| Reade 2009 (Reade <i>et al.</i> 2009) | ICU | OL-RCT D/H; N=20 | D>H |
| Devlin 2010 (Devlin <i>et al.</i> 2010) | ICU | DB-RCT Q/P; N=36 | Q>P |

Abbreviations: C, chlorpromazine; D, dexmedetomidine; DB, double blind; H, haloperidol; HIV, human immunodeficiency virus; ICU, intensive care unit, L, lorazepam; M, midazolam; O, olanzapine; OL, open label; Q, quetiapine; R, risperidone; RCT, randomized controlled trial; SB, single blind; X, control arm with no medications given

B.3. Rationale. Given clinical equipoise in regard to the use of benzodiazepine as adjuvant therapy for delirium, a randomized controlled trial is warranted to provide a better understanding of lorazepam's effect. With concurrent use of a neuroleptic, single dose lorazepam may provide more rapid control of agitation and restlessness, decrease anxiety, and reduce delirium recall through its anterograde amnesic effect. Adjuvant use of benzodiazepine may also reduce delirium related distress in patients, caregivers and healthcare professionals.

C. Experimental Approach

C.1. Overall Study design. This is an investigator-initiated study. We propose a 2-arm, double blind, parallel randomized controlled trial of lorazepam and placebo for cancer patients with delirium admitted to our acute palliative care unit (Figure 1). The main goal of this study is to determine the effect of lorazepam/placebo as an adjuvant to haloperidol on agitated delirium. After obtaining consent from the legally authorized representative, eligible patients will be given a single dose of lorazepam or placebo, in addition to a standardized doses of haloperidol (8 mg/day). Based on our experience conducting symptom control trials,

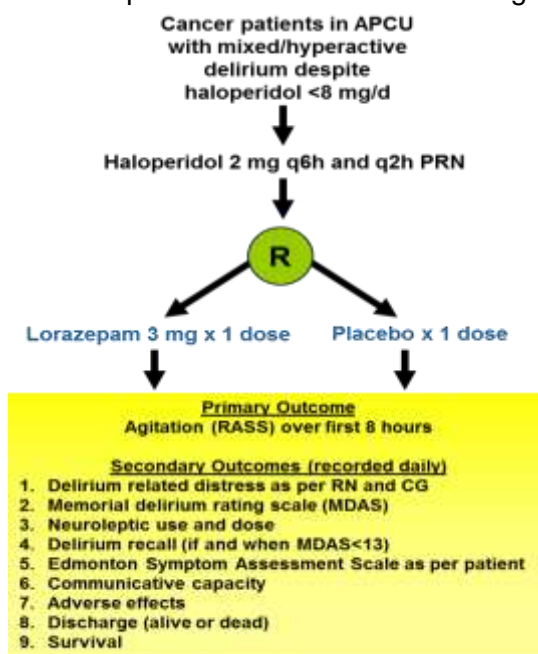


Figure 1. Study Flow Chart

this study is feasible and would not add undue burden to patients or caregivers.

C.2. Eligibility criteria. The eligibility criteria are shown in Table 2.

C.3. Study screening. Patients identified to be delirious on the APCU will be approached. Informed consent from the legally authorized representative will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

Table 2. Study Eligibility Criteria

Inclusion Criteria

1. **[Patients]** Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent or incurable disease)
2. **[Patients]** Admitted to Acute Palliative Care Unit
3. **[Patients]** Delirium as per DSM-IV-TR criteria
4. **[Patients]** Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
5. **[Patients]** Memorial delirium rating scale ≥ 13
6. **[Patients]** On scheduled haloperidol of < 8 mg in the last 24 hours
7. **[Patients]** Age 18 or older
8. **[Patients]** Legally authorized representative consent
9. **[Family Caregivers]** Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
10. **[Family Caregivers]** Age 18 or older
11. **[Family Caregivers]** At the patient's bedside at least 4 hours each day during patient delirium episode
12. **[Family Caregivers]** Able to communicate in English

Exclusion Criteria

1. **[Patients]** Life expectancy < 3 days (based on clinical signs of impending death)
2. **[Patients]** History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
3. **[Patients]** History of neuroleptic malignant syndrome
4. **[Patients]** History of Parkinson's disease or dementia
5. **[Patients]** History of seizure disorder
6. **[Patients]** History of hypersensitivity to haloperidol or benzodiazepine
7. **[Patients]** On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
8. **[Patients]** Previously documented and persistent QTc prolongation (> 500 ms)
9. **[Patients]** Heart failure exacerbation at the time of enrollment

C.4. Randomization.

Patient randomization will be conducted through the Clinical Oncology Research System (CORE) at MD Anderson Cancer Center.

C.5. Blinding. Patients, caregivers, nurses and the research staff conducting the assessment will be blinded to the treatment assignment. Lorazepam will be dispensed by Dispensing Pharmacy at MD Anderson using a syringe. Placebo (normal saline) will be in a pre-loaded syringe identical in appearance to lorazepam.

C.6. Research staff. An orientation will be held with research staff involved in this study to introduce them with the study design, and standardize the provision of each intervention.

C.7. Study Interventions. The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epi-

lepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg in 25 cc of 0.9% normal saline infused intravenously over 1.5 minutes x1 dose. This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events.(Greenblatt *et al.* 1989) Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg (Greenblatt *et al.* 1977, Kraus *et al.* 1978, Wermeling *et al.* 2001).

For patients randomized to receive placebo, 25 cc of preservative free 0.9% normal saline will be administered.

The use of haloperidol will not be blinded. Haloperidol is the most commonly used neuroleptic to treat delirium in our palliative care unit. Table 3 outlines how neuroleptics will be used systematically. After the study is complete, the treating physician may choose to continue or change the treatment regimen.

Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg IV will be given along with either lorazepam or placebo.

Table 3. Dose levels for haloperidol

| Dose level | Regular dose | As needed dose for agitation/restlessness | Criteria for escalation to next dose level |
|------------|-----------------------------------|---|---|
| 1 | Haloperidol 2 mg IV q6h regularly | Haloperidol 2 mg IV q1h PRN | Use of 2 mg PRN 3 or more times in last 4 hours |
| 2 | Haloperidol 3 mg IV q6h regularly | Haloperidol 3 mg IV q1h PRN | Use of 3 mg PRN 3 or more times in last 4 hours |
| 3 | Call MD | Call MD | |

C.8. Co-Interventions. Other than the study medications, management of delirium will proceed as per standard of care. This include treatment of any potentially reversible causes and environmental measures. Use of neuroleptics other than haloperidol and chlorpromazine is not permitted while on study. We will document the use of all neuroleptics, benzodiazepines (regular and as needed) and opioids given at enrollment and during the study period.

C.9. Feasibility endpoints. We will document the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall (if no longer delirious)

C.10. Study assessments. See Table 4 for a detailed description of all study assessments.

| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
|---|----------|--|-----------------------------|
| Demographics and cancer diagnosis (RS/MD) ¹ | ✓ | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ³ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (Pt/CG) ⁴ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ⁵ | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (Pt/RS) ⁶ | ✓ | | |

| | | | |
|--|---|--------------------------|-------------------|
| Memorial Delirium Assessment Scale (Pt/RS) ⁷ | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
| Delirium Experience Questionnaire (RN and CG) ⁸ | ✓ | ✓ | ✓ |
| Adverse effects (RS) ⁹ | ✓ | ✓ | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | ✓ | ✓ | ✓ |
| Clinical Impression (MD) ¹¹ | ✓ | ✓ | ✓ |
| Delirium Recall Questionnaire (Pt) ¹² | | | Once when MDAS<13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |

Abbreviation: CG, caregiver; MD, physician; Pt, patient; RS, research staff

¹ patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, days in palliative care unit, and potential cause(s) of delirium. The PCU attending physician will provide information on DSM-IV diagnosis and causes of delirium.

² an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag *et al.* 1984).

³ medications used to treat delirium, including scheduled and as needed haloperidol, chlorpromazine, other neuroleptics and benzodiazepines will be recorded. We will also document the need for palliative sedation.

⁴ a 10-item symptom battery validated to assess the symptom burden over the last 24 hours (Bruera *et al.* 1991). Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being using a numeric rating scale from 0 (best) to 10 (worst). It may be completed by patients and/or caregivers.

⁵ a validated 10 point numeric rating scale that ranges from -5 (unarousable) to +4 (very agitated), where 0 denotes a calm and alert patient.(Ely *et al.* 2003, Sessler *et al.* 2002). This will be assessed by the bedside nurse. As an exploratory outcome, caregivers will also be asked to provide an assessment.

⁶ a 16-item scale validated for assessment of delirium over the last 24 hours.(Trzepacz *et al.* 2001) Each item is assigned a score between 0 (normal) and 2 or 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (all 16 items, max 46 points). If an item could not be rated, a midway score was assigned. We will use three words to assess short-term memory, months of the year backwards to help rate attention, and copying intersecting pentagons and drawing a clockface to help assess visuoconstructional ability, and parts of a pen and/or watch to assess naming. A total score of 18 or more suggests delirium. This will be administered to the patient by our research staff.

⁷ a 10-item clinician-rated assessment scale validated for assessment of delirium in cancer patients.(Breitbart *et al.* 1997, Fadul *et al.* 2007) It examines level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30 with a higher score indicating worse delirium. A score of 13 or higher suggests delirium. This will be administered to the patient by our research staff.⁸ our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress for themselves similar to a previous study (Bruera *et al.* 2009). These include disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. All respondents will be asked to recall the frequency of these symptoms scoring from 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. In addition, they will be asked to score the emotional distress for themselves associated with each delirium symptom on a scale from 0-4 (0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed).

⁹ adverse effects related to the use of benzodiazepine and neuroleptic will be documented using NCI CTCAE v4.0 and UKU assessment for selected side effects (sedation, seizures and extrapyramidal side effects).

¹⁰ family caregivers and nurses will be asked to provide their perception of the patient's ability to hear, speak and understand.

¹¹ scored by attending physician as a single overall impression of delirium severity on a numeric rating scale ranging from 1 (no delirium) to 7 (very severe delirium) points.

¹² delirium recall and related distress will be assessed only in patients who have recovered from a delirium episode using the delirium experience questionnaire(Bruera *et al.* 2009): 1. Do you remember being confused? (Yes or No); 2. If no, are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numerical rating scale with 0=not at all, and 4=extremely); 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers will be audiotaped and transcribed verbatim).

¹³ dead or alive at the end of palliative care unit stay

¹⁴ overall survival will be calculated from time of study entry to death or last day known alive

C.10. Stopping rules. Patients who developed severe reaction to the study agents (e.g. seizures, respiratory depression) will be taken off study, and treated with other medications as per

standard of care. Patients, caregivers and clinicians may also decide to withdraw from the clinical trial after reasons for dropout have been recorded.

C.11. Patient Safety, Monitoring, and Confidentiality. During the study, trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. A study physician will also be available by pager to address any concerns, distress or questions, and will attend to the patient as needed. Because this study is conducted in the terminally ill population with survival in terms of days or weeks, a high mortality of enrolled patients is expected. Our study only involves a single dose of lorazepam and thus we believe that severe side effects from the experimental intervention is unlikely. Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board, and the Data Safety and Monitoring Board. Patient confidentiality will be ensured by use of patient initials, secure storage of clinical data, and anonymous reporting.

D. Statistical Analysis

D.1. Sample Size Calculation. For between arm comparison (primary objective), 17 patients per arm provides 80% power to detect an effect size as small as 1.0 in RASS between arms when $\alpha=0.5\%$ using two-sided t-tests. Feasibility (secondary objective #2) will be assessed via the proportion of patients completing the study, defined as having the primary outcome (RASS score) available over the first 8 h after medication administration; an observed proportion less than 50% will be a clear indication that future studies based on this methodology are not feasible. The proportion and associated 95% confidence interval (CI) for patients completing the study will be estimated using all 34 patients; a 95% CI for our expected 65% completion rate will be (49%, 81%).

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number and demographic specifications). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principle investigators and co-investigators, will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities. The data will be kept by the principle investigator in a locked file cabinet.

Final disposition of study records: These data will be used only for this research study data files will be destroyed 5 years after publication of the findings.

F. References

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eTable 1. Key Revisions related to Study Objectives

| IRB Approval Date | Change | Rationale |
|-------------------|--|---|
| 5/2/2014 | <p>Added Secondary Objective #4:</p> <p>To explore the feasibility of collecting saliva samples and detecting changes in biomarker levels (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) in association with delirium severity.</p> | <p>Added that the biomarkers will also be analyzed in addition to the collected variables</p> |
| 11/5/2014 | <p>Revised Secondary Objectives:</p> <p>Secondary objectives:</p> <p>2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.</p> <p>3. To evaluate proportion of patients who consent and are randomized to study however drop out before being treated or before finishing 8-hour RASS assessment; and the reasons of drop-outs will be documented and reported.</p> <p>4. To explore the changes in biomarker levels in saliva samples (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) over time and in association with delirium severity.</p> | <p>We no longer wish to include feasibility as part of our study objectives as per our statistician, there is no need to estimate feasibility for 34 patients. For the secondary objectives, we are actually interested in knowing the proportion of patients who drop out before getting treatment or before finishing 8-hour RASS assessment, and the reasons. Therefore we removed feasibility from the protocol and abstract.</p> |
| 9/24/2015 | <p>Revised Objectives:</p> <p>Primary objectives:</p> <p>1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on the intensity of agitation (Richmond Agitation Sedation Scale) over 8 hours.</p> <p>2. To assess the within-arm effect of single-dose lorazepam or placebo, as an adjuvant agent with haloperidol, on agitation intensity (Richmond Agitation Sedation Scale) over 8 hours in patients admitted to an acute palliative care unit.</p> <p>Secondary objectives:</p> <p>1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4)</p> | <p>We submitted this study to NIH for an R21 application over a year ago. After a long re-submission process, this study has finally been approved for funding. Because the R21 has an identical study design but a more conservative study aim, we would like to reconcile the current study protocol and the R21 by adding this objective. We have consulted this with NIH Program officer as well as our biostatistician Dr. Hess. Both endorse these modifications. The resulting larger sample</p> |

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| | <p>delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.</p> <p>2. To evaluate proportion of patients who consent and are randomized to study however drop out before being treated or before finishing 8-hour RASS assessment; and the reasons of drop-outs will be documented and reported.</p> <p>3. To explore the changes in biomarker levels in saliva samples (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) over time and in association with delirium severity.</p> <p>4. To examine the inter-rater reliability of RASS in the APCU setting between the bedside nurse and the research nurse at the time of study enrollment.</p> | <p>size will adequately address the re-defined objective (see sample size calculation).</p> |
| <p>3/24/2017</p> | <p>Added Secondary Objectives:</p> <p>5. To conduct exploratory analyses on RASS as an outcome.</p> <p>6. To examine the proportion of patients enrolled onto the delirium trial who achieved control of agitation and did not require the randomized study medication.</p> <p>7. To identify patient factors associated with control of agitated delirium.</p> | <p>Objective 5: This exploratory analyses will provide preliminary data to examine RASS-derived metrics for potential use in future trials</p> <p>Objectives 6 and 7: This would allow us to understand the effect of open-label haloperidol on agitation in the observation period prior to randomized study medication administration.</p> |

eTable 2. Key Revisions related to Eligibility Criteria

| IRB Approval Date | Change | Rationale |
|-------------------|---|---|
| 7/31/2013 | Removed Exclusion Criteria #1: [Patients] Glasgow Coma Scale 8 or less Edited | We removed the criteria which included the Glasgow coma scale because patients with mixed delirium may sometimes have decreased level of consciousness. |
| 9/3/2013 | Added Exclusion #9: [Patients] Previously documented and persistent QTc prolongation (>500 ms) | In response to IRB Contingency, we have added these exclusion criteria to add a screening EKG to evaluate for QTC prolongation. At the palliative care unit, EKGs are typically not performed for patients on haloperidol, even at high doses. This is because (1) very few parenteral treatment options are available for patients with agitated delirium, and that it would not be ethical to withhold haloperidol even if QTc is somewhat prolonged given the short survival in this population; (2) alternative parenteral neuroleptic agents such as chlorpromazine can also cause QTc prolongation, and (3) haloperidol is associated with a relatively low risk of QTc prolongation relative to other neuroleptics (Leucht et al. Lancet 2013). Furthermore, our study's main intervention is lorazepam (vs. placebo), which is not known to increase QTc interval. Haloperidol doses used in this protocol (2 mg q2h IV and 2 mg PRN) are in keeping with the doses used in our clinical setting. At the same time, we understand the concerns of the reviewer. Thus, we have now added "previously documented and persistent QTc prolongation (>500 ms)" as an exclusion criteria. |
| 9/3/2013 | Added Exclusion #10: [Patients] Heart failure exacerbation at the time of enrollment | In response to the IRB's suggestion to consider graduated dosing of Lorazepam due to cardiovascular complications, we believe the one time dose of lorazepam given should be safe based on our clinical experience and the literature as highlighted in the protocol. To ensure extra safety based on the reviewer's comment, we have now added "heart failure exacerbation at the time of enrollment" as an exclusion criteria. |
| 9/3/2013 | Revised Inclusion #8: [Patients] Surrogate consent was changed to [Patients] Legally Authorized Representation consent | A legally authorized representative will be used to consent patients, per IRB contingency. |

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| 3/19/2014 | Removed Inclusion #5: [Patients] Memorial delirium rating scale ≥ 13 | DSM-IV criteria will already be used to determine eligibility. MDAS is redundant. |
| 6/11/2014 | Revised Eligibility #2 & #3: [Patients] History of myasthenia gravis or acute narrow angle glaucoma [Patients] Hepatic encephalopathy at the time of screening | To clarify nature of the exclusion criteria |
| 8/8/2014 | Removed Exclusion #1: [Patients] Life expectancy < 3 days (based on clinical signs of impending death) | It is difficult to predict patients with life expectancy < 3 days, and clinicians sometimes exclude patients who have a longer life expectancy. Furthermore, this clinical trial is appropriate for patients with a short life expectancy who have agitated delirium. |
| 9/3/2014 | Changes RASS Score ≥ 2 to ≥ 1 : Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 1 and the patient has significant restlessness/agitation/anxiety requiring breakthrough haloperidol. At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo. | Some patients have been agitated but did not receive study medication because the threshold has been too high. We have now clarified the timing when study medication should be administered. |
| 8/5/2016 | Removed Exclusion #2: [Patients] Hepatic encephalopathy at the time of screening and added "Uncontrolled" to #4 [Patients] Uncontrolled seizure disorder | Removed exclusion criterion #2: The target population for this study are patients with terminal delirium. The study medication, Lorazepam, should not cause additional risk for patients with hepatic encephalopathy and may benefit them if the agitated delirium is controlled. |
| 8/5/2016 | Revised Exclusion #4: | Revised exclusion criterion #4: The target population for this study are patients with terminal delirium who can have a remote history of |

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| | [Patients] Uncontrolled seizure disorder | seizures for wide variety of reasons. The study medication, Lorazepam, should not pose additional risk to this population. |
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eTable 3: Key Revisions related to Statistical Analyses

| IRB Approval Date | Change | Rationale |
|-------------------|--|--|
| 11/5/2014 | <p>D.1. Sample Size Calculation. For between arm comparison (primary objective), 17 patients per arm provides 80% power to detect an effect size as small as 1.0 in changes of RASS between arms when $\alpha=0.5\%$ using two-sided t-tests. In this study, we will continue enrollment until 34 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.</p> <p>D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests. Because of the nature of our study population, many patients died or get discharged before requiring the study medication. Thus, we will use per protocol analysis to compare the two study arms among patients who received the medication.</p> | <p>We have enrolled 29 patients so far onto this study, but only 13 have received the study medication. This is because patients are extremely sick and many died before they were able to receive the study meds (which were only given when they develop an agitation episode). After discussion with our biostatistical team, we decided that we need to enroll 34 <u>evaluable</u> patients instead of just 34 patients, and conduct per protocol analysis. (note by author 6/30/17: this label is actually erroneous – and should be modified intention to treat instead)</p> |
| 9/24/2015 | <p>D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect an effect size of 0.79 (0.50 mean difference, based on a within-group standard deviation of 0.63) in RASS between arms when $\alpha=5\%$ using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately using paired t-test (or Wilcoxon signed rank test if data are not normally distributed). Secondary comparisons between arms will be performed using linear mixed models (also known as repeated measures ANOVA). For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have 90% power to</p> | <p>Per DSMB designee's request on 9/2/15 to consult with our statistical collaborator and revise the statistical plan. We have consulted with Dr. Hess and Ms. Diane Liu and revised the sample size calculations section.</p> |

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| | <p>detect an effect size of 0.186 if the correlation between repeated measures is 0.05 and an effect size of 0.160 if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.</p> | |
| 10/9/2015 | <p>D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect an effect size of 0.79 (0.50 mean difference, based on a within-group standard deviation of 0.63) in RASS between arms when alpha=5% using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately using paired t-test (or Wilcoxon signed rank test if data are not normally distributed). Secondary comparisons between arms will be performed using linear mixed models (also known as repeated measures ANOVA). For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have 90% power to detect an effect size of 0.34 if the correlation between repeated measures is 0.5 and an effect size of 0.28 if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.</p> | <p>In order to have 90% power to detect an effect size of 0.160 based on the repeated measures ANOVA, the assumed correlation should be 0.03 rather than 0.3. However, even if the assumption of a correlation of 0.03 (or 0.05) was intended, please either provide a rationale for the assumptions of such low correlations, or perhaps better assume a correlation with a larger range such as from 0.3 to 0.5, in which case the corresponding detectable effect size will become larger (thus being more conservative in detecting between-group differences).</p> |
| 3/24/2017 | <p>Revised Data Analysis Section: (Post-Hoc)</p> <p>D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for</p> | <p>Objective 5: This exploratory analyses will provide preliminary data to examine RASS-derived metrics for potential use in future trials</p> |

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| | <p>the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests. Because of the nature of our study population, many patients died or get discharged before requiring the study medication. Thus, we will use per protocol analysis to compare the two study arms among patients who received the medication. We will determine the inter-rater reliability of RASS between the bedside nurse and the research nurse at the time of study enrollment using kappa statistic.</p> <p>To address objective 5, we will be examining multiple variations of RASS-derived metrics as outcome variables and how they behave within each study arm and between study arms, such as</p> <ul style="list-style-type: none"> · Time to achieve RASS within target range for several consecutive readings, where the target range may be either 0 to -2 or 0 to -3, the number of consecutive readings may vary between 2 and 6 · The proportion of patients who achieved RASS within target range for a defined % of time within the first 8 hours, where the target range may be either 0 to -2 or 0 to -3, the defined % of time may vary between 50-100% · We will also be examining how these RASS-derived metrics correlate with the magnitude of RASS reduction <p>To address objectives 6 and 7, we will estimate the proportion of patients enrolled onto the delirium trial who achieved control of agitation and did not require study medication, with 95% confidence interval. We will summarize the demographic/clinical characteristics separately for the patients who achieved control of agitation and did not require study medication and for those that developed agitation and received treatment for agitation. We will evaluate the time from registration to agitation in which patients who never developed agitation before discharge will be censored at discharge. Any death before charge without the development of agitation will be considered as a competing risk. The cumulative incidence of agitation will be estimated using the competing risk analysis and can be compared between different patient groups using Gray's test [Pintilie M 2006; Gray RJ Ann Stat 1988]. To assess the effects of covariates on the cumulative incidence function for agitation, we will use the univariate and multivariate proportional hazards</p> | <p>Objectives 6 and 7: This would allow us to understand the effect of open-label haloperidol on agitation in the observation period prior to randomized study medication administration.</p> <p>This study is CNPE. We do not plan on enrolling any new patients.</p> |
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| | models of Fine and Gray [Fine J Am Stat Assoc 1999]. Other statistical methods may be employed when appropriate. | |
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eAppendix 2. Detailed History of Protocol Revisions

Select a Committee to receive this memo from the list:

To: **CRC** 6/24/2013 1:25:36 AM
From: David Hui
CC: Julio A. Allo, Susan Frisbee-Hume, Vera J. DeLaCruz, Shakia D. Jones, CRC PBHSRC Help Desk
Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit
MDACC Protocol ID #: 2013-0345
Version: 01
Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 01

The above protocol is being resubmitted to the Office of Protocol Research (CRC).

Please indicate below the reason for re-submission.

- CRC meeting contingencies
- CRC continuing review contingencies
- CRC revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
Clarification and revisions of appendices, clarification of dose and study drug administration.

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol/Abstract

Section: Table 2: Study Eligibility Criteria/ Eligibility Criteria

Paragraph:

Page: 4

Old Text (if applicable):

| |
|---|
| <p>Inclusion Criteria</p> <ol style="list-style-type: none">1. [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent, or incurable disease)2. [Patients] Admitted to Acute Palliative Care Unit (APCU)3. [Patients] Delirium as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria4. [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours5. [Patients] Memorial delirium rating scale ≥ 136. [Patients] On scheduled haloperidol for delirium of < 8 mg in the last 24 hours7. [Patients] Age 18 or older8. [Patients] Surrogate consent9. [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)10. [Family Caregivers] Age 18 or older11. [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium episode12. [Family Caregivers] Able to communicate in English <p>Exclusion Criteria</p> <ol style="list-style-type: none">1. [Patients] Glasgow Coma Scale 8 or less2. [Patients] Life expectancy < 3 days3. [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy4. [Patients] History of neuroleptic malignant syndrome5. [Patients] History of Parkinson's disease or dementia6. [Patients] History of seizure disorder7. [Patients] History of prolonged QTc interval (> 500 ms)8. [Patients] History of hypersensitivity to haloperidol or benzodiazepine9. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours |
|---|

New Text:

Inclusion Criteria

1. [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent or incurable disease)
2. [Patients] Admitted to Acute Palliative Care Unit
3. [Patients] Delirium as per DSM-IV-TR criteria
4. [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
5. [Patients] Memorial delirium rating scale ≥ 13
6. [Patients] On scheduled haloperidol for delirium of < 8 mg in the last 24 hours
7. [Patients] Age 18 or older
8. [Patients] Surrogate consent
9. [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
10. [Family Caregivers] Age 18 or older
11. [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium

episode

12. [Family Caregivers] Able to communicate in English

Exclusion Criteria

1. [Patients] Life expectancy <3 days (**based on clinical signs of impending death**)
2. [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
3. [Patients] History of neuroleptic malignant syndrome
4. [Patients] History of Parkinson's disease or dementia
5. [Patients] History of seizure disorder
6. [Patients] History of prolonged QTc interval (>500 ms)
7. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
8. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours

Scientific Rationale: We have revised our eligibility criteria to clarify that the life expectancy is based on clinical signs of impending death. This will be based on various clinical signs of impending death, such as (but not limited to) respiration with mandibular movement, inability to close eyelids, hyperextension of neck, drooping of nasolabial fold, inability to respond to verbal stimuli, non-reactive pupils, Cheyne Stokes breathing, pulselessness of radial artery etc). These signs have been shown by us and others to be highly specific for impending death. We have now revised the eligibility criteria to reflect this detail. We also removed the criteria which included the Glasgow coma scale. In addition we removed "for delirium" from inclusion criteria #6 to minimize confusion.

»»» Revised Text # 2

Document: Protocol

Section: C.7.

Paragraph: 1

Page: 5

Old Text (if applicable):

C.7. Study Interventions. The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg IV x1 dose. This dose has been used in previous studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events.(Greenblatt *et al.* 1989)

New Text:

C.7. Study Interventions. The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg IV **bolus over 1.5 minutes** x1 dose. This dose has been used in previously studies and found to provide a

physiologic effect lasting at least 8 hours without significant adverse events.(Greenblatt *et al.* 1989). **Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg (Greenblatt *et al.* 1977, Kraus *et al.* 1978, Wermeling *et al.* 2001).**

Scientific Rationale: We are clarifying that the 3 mg dose was chosen after careful considerations with specialists in the field, including Dr. Eduardo Bruera and Dr. William Breitbart. We aim to balance the risks and benefits of this medication. Given that this is a single dose study, we believe it is important to ensure an adequate therapeutic dose, particularly when these patients have a RASS score of at least +2 (i.e. at least moderate agitation). We will be monitoring patients carefully throughout the entire PCU study to document any adverse effects on delirium, and patients will have immediate access to expert care in the PCU for management of delirium/drowsiness. We have now also added more supporting literature for the use of this dose. We have also now stated that 3 mg will be given over 1.5 minutes IV bolus.

»»» Revised Text # 3

Document: Abstract

Section: Proposed Treatment/Study Plan -- Study Interventions

Paragraph: 6

Page:

Old Text (if applicable):

The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg IV x1 dose . This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events.

New Text:

The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg IV **bolus over 1.5 minutes** x1 dose . This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events. **Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg.**

Scientific Rationale: We are clarifying that the 3 mg dose was chosen after careful considerations with specialists in the field, including Dr. Eduardo Bruera and Dr. William Breitbart. We aim to balance the risks and benefits of this medication. Given that this is a single dose study, we believe it is important to ensure an adequate therapeutic dose, particularly when these patients have a RASS score of at least +2 (i.e. at least moderate agitation). We will be monitoring patients carefully throughout the entire PCU study to document any adverse effects on delirium, and patients will have immediate access to expert care in the PCU for management of delirium/drowsiness. We have now also added more supporting literature for the use of this dose. We have also now stated that 3 mg will be given over 1.5 minutes IV bolus.

»»» Revised Text # 4

Document: Protocol/Abstract

Section: Table 4.

Paragraph:

Page: 6

Old Text (if applicable):

| Table 4. Summary of Study Assessments | |
|--|---|
| Assessments (Person completing) | Baseline Day 1 Day 2 daily until discharge |
| Demographics and cancer diagnosis (RS) | 1 |
| Karnofsky performance status (RS) | 2 |
| Medication use (RS) | 3 |
| Edmonton Symptom Assessment Scale (Pt/CG) | 4 |
| Richmond Agitation Sedation Scale (RN, CG) | 5 Q30 min until 2 h, Q1h until 8 h, then at 24 h |
| Delirium Rating Scale-Revised-98 (Pt) | 6 |
| Memorial Delirium Rating Scale | 7 |
| Delirium Experience Questionnaire (RN and CG) | 8 |
| Adverse effects (assessment of Pt) | 9 |
| Communication capacity (RN and CG) | 10 |
| Clinical Impression (MD) | 11 |
| Delirium Recall Questionnaire (Pt) | 12 Once when MDAS < 13 |
| Discharge outcome (RS) | 13 Once at discharge |
| Overall survival (RS) | 14 End of study |
| Abbreviation: CG, caregiver; MD, physician; Pt, patient; RN, registered bedside nurse; RS, research staff | |
| 1 patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, days in palliative care unit, and potential cause(s) of delirium. | |
| 2 an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag <i>et al.</i> 1984). | |
| 3 medications used to treat delirium, including scheduled and as needed haloperidol, chlorpromazine, other neuroleptics and benzodiazepines will be recorded. We will also document the need for palliative sedation. | |
| 4 a 10-item symptom battery validated to assess the symptom burden over the last 24 hours (Bruera <i>et al.</i> 1991). Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being using a numeric rating scale from 0 (best) to 10 (worst). | |
| 5 a validated 10 point numeric rating scale that ranges from -5 (unarousable) to +4 (very agitated), where 0 denotes | |

a calm and alert patient.(Ely *et al.* 2003, Sessler *et al.* 2002). This will be assessed by the bedside nurse. As an exploratory outcome, caregivers will also be asked to provide an assessment.

6 a 16-item scale validated for assessment of delirium over the last 24 hours.(Trzepacz *et al.* 2001) Each item is assigned a score between 0 (normal) and 2 or 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (all 16 items, max 46 points). If an item could not be rated, a midway score was assigned. We will use three words to assess short-term memory, months of the year backwards to help rate attention, and copying intersecting pentagons and drawing a clockface to help assess visuoconstructional ability, and parts of a pen and/or watch to assess naming. A total score of 18 or more suggests delirium.

7 a 10-item clinician-rated assessment scale validated for assessment of delirium in cancer patients.(Breitbart *et al.* 1997, Fadul *et al.* 2007) It examines level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30 with a higher score indicating worse delirium. A score of 13 or higher suggests delirium.

8 our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress for themselves similar to a previous study (Bruera *et al.* 2009). These include disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. All respondents will be asked to recall the frequency of these symptoms scoring from 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. In addition, they will be asked to score the emotional distress for themselves associated with each delirium symptom on a scale from 0-4 (0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed).

9 adverse effects related to the use of benzodiazepine and neuroleptic will be documented using NCI CTCAE v4.0 and UKU assessment for selected side effects (sedation, seizures and extrapyramidal side effects).

10 family caregivers and nurses will be asked to provide their perception of the patient's ability to hear, speak and understand.

11 scored by attending physician as a single overall impression of delirium severity on a numeric rating scale ranging from 1 (no delirium) to 7 (very severe delirium) points.

12 delirium recall and related distress will be assessed only in patients who have recovered from a delirium episode using the delirium experience questionnaire(Bruera *et al.* 2009): 1. Do you remember being confused? (Yes or No); 2. If no, are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numerical rating scale with 0=not at all, and 4=extremely); 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers will be audiotaped and transcribed verbatim).

13 dead or alive at the end of palliative care unit stay

14 overall survival will be calculated from time of study entry to death or last day known alive

New Text:

| Table 4. Summary of Study Assessments |
|--|
| Assessments (Person completing) |
| Demographics and cancer diagnosis (RS/MD)1 |
| Karnofsky performance status (RS)2 |
| Neuroleptics/benzodiazepines use (RS)3 |
| Edmonton Symptom Assessment Scale (Pt/CG)4 |
| Richmond Agitation Sedation Scale (RN, CG)5Q30 min until 2 h, Q1h until 8 h, then at 24 h |
| Delirium Rating Scale-Revised-98 (Pt/RS)6 |
| Memorial Delirium Rating Scale (Pt/RS)7 |
| Delirium Experience Questionnaire (RN and CG)8 |
| Adverse effects (RS)9 |
| Communication capacity (RN and CG)10 |
| Clinical Impression (MD)11 |
| Delirium Recall Questionnaire (Pt)12Once when MDAS<13 |
| Discharge outcome (RS)13Once at discharge |
| Overall survival (RS)14End of study |
| Abbreviation: CG, caregiver; MD, physician; Pt, patient; RS, research staff 1 patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, days in palliative care unit, and potential cause(s) of delirium. The PCU attending physician will |

provide information on DSM-IV diagnosis and causes of delirium.

2 an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag *et al.* 1984).

3 medications used to treat delirium, including scheduled and as needed haloperidol, chlorpromazine, other neuroleptics and benzodiazepines will be recorded. We will also document the need for palliative sedation.

4 a 10-item symptom battery validated to assess the symptom burden over the last 24 hours (Bruera *et al.* 1991). Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being using a numeric rating scale from 0 (best) to 10 (worst). **It may be completed by patients and/or caregivers.**

5 a validated 10 point numeric rating scale that ranges from -5 (unarousable) to +4 (very agitated), where 0 denotes a calm and alert patient.(Ely *et al.* 2003, Sessler *et al.* 2002). This will be assessed by the bedside nurse. As an exploratory outcome, caregivers will also be asked to provide an assessment.

6 a 16-item scale validated for assessment of delirium over the last 24 hours.(Trzepacz *et al.* 2001) Each item is assigned a score between 0 (normal) and 2 or 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (all 16 items, max 46 points). If an item could not be rated, a midway score was assigned. We will use three words to assess short-term memory, months of the year backwards to help rate attention, and copying intersecting pentagons and drawing a clockface to help assess visuoconstructional ability, and parts of a pen and/or watch to assess naming. A total score of 18 or more suggests delirium. **This will be administered to the patient by our research staff.**

7 a 10-item clinician-rated assessment scale validated for assessment of delirium in cancer patients.(Breitbart *et al.* 1997, Fadul *et al.* 2007) It examines level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30 with a higher score indicating worse delirium. A score of 13 or higher suggests delirium. **This will be administered to the patient by our research staff.**

8 our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress for themselves similar to a previous study (Bruera *et al.* 2009). These include disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. All respondents will be asked to recall the frequency of these symptoms scoring from 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. In addition, they will be asked to score the emotional distress for themselves associated with each delirium symptom on a scale from 0-4 (0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed).

9 adverse effects related to the use of benzodiazepine and neuroleptic will be documented using NCI CTCAE v4.0 and UKU assessment for selected side effects (sedation, seizures and extrapyramidal side effects).

10 family caregivers and nurses will be asked to provide their perception of the patient's ability to hear, speak and understand.

11 scored by attending physician as a single overall impression of delirium severity on a numeric rating scale ranging from 1 (no delirium) to 7 (very severe delirium) points.

12 delirium recall and related distress will be assessed only in patients who have recovered from a delirium episode using the delirium experience questionnaire(Bruera *et al.* 2009): 1. Do you remember being confused? (Yes or No); 2. If no, are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numerical rating scale with 0=not at all, and 4=extremely); 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers will be audiotaped and transcribed verbatim).

13 dead or alive at the end of palliative care unit stay

14 overall survival will be calculated from time of study entry to death or last day known alive

Scientific Rationale: We have made Table 4 consistent with the appendices regarding who will be administering the surveys and the descriptions of the information being collected.

»»» Revised Text # 5

Document: Appendices

Section: Appendix U

Paragraph:

Page:

Old Text (if applicable):

Type of Funding:

- NCI
- NIH (other than NCI)
- DOD
- Other peer reviewed funding (e.g. NSF or ACS etc.)
- Industry
- Departmental Funds
- Donor Funds
- Unfunded
- Not known at this time
- Other:

New Text:

Type of Funding:

- NCI
- NIH (other than NCI)
- DOD
- Other peer reviewed funding (e.g. NSF or ACS etc.)
- Industry
- Departmental Funds
- Donor Funds
- Unfunded
- Not known at this time
- Other:
MDACC will be the source of department funds to support this project.

Scientific Rationale: We are clarifying that the funding to support this protocol in the department are coming from MDACC.

»»» Revised Text # 6

Document: Appendices

Section: Appendix D

Paragraph:

Page:

Old Text (if applicable):

1. Richmond Agitation ~~Delirium~~ Scale (-5 to +4) Between Enrollment and Study Medication Administration:

3. Richmond Agitation ~~Delirium~~ Scale (-5 to +4) After Study Medication:

4. Daily Data Collection

| | Day 1 (day of study med <u>prior to</u> admin) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---|---|-------|-------|-------|-------|-------|
| Research staff initials | | | | | | |
| Date (MM/DD/YY) | | | | | | |
| Edmonton Symptom Assessment Scale | | | | | | |
| Pain (0-10) | | | | | | |
| Fatigue (0-10) | | | | | | |
| Nausea (0-10) | | | | | | |
| Depression (0-10) | | | | | | |
| Anxiety (0-10) | | | | | | |
| Drowsiness (0-10) | | | | | | |
| Appetite (0-10) | | | | | | |
| Well being (0-10) | | | | | | |
| Shortness of breath (0-10) | | | | | | |
| Sleep (0-10) | | | | | | |
| Delirium rating scale (0-46) | | | | | | |
| Memorial delirium rating scale (0-30) | | | | | | |
| Richmond agitation delirium scale (-5 to +4) | | | | | | |
| Clinical global impression (1-7) | | | | | | |

New Text:

1. Richmond Agitation **Sedation** Scale (-5 to +4) Between Enrollment and Study Medication Administration:

3. Richmond Agitation **Sedation** Scale (-5 to +4) After Study Medication:

4. Daily Data Collection

| | Day 1 (day of study med <u>prior to</u> admin) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|-------------------------|---|-------|-------|-------|-------|-------|
| Research staff initials | | | | | | |
| Date (MM/DD/YY) | | | | | | |
| | | | | | | |

| | | | | | | |
|---|--|--|--|--|--|--|
| Edmonton Symptom Assessment Scale | | | | | | |
| Pain (0-10) | | | | | | |
| Fatigue (0-10) | | | | | | |
| Nausea (0-10) | | | | | | |
| Depression (0-10) | | | | | | |
| Anxiety (0-10) | | | | | | |
| Drowsiness (0-10) | | | | | | |
| Appetite (0-10) | | | | | | |
| Well being (0-10) | | | | | | |
| Shortness of breath (0-10) | | | | | | |
| Sleep (0-10) | | | | | | |
| Delirium rating scale (0-46) | | | | | | |
| Memorial delirium rating scale (0-30) | | | | | | |
| Richmond agitation sedation scale (-5 to +4) | | | | | | |
| Clinical global impression (1-7) | | | | | | |

Scientific Rationale: We have corrected the word delirium to sedation.

»»» Revised Text # 7

Document: Appendices

Section: Appendix E

Paragraph:

Page:

Old Text (if applicable):

Appendix E. Richmond Agitation ~~Delirium~~ Scale (RASS, Daily or More Frequently in first 12 hours)

New Text:

Appendix E. Richmond Agitation **Sedation** Scale (RASS, Daily or More Frequently in first 12 hours)

Scientific Rationale: We have corrected the word delirium to sedation.

»»» Revised Text # 8

Document: Appendices

Section: Appendix F

Paragraph:

Page:

Old Text (if applicable):

Appendix F. Delirium Rating Scale (DRS, Daily)

New Text:

Appendix F. Delirium Rating Scale (DRS, **Baseline**)

Scientific Rationale: We have corrected this to say baseline.

»»» Revised Text # 9

Document: Appendices

Section: Appendix I

Paragraph:

Page:

Old Text (if applicable):

Appendix I. Delirium ~~Related Distress~~: Caregiver (Daily)

New Text:

Appendix I. Delirium **Experience Questionnaire**: Caregiver (Daily)

Scientific Rationale: We have changed the title as it asks about delirium experience.

»»» Revised Text # 10

Document: Appendices

Section: Appendix J

Paragraph:

Page:

Old Text (if applicable):

Appendix J. Delirium Related Distress: Nurse (Daily)

New Text:

Appendix J. Delirium Experience Questionnaire: Nurse (Daily)

Scientific Rationale: We have changed the title as it asks about delirium experience.

»»» Revised Text # 11

Document: Appendices

Section: Appendix N

Paragraph:

Page: 2

Old Text (if applicable):

| | Day 1 (day of enrollment) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---------------------------------|---|--------------|--------------|--------------|--------------|--------------|
| Research staff initials | | | | | | |
| Date (MM/DD/YY) | | | | | | |
| Awake | | | | | | |
| Communicate | | | | | | |
| Communicate meaningfully | | | | | | |
| Sleeping | | | | | | |
| Agitated | | | | | | |

New Text:

N/A

Scientific Rationale: We have deleted these unnecessary tables.

»»» Revised Text # 12

Document: Appendices

Section: Appendix O

Paragraph:

Page:

Old Text (if applicable):

| | Day-1 (day-of enrollment } | Day-2 | Day-3 | Day-4 | Day-5 | Day-6 |
|---------------------------------|---|--------------|--------------|--------------|--------------|--------------|
| Research staff initials | | | | | | |
| Date (MM/DD/YY) | | | | | | |
| Awake | | | | | | |
| Communicate | | | | | | |
| Communicate meaningfully | | | | | | |
| Sleeping | | | | | | |
| Agitated | | | | | | |

New Text:
N/A

Scientific Rationale: We have deleted these unnecessary tables.

»»» Revised Text # 13

Document: Appendices

Section: Appendix V

Paragraph:

Page:

Old Text (if applicable):

N/A

New Text:

KARNOFSKY PERFORMANCE SCALE

Point

Description

| | |
|------------|--|
| 100 | Normal, no complaints, no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 80 | Normal activity with effort; some signs or symptoms of disease |
| 70 | Cares for self, unable to carry on normal activity or to do active work |
| 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled, requires special care and assistance |
| 30 | Severely disabled, hospitalization indicated. Death not imminent |
| 20 | Very sick, hospitalization indicated. Death not imminent |
| 10 | Moribund, fatal processes progressing rapidly |
| 0 | Dead |

Scientific Rationale: We have added the Karnofsky score as an appendix.

Edit History:

Julio A. Allo 6/24/2013 -- Sent

Julio A. Allo 06/24/2013 -- Edited

Julio A. Allo 06/23/2013 -- Edited

Julio A. Allo 06/18/2013 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

8/20/2013 4:23:13 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 02

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 02

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
replaced "Surrogate consent" with "legally authorized representative consent",
clarified number of patients in informed consent document, revised eligibility

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Informed Consent

Section: **3. DESCRIPTION OF STUDY**

Paragraph:

Page:

Old Text (if applicable): Up to 20-patients will take part in this study. All will be enrolled at MD Anderson.

New Text: Up to 34 patients will take part in this study. All will be enrolled at MD Anderson.

Scientific Rationale: revised to keep consistent with protocol and abstract, per IRB contingency

»»» Revised Text # 2

Document: Protocol and Abstract

Section: **Table 2. Study Eligibility Criteria** / Eligibility

Paragraph: Exclusion Criteria

Page: 4

Old Text (if applicable): n/a

New Text:

- 9. [Patients] Previously documented and persistent QTc prolongation (>500 ms)**
- 10. [Patients] Heart failure exacerbation at the time of enrollment**

Scientific Rationale:

#9 In response to IRB Contingency, we have added these exclusion criteria to add a screening EKG to evaluate for QTC prolongation. At the palliative care unit, EKGs are typically not performed for patients on haloperidol, even at high doses. This is because (1) very few parenteral treatment options are available for patients with agitated delirium, and that it would not be ethical to withhold haloperidol even if QTc is somewhat prolonged given the short survival in this population; (2) alternative parenteral neuroleptic agents such as chlorpromazine can also cause QTc prolongation, and (3) haloperidol is associated with a relatively low risk of QTc prolongation relative to other neuroleptics (Leucht et al. Lancet 2013). Furthermore, our study's main intervention is lorazepam (vs. placebo), which is not known to increase QTc interval. Haloperidol doses used in this protocol (2 mg q2h IV and 2 mg PRN) are in keeping with the doses used in our clinical setting. At the same time, we understand the concerns of the reviewer. Thus, we have now added "previously documented and persistent QTc prolongation (>500 ms)" as an exclusion criteria.

#10: In response to the IRB's suggestion to consider graduated dosing of Lorazepam due to

cardiovascular complications, we believe the one time dose of lorazepam given should be safe based on our clinical experience and the literature as highlighted in the protocol. To ensure extra safety based on the reviewer's comment, we have now added "heart failure exacerbation at the time of enrollment" as an exclusion criteria.

»»» Revised Text # 3

Document: Abstract / Protocol

Section: Eligibility (Inclusion)

Paragraph: #8

Page:

Old Text (if applicable): [Patients] ~~Surrogate consent~~

New Text: [Patients] **Legally Authorized Representative consent**

Scientific Rationale: A legally authorized representative will be used to consent patients, per IRB contingency.

»»» Revised Text # 4

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Study Interventions (#4)

Page:

Old Text (if applicable): Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the ~~surrogate decision maker~~ signs the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

New Text: Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the **legally authorized representative** signs the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

Scientific Rationale: A legally authorized representative will be used to consent patients, per IRB contingency.

»»» Revised Text # 5

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: #1

Page:

Old Text (if applicable): This is an investigator-initiated study. We propose a 2-arm, double blind, parallel randomized controlled trial of lorazepam and placebo for cancer patients with delirium admitted to our acute palliative care unit (Figure 1). The main goal of this study is to determine the effect of lorazepam/placebo as an adjuvant to haloperidol on agitated delirium. After ~~surrogate~~ consent, eligible patients will be given a single dose of lorazepam or placebo, in addition to a standardized dose of haloperidol (8 mg/day). Based on our experience conducting symptom control trials, this study is feasible and would not add undue burden to patients or caregivers.

New Text: This is an investigator-initiated study. We propose a 2-arm, double blind, parallel randomized controlled trial of lorazepam and placebo for cancer patients with delirium admitted to our acute palliative care unit (Figure 1). The main goal of this study is to determine the effect of lorazepam/placebo as an adjuvant to haloperidol on agitated delirium. After **obtaining consent from legally authorized representative**, eligible patients will be given a single dose of lorazepam or placebo, in addition to a standardized dose of haloperidol (8 mg/day). Based on our experience conducting symptom control trials, this study is feasible and would not add undue burden to patients or caregivers.

Scientific Rationale: A legally authorized representative will be used to consent patients, per IRB contingency.

»»» Revised Text # 6

Document: Abstract/Protocol Attachment

Section: Proposed Treatment/Study Plan, C.3. Study Screening

Paragraph: Screening

Page:

Old Text (if applicable): Patients identified to be delirious in the APCU will be approached. Informed consent from the ~~surrogate caregiver~~ will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the ~~surrogate decision makers have signed the informed consent~~.

New Text: Patients identified to be delirious in the APCU will be approached. Informed consent from the **legally authorized representative** will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the **legally authorized representative has** signed the informed consent.

Scientific Rationale: A legally authorized representative will be used to consent patients, per IRB contingency.

»»» Revised Text # 7

Document: Protocol

Section: C.7 Study Interventions

Paragraph: 4

Page: 5

Old Text (if applicable): Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the ~~surrogate decision maker~~ signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg IV will be given along with either lorazepam or placebo.

New Text: Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the **legally authorized representative** signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg IV will be given along with either lorazepam or placebo.

Scientific Rationale: A legally authorized representative will be used to consent patients, per IRB contingency.

»»» Revised Text # 8

Document: Informed Consent

Section: **LEGALLY AUTHORIZED REPRESENTATIVE (LAR)**

Paragraph:

Page:

Old Text (if applicable): n/a

New Text: n/a

Scientific Rationale: There is a section in the ICD for the legally authorized representative to sign to provide informed consent.

Edit History:

Vera J. DeLaCruz 8/20/2013 -- Sent
Vera J. DeLaCruz 08/20/2013 -- Edited
Vera J. DeLaCruz 8/20/2013 -- Sent
Vera J. DeLaCruz 08/20/2013 -- Edited
Vera J. DeLaCruz 08/20/2013 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

10/4/2013 2:17:41 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 03

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 03

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
Added details for administration of study medication

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Abstract

Section: **Eligibility**

Paragraph: Exclusion

Page:

Old Text (if applicable):

- 1) [Patients] Life expectancy <3 days (based on clinical signs of impending death)
- 2) [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
- 3) [Patients] History of neuroleptic malignant syndrome
- 4) [Patients] History of Parkinson's disease or dementia
- 5) [Patients] History of seizure disorder
- 6) ~~[Patients] History of prolonged QTc interval (>500 ms)~~
- 7) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 8) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 9) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 10) [Patients] Heart failure exacerbation at the time of enrollment

New Text:

- 1) [Patients] Life expectancy <3 days (based on clinical signs of impending death)
- 2) [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
- 3) [Patients] History of neuroleptic malignant syndrome
- 4) [Patients] History of Parkinson's disease or dementia
- 5) [Patients] History of seizure disorder
- 6) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 7) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 8) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 9) [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: Deleted because it is a duplication of criterion #8

»»» Revised Text # 2

Document: Abstract

Section: Study Interventions

Paragraph: 1 and 2

Page:

Old Text (if applicable):

The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg ~~IV bolus~~ over 1.5 minutes x1 dose . This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events. Indeed, a majority of studies examining the effects of single

dose lorazepam used between 2 mg and 5 mg.

For patients randomized to receive placebo, preservative free 0.9% normal saline will be prepared in a syringe identical in appearance and volume to lorazepam they would otherwise get if they were in the lorazepam arm.

New Text:

The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg in **25 cc of 0.9% normal saline infused intravenously** over 1.5 minutes x1 dose. This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events.(Greenblatt *et al.* 1989) Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg.

For patients randomized to receive placebo, **25 cc** of preservative free 0.9% normal saline will be **administered**.

Scientific Rationale: Added details for administration of study medication after discussion with pharmacy and nursing

»»» Revised Text # 3

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Table 4

Page:

Old Text (if applicable):

| | | | |
|---|---|--|---|
| Richmond Agitation Sedation Scale (RN, CG)5 | ✓ | Q30 min until 2 h, Q1h until 8 h, then at 24 h | ✓ |
|---|---|--|---|

| | | | |
|---|---|---|---|
| Memorial Delirium Rating Scale (Pt/RS)7 | ✓ | ✓ | ✓ |
|---|---|---|---|

New Text:

| | | | |
|---|---|-----------------------------|---|
| Richmond Agitation Sedation Scale (RN, CG)5 | ✓ | 0 min, Q30 min x2 h, | ✓ |
|---|---|-----------------------------|---|

| | | | |
|------|--|-----------------------------|--|
| CG)5 | | Q1h until 8 h, then at 24 h | |
|------|--|-----------------------------|--|

| | | | |
|---|---|---------------------------------|---|
| Memorial Delirium Assessment Scale (Pt/RS)7 | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
|---|---|---------------------------------|---|

Scientific Rationale: Minor adjustments to assessment schedule for RASS and MDAS

»»» Revised Text # 4

Document: Protocol

Section: C. Experimental Approach (Table 2. Study Eligibility Criteria)

Paragraph: Exclusion Criteria

Page: 4

Old Text (if applicable):

- 1) [Patients] Life expectancy <3 days (based on clinical signs of impending death)
- 2) [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
- 3) [Patients] History of neuroleptic malignant syndrome
- 4) [Patients] History of Parkinson's disease or dementia
- 5) [Patients] History of seizure disorder
- 6) ~~[Patients] History of prolonged QTc interval (>500 ms)~~
- 7) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 8) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 9) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 10) [Patients] Heart failure exacerbation at the time of enrollment

New Text:

- 1) [Patients] Life expectancy <3 days (based on clinical signs of impending death)
- 2) [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy
- 3) [Patients] History of neuroleptic malignant syndrome
- 4) [Patients] History of Parkinson's disease or dementia
- 5) [Patients] History of seizure disorder
- 6)** [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 7)** [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 8)** [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 9)** [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: Deleted because it is a duplication of criterion #8. Renumbered due to deletion of criterion.

»»» Revised Text # 5

Document: Protocol

Section: **C.7. Study Interventions**

Paragraph: 1

Page: 5

Old Text (if applicable): The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg ~~IV bolus~~ over 1.5 minutes x1 dose . This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events. (Greenblatt *et al.* 1989) Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg. (Greenblatt *et al.* 1977, Kraus *et al.* 1978, Wermeling *et al.* 2001).

~~For patients randomized to receive placebo, preservative free 0.9% normal saline will be prepared in a syringe identical in appearance and volume to lorazepam they would otherwise get if they were in the lorazepam arm.~~

New Text: The commercial supply of lorazepam and normal saline will be purchased. Lorazepam was chosen for this study because it has a rapid onset of action (5-20 minutes), a moderate duration of action (hours), a short half life (12.9 hours), a low risk of accumulation, and no major active metabolites. Its bioavailability is predictable when given intravenously. Lorazepam was FDA approved (ANDA 074243) in 1994 for (1) anxiety, (2) insomnia, due to anxiety or situational stress, (3) premedication for anesthetic procedure, or (4) status epilepticus. It is also used commonly in acute care and hospice setting for management of delirium, as recommended in various guidelines. It will be given as 3 mg **in 25 cc of 0.9% normal saline infused intravenously** over 1.5 minutes x1 dose. This dose has been used in previously studies and found to provide a physiologic effect lasting at least 8 hours without significant adverse events.(Greenblatt *et al.* 1989) Indeed, a majority of studies examining the effects of single dose lorazepam used between 2 mg and 5 mg (Greenblatt *et al.* 1977, Kraus *et al.* 1978, Wermeling *et al.* 2001).

For patients randomized to receive placebo, **25 cc of** preservative free 0.9% normal saline will be **administered.**

Scientific Rationale: Added details for administration of study medication after discussion with pharmacy and nursing

»»» Revised Text # 6

Document: Protocol

Section: C.10. Study assessments

Paragraph: Table 4

Old Text (if applicable):

| | | | |
|---|---|--|---|
| Richmond Agitation Sedation Scale (RN, CG)5 | ✓ | Q30 min until-2 h, Q1h until 8 h, then at 24 h | ✓ |
|---|---|--|---|

| | | | |
|---|---|---|---|
| Memorial Delirium Rating Scale (Pt/RS)7 | ✓ | ✓ | ✓ |
|---|---|---|---|

New Text:

| | | | |
|---|---|---|---|
| Richmond Agitation Sedation Scale (RN, CG)5 | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
|---|---|---|---|

| | | | |
|---|---|---------------------------------|---|
| Memorial Delirium Assessment Scale (Pt/RS)7 | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
|---|---|---------------------------------|---|

Scientific Rationale: Minor adjustments to assessment schedule for RASS and MDAS

»»» Revised Text # 7

Document: Appendix I

Section: n/a

Paragraph: n/a

Page: n/a

Old Text (if applicable):

| | | |
|------------------------|--|---|
| | Please indicate how often did you notice the following symptom in the patient? 0=not present 1=a little of the time 2=some of the time 3=good part of the time 4=most of the time | Please indicate how much distress YOU experienced as a result of each symptom? 0=no distress 1=a little 2=a fair amount 3=very much 4=extremely distressed |
| Disorientation to time | | |

| | | |
|-------------------------|--|--|
| Disorientation to place | | |
| Visual hallucinations | | |
| Tactile hallucinations | | |
| Auditory hallucinations | | |
| Delusional thoughts | | |
| Psychomotor agitation | | |

New Text:

| | Please indicate how often did you notice the following symptom in the patient? 0=not present 1=a little of the time 2=some of the time 3=good part of the time 4=most of the time | Please indicate how much distress YOU experienced as a result of each symptom? 0=no distress 1=a little 2=a fair amount 3=very much 4=extremely distressed |
|---|--|---|
| Disorientation to time | | |
| Disorientation to place | | |
| Visual hallucinations ("seeing") | | |
| Tactile hallucinations ("touching") | | |
| Auditory hallucinations ("hearing") | | |
| Delusional thoughts ("false beliefs") | | |
| Psychomotor agitation ("moving") | | |

Scientific Rationale: Added wording for clarification

»»» Revised Text # 8

Document: Protocol (attachment)

Section: Header

Paragraph: n/a

Page: all

Old Text (if applicable): 2013-0345
~~08/20/2013~~

New Text: 2013-0345
10/04/2013

Scientific Rationale: Updated header date to match date of revision

Edit History:

Vera J. DeLaCruz 10/4/2013 -- Sent
Vera J. DeLaCruz 10/04/2013 -- Edited
Vera J. DeLaCruz 10/4/2013 -- Sent
Vera J. DeLaCruz 10/04/2013 -- Edited
Vera J. DeLaCruz 10/04/2013 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

12/16/2013 12:13:10 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 04

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 04

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|---|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input checked="" type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol and Abstract

Section: **C. Experimental Approach** / Proposed Treatment/Study Plan

Paragraph: **C.4. Randomization / Randomization**

Page: 4

Old Text (if applicable):

Patient randomization will be conducted through the ~~Clinical Trial Conduct website-
<https://biostatistics.mdanderson.org/ClinicalTrialConduct>), which is maintained by the
Department of Biostatistics at MD Anderson Cancer Center. The trial statistician will train the
users (pharmacists or research nurses) in the use of this website for randomizing patients.
Patients will be stratified by RASS score (2 vs. 3-4).~~

New Text:

Patient randomization will be conducted through the **Clinical Oncology Research System (COrE)** at MD Anderson Cancer Center.

Scientific Rationale: Stratification by RASS will no longer be performed to simplify the operational logistics of our process. Equal randomization trials without stratification are best performed by COrE.

Edit History:

Vera J. DeLaCruz 12/16/2013 -- Sent

Vera J. DeLaCruz 12/16/2013 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

1/8/2014 8:41:22 AM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 05

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 05

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
revised patient randomization method from CORE to CTC website, minor changes in appendices to match info in protocol

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: **C.4. Randomization.**

Paragraph: 1

Page: 4

Old Text (if applicable):

Patient randomization will be conducted through the ~~Clinical Oncology Research System (CORE)~~ at MD Anderson Cancer Center.

New Text:

Patient randomization will be conducted through the **Clinical Trial Conduct website (<https://biostatistics.mdanderson.org/ClinicalTrialConduct>), which is maintained by the Department of Biostatistics** at MD Anderson Cancer Center. **The trial statistician will train the users (pharmacists or research nurses) in the use of this website for randomizing patients.**

Scientific Rationale: After further discussion with Pharmacy, we would like to change the randomization method from CORE to CTC (Clinical Trial Conduct).

»»» Revised Text # 2

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph:

Page:

Old Text (if applicable):

Randomization.

Patient randomization will be conducted through the ~~Clinical Oncology Research System (CORE)~~ at MD Anderson Cancer Center.

New Text:

Randomization.

Patient randomization will be conducted through the **Clinical Trial Conduct website (<https://biostatistics.mdanderson.org/ClinicalTrialConduct>), which is maintained by the Department of Biostatistics** at MD Anderson Cancer Center. **The trial statistician will train the users (pharmacists or research nurses) in the use of this website for randomizing patients.**

Scientific Rationale: After further discussion with Pharmacy, we would like to change the randomization method from CORE to CTC (Clinical Trial Conduct).

»»» Revised Text # 3

Document: Appendix A

Section: **Exclusion Criteria**

Paragraph:

Page:

Old Text (if applicable):

| Exclusion Criteria | | | |
|---------------------------|---|---|--|
| 1. | [Patients] Glasgow Coma Scale 8 or less | | |
| 2. | [Patients] Life expectancy <3 days | - | |
| 3. | [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy | - | |
| 4. | [Patients] History of neuroleptic malignant syndrome | - | |
| 5. | [Patients] History of Parkinson's disease or dementia | - | |
| 6. | [Patients] History of seizure disorder | - | |
| 7. | [Patients] History of prolonged QTc interval (>500 ms) | - | |
| 8. | [Patients] History of hypersensitivity to haloperidol or benzodiazepine | - | |
| 9. | [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours | - | |

New Text:

| | | | |
|----|---|---|--|
| 1. | [Patients] Life expectancy <3 days (based on clinical signs of impending death) | - | |
| 2. | [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or hepatic encephalopathy | - | |
| 3. | [Patients] History of neuroleptic malignant syndrome | - | |
| 4. | [Patients] History of Parkinson's disease or dementia | - | |
| 5. | [Patients] History of seizure disorder | - | |
| 6. | [Patients] Previously documented and persistent QTc prolongation (>500 ms) | - | |
| 7. | [Patients] History of hypersensitivity to haloperidol or benzodiazepine | - | |
| 8. | [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours | | |
| 9. | [Patients] Heart failure exacerbation at the time of enrollment | - | |

Scientific Rationale: Revised table to match Eligibility criteria listed in the Protocol document.

»»» Revised Text # 4

Document: Appendix D

Section: **3. Richmond Agitation Sedation Scale (-5 to +4) After Study Medication:**

Paragraph:

Page:

Old Text (if applicable):

| | |
|--|----------------|
| Date: _____ | |
| Time | RN RASS |
| 0 h (just prior to medication administration) | |
| 30 min | |
| 60 min | |
| 90 min | |
| 120 min | |
| 3 h | |
| 4 h | |
| 5 h | |
| 6 h | |
| 7 h | |
| 8 h | |

New Text:

| | | |
|--|-----------|------------------|
| Date: _____ | | |
| Time | RN | RASS MDAS |
| 0 h (just prior to medication administration) | | |
| 30 min | | |
| 60 min | | |
| 90 min | | |
| 120 min | | |
| 3 h | | |
| 4 h | | |
| 5 h | | |
| 6 h | | |
| 7 h | | |
| 8 h | | |

To bedside RN: If you have completed Table 3 (i.e. documented RASS/MDAS for 8 hours after drug administration), please put this form in the delirium study folder on the ICS desk. Otherwise, please keep it in the bedside chart for the next bedside RN. Thanks!!!

Scientific Rationale: We wish to collect MDAS score at 0, 2, 4 and 8 hours after administration of study medication

»»» Revised Text # 5

Document: Appendix D

Section: **4. Daily Data Collection**

Paragraph:

Page:

Old Text (if applicable):

Delirium rating scale (0-46)

New Text:

ESAS completed by pt/CG/both

Scientific Rationale: We no longer need to collect delirium rating, however we would like to know who completed the ESAS

Edit History:

Vera J. DeLaCruz 1/8/2014 -- Sent

Vera J. DeLaCruz 01/08/2014 -- Edited

Vera J. DeLaCruz 01/07/2014 -- Edited

Vera J. DeLaCruz 01/07/2014 -- Created

To: **IRB** 2/14/2014 2:31:38 PM
From: Craig W. Carson
CC: Julio A. Allo, Susan Frisbee-Hume, Vera J. DeLaCruz
Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit
MDACC Protocol ID #: 2013-0345
Version: 06
Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 06

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
Consent Template Update

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Informed Consent

Section: All Boilerplate Sections

Paragraph: All Boilerplate Paragraphs

Page: All

Old Text (if applicable): All Boilerplate Paragraphs



New Text: [Clinical_ICD_Version 12_Tracked Changes.doc](#)

Scientific Rationale: Updating the consent to the new template

Edit History:

Yadira L. Cortez 2/14/2014 -- Sent

Craig W. Carson 02/04/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

3/11/2014 3:13:16 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 07

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 07

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: Table 2. Study Eligibility Criteria

Paragraph: Inclusion Criteria

Page: 4

Old Text (if applicable):

1. [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent or incurable disease)
2. [Patients] Admitted to Acute Palliative Care Unit
3. [Patients] Delirium as per DSM-IV-TR criteria
4. [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
5. ~~[Patients] Memorial delirium rating scale ≥ 13~~
6. [Patients] On scheduled haloperidol of < 8 mg in the last 24 hours
7. [Patients] Age 18 or older
8. [Patients] Legally authorized representative consent
9. [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
10. [Family Caregivers] Age 18 or older
11. [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium episode
12. [Family Caregivers] Able to communicate in English

New Text:

1. [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic, recurrent or incurable disease)
2. [Patients] Admitted to Acute Palliative Care Unit
3. [Patients] Delirium as per DSM-IV-TR criteria
4. [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
5. [Patients] On scheduled haloperidol of ≤ 8 mg in the last 24 hours
6. [Patients] Age 18 or older
7. [Patients] Legally authorized representative consent
8. [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
9. [Family Caregivers] Age 18 or older
10. [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium episode
11. [Family Caregivers] Able to communicate in English

Scientific Rationale: DSM-IV criteria will already be used to determine eligibility. MDAS is redundant. Minor adjustment of regular Haldol dose requirement to be more inclusive (#5); Added comma after "metastatic".

»»» Revised Text # 2

Document: Protocol

Section: **C.7. Study Interventions.**

Paragraph:

Page: 5

Old Text (if applicable):

For patients randomized to receive placebo, 25 cc of preservative free 0.9% normal saline will be administered.

New Text:

For patients randomized to receive placebo, 25 cc of preservative free 0.9% normal saline will be administered. **To ensure maximal blinding, the study medication (lorazepam/placebo) will be administered by one nurse (e.g. charge nurse) while the nursing study assessments (i.e. MDAS/RASS immediate before and up to 8 h after study medication) will be conducted by a separate nurse (e.g. the bedside nurse). APCU nurses will be instructed not to discuss the identity of the study medication.**

Scientific Rationale: Included procedures on optimizing the blinding process

»»» Revised Text # 3

Document: Protocol

Section: Table 4. Summary of Study Assessments

Paragraph:

Page: 6

Old Text (if applicable):

| | | | |
|--|--|--|-------------------|
| Demographics and cancer diagnosis (RS/MD)1 | | | |
| Karnofsky performance status (RS)2 | | | |
| Neuroleptics/benzodiazepines use (RS)3 | | | |
| Edmonton Symptom Assessment Scale (Pt/CG)4 | | | |
| Richmond Agitation Sedation Scale (RN, CG)5 | | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | |
| Delirium Rating Scale-Revised-98 (Pt/RS)6 | | | |
| Memorial Delirium Assessment Scale (Pt/RS)7 | | 0 h, 2 h, 4 h, 8 h, 24 h | |
| Delirium Experience Questionnaire (RN and CG)8 | | | |
| Adverse effects (RS)9 | | | Day 3 only |
| Communication capacity (RN and CG)10 | | | |
| Clinical Impression (MD)11 | | | |
| Delirium Recall Questionnaire (Pt)12 | | | Once when MDAS<13 |
| Discharge outcome (RS)13 | | | Once at discharge |
| Overall survival (RS)14 | | | End of study |

New Text:

| | | | |
|-----------------------------------|--|--|--|
| Demographics and cancer diagnosis | | | |
|-----------------------------------|--|--|--|

| | | | |
|--|--|--|-------------------|
| (RS/MD)1 | | | |
| Karnofsky performance status (RS)2 | | | |
| Neuroleptics/benzodiazepines use (RS)3 | | | |
| Edmonton Symptom Assessment Scale (Pt/CG)4 | | | |
| Richmond Agitation Sedation Scale (RN, CG)5 | | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | |
| Delirium Rating Scale-Revised-98 (Pt/RS)6 | | | |
| Memorial Delirium Assessment Scale (Pt/RS)7 | | 0 h, 2 h, 4 h, 8 h, 24 h | |
| Respiratory rate | | 0 h, Q1h until 8 h | |
| Delirium Experience Questionnaire (RN and CG)8 | | | |
| Adverse effects (RS)9 | | | Day 3 only |
| Communication capacity (RN and CG)10 | | | |
| Clinical Impression (MD)11 | | | |
| Delirium Recall Questionnaire (Pt)12 | | | Once when MDAS<13 |
| Discharge outcome (RS)13 | | | Once at discharge |
| Overall survival (RS)14 | | | End of study |

Scientific Rationale: Added respiratory rate as an assessment to monitor for apnea-related study medication use

»»» Revised Text # 4

Document: Protocol

Section: **C.5. Blinding.**

Paragraph:

Page: 4

Old Text (if applicable):

Patients, caregivers, nurses and the research staff conducting the assessment will be blinded to the treatment assignment. Lorazepam will be dispensed by Dispensing Pharmacy at MD Anderson using a syringe. Placebo (normal saline) will be in a ~~pre-loaded syringe~~ identical in appearance to lorazepam.

New Text: Patients, caregivers, nurses and the research staff conducting the assessment will be blinded to the treatment assignment. Lorazepam will be dispensed by Dispensing Pharmacy at MD Anderson using an **IV piggyback bag**. Placebo (normal saline) will be in an **IV piggyback bag** identical in appearance to lorazepam.

Scientific Rationale: Correction of prior oversight and consistency with the rest of the protocol.

»»» Revised Text # 5

Document: Appendix A

Section: **Inclusion Criteria**

Paragraph:

Page:

Old Text (if applicable):

| Inclusion Criteria | |
|---------------------------|--|
| 1. | [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent or incurable disease) |
| 2. | [Patients] Admitted to Acute Palliative Care Unit |
| 3. | [Patients] Delirium as per DSM-IV-TR criteria |
| 4. | [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours |
| 5. | [Patients] Memorial delirium rating scale ≥ 13 |
| 6. | [Patients] On scheduled haloperidol for delirium of < 8 mg in the last 24 hours |
| 7. | [Patients] Age 18 or older |
| 8. | [Family Caregivers] Surrogate consent |
| 9. | [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner) |
| 10. | [Family Caregivers] Age 18 or older |
| 11. | [Family Caregivers] At the patient's bedside at least 4 hours each day during delirium episode |
| 12. | [Family Caregivers] Able to communicate in English |

New Text:

| Inclusion Criteria | |
|---------------------------|--|
| 1. | [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic, recurrent or incurable disease) |
| 2. | [Patients] Admitted to Acute Palliative Care Unit |
| 3. | [Patients] Delirium as per DSM-IV-TR criteria |
| 4. | [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours |
| 5. | [Patients] On scheduled haloperidol for delirium of ≤ 8 mg in the last 24 hours |
| 6. | [Patients] Age 18 or older |
| 7. | [Family Caregivers] Surrogate consent |
| 8. | [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner) |
| 9. | [Family Caregivers] Age 18 or older |
| 10. | [Family Caregivers] At the patient's bedside at least 4 hours each day during delirium episode |
| 11. | [Family Caregivers] Able to communicate in English |



2013-0345 Appendix A_Screening Form 02-21-2014.docx

Scientific Rationale: DSM-IV criteria will already be used to determine eligibility. MDAS is redundant. Minor adjustment of regular Haldol dose requirement to be more inclusive (#5). Revised to

match protocol and abstract; Added comma after "metastatic".

»»» Revised Text # 6

Document: Abstract

Section: Eligibility Inclusion

Paragraph:

Page: 3

Old Text (if applicable):

- 1) [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent, or incurable disease)
- 2) [Patients] Admitted to Acute Palliative Care Unit (APCU)
- 3) [Patients] Delirium as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria
- 4) [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
- 5) ~~[Patients] Memorial delirium rating scale ≥ 13~~
- 6) [Patients] On scheduled haloperidol of < 8 mg in the last 24 hours
- 7) [Patients] Age 18 or older
- 8) [Patients] Legally Authorized Representative consent
- 9) [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
- 10) [Family Caregivers] Age 18 or older
- 11) [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium episode
- 12) [Family Caregivers] Able to communicate in English

New Text:

- 1) [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic, recurrent, or incurable disease)
- 2) [Patients] Admitted to Acute Palliative Care Unit (APCU)
- 3) [Patients] Delirium as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria
- 4) [Patients] Hyperactive/mixed delirium with RASS ≥ 2 in the last 24 hours
- 5) [Patients] On scheduled haloperidol of ≤ 8 mg in the last 24 hours
- 6)** [Patients] Age 18 or older
- 7)** [Patients] Legally Authorized Representative consent
- 8)** [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
- 9)** [Family Caregivers] Age 18 or older
- 10)** [Family Caregivers] At the patient's bedside at least 4 hours each day during patient delirium episode
- 11)** [Family Caregivers] Able to communicate in English

Scientific Rationale: DSM-IV criteria will already be used to determine eligibility. MDAS is redundant. Minor adjustment of regular Haldol dose requirement to be more inclusive (#5). Added comma after "metastatic".

»»» Revised Text # 7

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: 4

Page:

Old Text (if applicable):

Blinding: Patients, caregivers, nurses and the research staff conducting the assessment will be blinded to the treatment assignment. Lorazepam will be dispensed by Dispensing Pharmacy at MD Anderson using a ~~syringe~~. Placebo (normal saline) will be in a ~~pre-loaded syringe~~ identical in appearance to lorazepam.

New Text:

Blinding: Patients, caregivers, nurses and the research staff conducting the assessment will be blinded to the treatment assignment. Lorazepam will be dispensed by Dispensing Pharmacy at MD Anderson using an **IV piggyback bag**. Placebo (normal saline) will be in an **IV piggyback bag** identical in appearance to lorazepam.

Scientific Rationale: Correction of prior oversight and consistency with the rest of the protocol.

»»» Revised Text # 8

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Table 4 Summary of Study Assessments

Page:

Old Text (if applicable):

Table 4. Summary of Study Assessments

| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
|--|----------|---|-----------------------------|
| Demographics and cancer diagnosis (RS/MD) ¹ | | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ¹ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (CEI, CG) ¹ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ¹ | ✓ | 0 min, 030 min x 2 h, 01h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (CEI, RS) ¹ | | 0 h, 2 h, 4 h, 8 h, 24 h | |
| Memorial Delirium Assessment Scale (CEI, RS) ¹ | | | |
| Delirium Experience Questionnaire (RN and CG) ¹ | | | |
| Adverse effects (RS) ⁹ | | | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | | | ✓ |
| Clinical Impression (MD) ¹¹ | | | |
| Delirium Recall Questionnaire (CEI) ¹² | | | Once when MDAS < 13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |

Abbreviation: CG, caregiver; MD, physician; O, patient; RS, research staff

¹ patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, comorbidities, days in palliative care unit, and potential cause(s) of delirium. The PCU attending physician will provide information on DSM-IV diagnosis and causes of delirium.

² an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag *et al.* 1984).

a medications used to treat delirium, including scheduled and as needed haloperidol, chlorpromazine, other neuroleptics and benzodiazepines will be recorded. We will also document the need for palliative sedation.

³ a 10-item symptom battery validated to assess the symptom burden over the last 24 hours (Bruera *et al.* 1991). Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being using a numeric rating scale from 0 (best) to 10 (worst). It may be completed by patients and/or caregivers.

a validated 10-point numeric rating scale that ranges from -5 (calm and alert patient) to +4 (very agitated), where 0 denotes a calm and alert patient (Ely *et al.* 2003, Sessler *et al.* 2002). This will be assessed by the bedside nurse. As an exploratory outcome, caregivers will also be asked to provide an assessment.

⁴ a 16-item scale validated for assessment of delirium over the last 24 hours (Trzepacz *et al.* 2001). Each item is assigned a score between 0 (normal) and 2 or 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (all 16 items, max 46 points). If an item could not be rated, a mid-way score is assigned. We will use three words to assess short-term memory, months of the year back words to help rate attention, and copying intersecting pentagons and drawing a line to help assess visual-spatial ability, and parts of a pen and/or watch to assess naming. A total score of 18 or more suggests delirium. This will be administered to the patient by our research staff.

⁵ a 10-item clinician-rated assessment scale validated for assessment of delirium in cancer patients (Breitbart *et al.* 1997, Fadul *et al.* 2007). It examines level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0-10 for a total score between 0-30 with a higher score indicating delirium. A score of 13 or higher suggests delirium. This will be administered to the patient by our research staff. Our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress for themselves similar to a previous study (Bruera *et al.* 2009). These include disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. All respondents will be asked to recall the frequency of these symptoms scoring from 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. In addition, they will be asked to score the emotional distress for themselves associated with each delirium symptom on a scale from 0-4 (0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed).

adverse effects related to the use of benzodiazepine and neuroleptic will be documented using NCI CTCAE v4.0 and UKU assessment for selected side effects: sedation, seizures and extrapyramidal side effects.

⁶ family caregivers and nurses will be asked to provide their perception of the patient's ability to hear, speak and understand.

⁷ scored by attending physician as a single overall impression of delirium severity on a numeric rating scale ranging from 1 (no delirium) to 7 (very severe delirium) points.

⁸ delirium recall and related distress will be assessed only in patients who have recovered from a delirium episode using the delirium experience questionnaire (Bruera *et al.* 2009): 1. Do you remember being confused? (Yes or No); 2. If no, are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numerical rating scale with 0=not at all, and 4=extremely); 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers will be audiotaped and transcribed verbatim).

⁹ dead or alive at the end of palliative care unit stay

¹⁰ overall survival will be calculated from time of study entry to death or last day known alive

New Text:

Table 4 Summary of Study Assessments
Assessments (Person completing)

| | Baseline | Day 1 | Day 2 daily until discharge |
|--|----------|---|-----------------------------|
| Demographics and cancer diagnosis (RS/MO) | | | |
| Karnofsky performance status (RS) [*] | / | | |
| Neuroleptic Side Effect Scale (RS) | / | / | / |
| Edmonton Symptom Assessment Scale (Pt/CG) ¹ | / | / | / |
| Richmond Agitation Sedation Scale (RN,CG) ² | / | 0 min, 30 min x 2 h, 2 h until 8 h, then at 24 h | / |
| Delirium Rating Scale-Revised-98 (Pt/RS) ³ | / | | |
| Memorial Delirium Assessment Scale (PvRS) ⁴ | / | 0 h, 2 h, 4 h, 8 h, 24 h | / |
| Respiratory rate | | 0 h, 0.5 h until 8 h | |
| Delirium Experience Questionnaire (RN and CG) ⁵ | / | / | / |
| Adverse effects (RS) ⁶ | / | / | Day 3 only |
| Communication capacity RN and CG) ⁶ | / | / | / |
| Clinical Impression (MO) ⁷ | / | / | / |
| Delirium Recall Questionnaire (Pt) ⁸ | | | Once Mem MDAS < 13 |
| Discharge outcome (RS) ⁹ | | | Once at discharge |
| Overall survival (RS) | | | End of study |

Abbreviation: CG, caregiver; MO, physician; Pt, patient; RS, research staff

¹ patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, comorbidities, days in palliative care unit, and potential cause(s) of delirium. The PCU attending physician will provide information on QSP, IV diagnosis and causes of delirium.

² a 11-point assessment scale that rates patients' functional status been 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag et al. 1984).

³ medications used to treat delirium, including scheduled and as needed haloperidol, chlorpromazine, other neuroleptics and benzodiazepines will be recorded. We will also document the need for sedative medication.

⁴ a 10-item symptom battery validated to assess the symptom burden over the last 24 hours (Brueca et al. 1991). Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, Shortness of breath, appetite, sleep, and feeling of well-being using a numeric rating scale from 0 (best) to 10 (worst). It may be completed by patients and/or caregiver.

⁵ a validated 10-point numeric rating scale that ranges from -5 (unarousable) to +4 (very agitated). 0 denotes a calm and alert patient (Ely et al. 2003, Sessler et al. 2002). This will be assessed by the bedside nurse. As an exploratory outcome, caregivers will also be asked to provide an assessment.

⁶ a 16-item scale validated for assessment of delirium over the last 24 hours (Trzepacz et al. 2001). Each item is assigned a score between 0 (normal) and 2 or 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (a 16 items, max 46 points). If an item could not be rated, a midway score was assigned. We will use three words to assess short-term memory, months of the year backwards to help rate attention, and copying interlocking pentagons and drawing a cube face to help assess visuoconstructive ability, and part of a pen and/or watch to assess naming. A total score of 18 or more suggests delirium. This will be administered to the patient by our research staff.

⁷ a 10-item clinical assessment scale validated for assessment of delirium in cancer patients (Breitbart et al. 1997, Fadul et al. 2007). It examines level of consciousness and orientation, memory, recall, attention, organized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30. With a higher score indicating worse delirium. A score of 13 or higher suggests delirium. This will be administered to the patient by our research staff.

⁸ our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress for themselves similar to a previous study (Suera et al. 2009). These include disorientation to time, disorientation to place, visual hallucinations, tactile hallucinations, auditory hallucinations, delusional thoughts and psychomotor agitation. All respondents will be asked to recall the frequency of these symptoms scoring from 0=not present, 1=a little of the time, 2=some of the time, 3=good part of the time, and 4=most or all of the time. In addition, they will be asked to score the emotional distress for themselves, assessed with each delirium symptom on a scale from 0-4 (0=no distress, 1=a little, 2=a fair amount, 3=very much and 4=extremely distressed).

⁹ adverse effects related to the use of benzodiazepine and neuroleptic will be documented using NCI CTCAE v4.0 and UKU assessment for sedative side effects (sedation, seizures and extrapyramidal side effects).

¹⁰ family caregivers and nurses will be asked to provide their perception of the patient's ability to hear, speak and understand.

¹¹ scored by attending physician as a single overall impression of delirium severity on a numeric rating scale ranging from 1 (no delirium) to 7 (very severe delirium) points.

¹² delirium recall and related distress will be assessed only in patients who have recovered from a delirium episode using the delirium experience questionnaire (Suera et al. 2009): 1. Do you remember being confused? (Yes or No); 2. If no, are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numeric rating scale) with 0=not at all and 4=extremely; 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers may be audiotaped and transcribed verbatim).

¹³ dead or alive at the end of palliative care unit stay

¹⁴ overall survival will be calculated from time of study entry to death or last day known alive

2. If 0 = are you distressed that you cannot remember? (Yes or No); 3. How distressed? (0-4 numeric rating scale) with 0 = not at all and 4 = extremely; 4. If you do remember being confused, was the experience distressing? (Yes or No); 5. How distressing? (0-4); and 6. Can you describe the experience? (Answers may be audiotaped and used verbatim).
Overall survival may be calculated from time of study entry to death or last day known alive.

Select a Committee to receive this memo from the list:

To: **IRB**

04/28/2014

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 08

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 08

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input checked="" type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
addition of secondary objective, added collection of saliva samples

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Collaborators Page

Section: n/a

Paragraph: n/a

Page: 1

Old Text (if applicable):

n/a

New Text:

UT Health Science Center at Houston

Duck-Hee Kang

Scientific Rationale: Dr. Kang will assist with the bioassays of the saliva samples at the UT School of Nursing Bioscience Laboratory. The hard copy signature will be sent via interoffice mail to OPR.



Kang_Collaborators Page SIGNED 04-2014.pdf

»»» Revised Text # 2

Document: Protocol

Section: Title Page

Paragraph: n/a

Page: 1

Old Text (if applicable):

Supportive Care Co-investigators: Dr. Eduardo Bruera, Dr. Donna Zhukovsky, Dr. Akhila Reddy, Dr. Sriram Yennu, Dr. Paul Walker, Dr. Seong Hoon Shin, Ms. Stacy Hall

New Text:

Supportive Care Co-investigators: Dr. Eduardo Bruera, Dr. Donna Zhukovsky, Dr. Akhila Reddy, Dr. Sriram Yennu, Dr. Paul Walker, Dr. Seong Hoon Shin, Ms. Stacy Hall, **Duck-Hee Kang**

Scientific Rationale: Dr. Kang will assist with the bioassays of the saliva samples at the UT School of Nursing Bioscience Laboratory.

»»» Revised Text # 3

Document: Protocol

Section: **A. Study Objectives**

Paragraph: 4

Page: 2

Old Text (if applicable):

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.

New Text:

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.
4. **To explore the feasibility of collecting saliva samples and detecting changes in biomarker levels (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) in association with delirium severity.**

Scientific Rationale: added that the biomarkers will also be analyzed in addition to the collected variables

»»» Revised Text # 4

Document: Protocol

Section: **B. Background and Significance**

Paragraph: B.4.

Page: 3-4

Old Text (if applicable):

n/a

New Text:

B.4. Understanding the pathogenesis of delirium is essential for better management of delirium; however, the pathophysiology of delirium remains largely unknown. Potential factors contributing to delirium include cholinergic deficiency, dysregulated stress response with hypercortisolemia, and increased inflammation (Cerejeira, Lagarto, & Mukaetova-Ladinska. 2014; Cerejeira, Nogueira, Luis, Vaz-Serra, & Mukaetova-Ladinska. 2012; Field, Gossen, & Cunningham. 2012; Hshieh, Fong, Marcantonio, & Inouye. 2008; Simone & Tan. 2011).

When exposed to stressful stimuli (e.g., injury, infection), the activation of the neuroendocrine systems closely interact with the immune system in coordinated regulations. Normal regulation includes the counterregulatory mechanisms, which include the release of anti-inflammatory

cytokines (e.g., interleukin-10), stress hormones, and acetylcholine from the vagus nerve. Acetylcholine interacts with immune cells by binding to their nicotine acetylcholine receptors (Tracey, 2009). Cholinergic anti-inflammatory pathway modulates immune responses and inflammation, whereas cytokines may also lead to cholinergic deficits (Hshieh et al., 2008). In delirium, these homeostatic mechanisms are thought to be disrupted leading to increased proinflammatory cytokines in the peripheral circulation (Cerejeira, Firmino, Vaz-Serra, & Mukaetova-Ladinska, 2010), which in turn activates brain parenchymal cells to produce inflammatory cytokines and other mediators in the brain (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Hopkins, 2007). Exaggerated neuroinflammatory reactions and neuronal and synaptic dysfunction lead to delirium (Cerejeira et al., 2010).

Delirium studies on inflammatory responses have so far produced mixed results when C-reactive protein (CRP) and pro- and anti-inflammatory cytokines (interleukin [IL]-1, -6 and -10) were examined. Speculation for inconsistent findings is that these biomarkers should have been assessed for the pro- to anti-inflammatory balance or interactions with markers of other neuroendocrine systems, not just as single cytokines (Cerejeira et al., 2011). Concurrent assessments suggest neural-immune interactions between cholinergic activity and cytokine responses in delirium (Cerejeira et al., 2012). Other postoperative delirium studies further suggest that “changes” in these biomarker levels, not just single level, are more informative to understand the risk for developing delirium (Cerejeira, Batista, Nogueira, Vaz-Serra, & Mukaetova-Ladinska, 2013; Plaschke et al., 2010). Taken together, we plan to explore the feasibility of assessing CRP, IL-1beta, IL-6, IL-10, cortisol, and cholinesterase activity from non-invasive biosamples of saliva over time.

Scientific Rationale: Added rationale for new objective of collecting saliva samples

»»» Revised Text # 5

Document: Protocol

Section: **C.10. Study assessments**

Paragraph: Table 4

Page: 6-7

Old Text (if applicable):

| Table 4. Summary of Study Assessments | | | |
|---|----------|--|-----------------------------|
| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
| Demographics and cancer diagnosis (RS/MD) ¹ | ✓ | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ³ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (Pt/CG) ⁴ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ⁵ | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (Pt/RS) ⁶ | ✓ | | |
| Memorial Delirium Assessment Scale (Pt/RS) ⁷ | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
| Respiratory rate | | 0 h, Q1h until 8 h | |
| Adverse effects (RS) ⁹ | ✓ | ✓ | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | ✓ | ✓ | ✓ |
| Clinical Impression (MD) ¹¹ | ✓ | ✓ | ✓ |
| Delirium Recall Questionnaire (Pt) ¹² | | | Once when MDAS<13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |

New Text:

| Table 4. Summary of Study Assessments | | | |
|---|----------|--|-----------------------------|
| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
| Demographics and cancer diagnosis (RS/MD) ¹ | ✓ | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ³ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (Pt/CG) ⁴ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ⁵ | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (Pt/RS) ⁶ | ✓ | | |
| Memorial Delirium Assessment Scale (Pt/RS) ⁷ | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
| Respiratory rate | | 0 h, Q1h until 8 h | |
| Adverse effects (RS) ⁹ | ✓ | ✓ | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | ✓ | ✓ | ✓ |
| Clinical Impression (MD) ¹¹ | ✓ | ✓ | ✓ |
| Delirium Recall Questionnaire (Pt) ¹² | | | Once when MDAS<13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |
| SalivaDio's Swab (non-invasive)¹⁵ | ✓ | ✓ | ✓ |

Scientific Rationale: added saliva swab to the list of assessments

»»» Revised Text # 6

Document: Protocol

Section: **C.10. Study assessments**

Paragraph: Table 4

Page: 7

Old Text (if applicable):

n/a

New Text:

¹⁵ Using the SalivaBio's Swab (SCS) Method, saliva (1-2 ml) will be collected once daily when other assessments are made from baseline until discharge or death. This swab method is designed for safe and effective saliva collection. An extra long (125mm) swab enables sample collector to hold one end firmly while placing the other end in subject's mouth to eliminate any choking hazard. A thin diameter (8mm) facilitates easy insertion into the mouth, and the swab is made of durable polymer which withstands chewing. If sample volume is limited, biomarker assessment will be done in the following order of priority: CRP, IL-6, IL-10, cholinesterase, cortisol, IL-1 beta. Collected samples will be kept in a freezer of the MDACC PCU in a biosafety bag and transported daily in a small portable cooler to the UT School of Nursing Bioscience Laboratory (SON 510-520) just across the street by a research assistant. Samples will be stored in -80oC freezer until batch assayed. The Bioscience Laboratory is fully equipped with all necessary equipment and a trained laboratory person will run the assays. Salivary biomarkers will be assessed using specific immunoassay kits from Salimetrics, LLC (State College, PA). All biomarker kits have shown high sensitivity and high precision, and these types of assays are routinely performed in this laboratory. The cost of bioassays will be covered by Dr. Kang.

Scientific Rationale: Added procedure for saliva collection, storage and transfer to Dr. Kang at the UT School of Nursing Bioscience Laboratory.

»»» Revised Text # 7

Document: Protocol

Section: **D. Statistical Analysis**

Paragraph: **D.2. Data Analysis**

Page: 8

Old Text (if applicable):

Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

New Text:

Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (**including biomarkers**) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

Scientific Rationale: added that the biomarkers will also be analyzed in addition to the collected variables

»»» Revised Text # 8

Document: Abstract

Section: Objectives

Paragraph: 3rd bullet

Page: 1

Old Text (if applicable):

Secondary objectives:

- To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress as observed by the nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
- To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.

New Text:

Secondary objectives:

- To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress as observed by the nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
- To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.
- **To explore the feasibility of collecting saliva samples and detecting changes in biomarker levels (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) in association with delirium severity.**

Scientific Rationale: added that the biomarkers will also be analyzed in addition to the collected variables

»»» Revised Text # 9

Document: Abstract

Section: Rationale

Paragraph: 7-9

Page: 3-4

Old Text (if applicable):

n/a

New Text:

Understanding the pathogenesis of delirium is essential for better management of delirium; however, the pathophysiology of delirium remains largely unknown. Potential factors contributing to delirium include cholinergic deficiency, dysregulated stress response with hypercortisolemia, and increased inflammation.

When exposed to stressful stimuli (e.g., injury, infection), the activation of the neuroendocrine systems closely interact with the immune system in coordinated regulations. Normal regulation includes the counterregulatory mechanisms, which include the release of anti-inflammatory cytokines (e.g., interleukin-10), stress hormones, and acetylcholine from the vagus nerve. Acetylcholine interacts with immune cells by binding to their nicotine acetylcholine receptors. Cholinergic anti-inflammatory pathway modulates immune responses and inflammation, whereas cytokines may also lead to cholinergic deficits. In delirium, these homeostatic mechanisms are thought to be disrupted leading to increased proinflammatory cytokines in the peripheral circulation, which in turn activates brain parenchymal cells to produce inflammatory cytokines and other mediators in the brain. Exaggerated neuroinflammatory reactions and neuronal and synaptic dysfunction lead to delirium.

Delirium studies on inflammatory responses have so far produced mixed results when C-reactive protein (CRP) and pro- and anti-inflammatory cytokines (interleukin [IL]-1, -6 and -10) were examined. Speculation for inconsistent findings is that these biomarkers should have been assessed for the pro- to anti-inflammatory balance or interactions with markers of other neuroendocrine systems, not just as single cytokines. Concurrent assessments suggest neural-immune interactions between cholinergic activity and cytokine responses in delirium. Other postoperative delirium studies further suggest that “changes” in these biomarker levels, not just single level, are more informative to understand the risk for developing delirium. Taken together, we plan to explore the feasibility of assessing CRP, IL-1beta, IL-6, IL-10, cortisol, and cholinesterase activity from non-invasive biosamples of saliva over time.

Scientific Rationale: Added rationale for new objective of collecting saliva samples

»»» Revised Text # 10

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Table 4

Page: 8

Old Text (if applicable):

| Table 4. Summary of Study Assessments | | | |
|---|----------|--|-----------------------------|
| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
| Demographics and cancer diagnosis (RS/MD) ¹ | ✓ | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ³ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (Pt/CG) ⁴ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ⁵ | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (Pt/RS) ⁶ | ✓ | | |
| Memorial Delirium Assessment Scale (Pt/RS) ⁷ | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
| Respiratory rate | | 0 h, Q1h until 8 h | |
| Adverse effects (RS) ⁹ | ✓ | ✓ | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | ✓ | ✓ | ✓ |
| Clinical Impression (MD) ¹¹ | ✓ | ✓ | ✓ |
| Delirium Recall Questionnaire (Pt) ¹² | | | Once when MDAS<13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |

New Text:

| Table 4. Summary of Study Assessments | | | |
|---|----------|--|-----------------------------|
| Assessments (Person completing) | Baseline | Day 1 | Day 2 daily until discharge |
| Demographics and cancer diagnosis (RS/MD) ¹ | ✓ | | |
| Karnofsky performance status (RS) ² | ✓ | | |
| Neuroleptics/benzodiazepines use (RS) ³ | ✓ | ✓ | ✓ |
| Edmonton Symptom Assessment Scale (Pt/CG) ⁴ | ✓ | ✓ | ✓ |
| Richmond Agitation Sedation Scale (RN, CG) ⁵ | ✓ | 0 min, Q30 min x2 h, Q1h until 8 h, then at 24 h | ✓ |
| Delirium Rating Scale-Revised-98 (Pt/RS) ⁶ | ✓ | | |
| Memorial Delirium Assessment Scale (Pt/RS) ⁷ | ✓ | 0 h, 2 h, 4 h, 8 h, 24 h | ✓ |
| Respiratory rate | | 0 h, Q1h until 8 h | |
| Adverse effects (RS) ⁹ | ✓ | ✓ | Day 3 only |
| Communication capacity (RN and CG) ¹⁰ | ✓ | ✓ | ✓ |
| Clinical Impression (MD) ¹¹ | ✓ | ✓ | ✓ |
| Delirium Recall Questionnaire (Pt) ¹² | | | Once when MDAS<13 |
| Discharge outcome (RS) ¹³ | | | Once at discharge |
| Overall survival (RS) ¹⁴ | | | End of study |
| SalivaDio's Swab (non-invasive)¹⁵ | ✓ | ✓ | ✓ |

Scientific Rationale: added saliva swab to the list of assessments

»»» Revised Text # 11

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Table 4

Page: 9

Old Text (if applicable):

n/a

New Text:

¹⁵ Using the SalivaBio's Swab (SCS) Method, saliva (1-2 ml) will be collected once daily when other assessments are made from baseline until discharge or death. This swab method is designed for safe and effective saliva collection. An extra long (125mm) swab enables sample collector to hold one end firmly while placing the other end in subject's mouth to eliminate any choking hazard. A thin diameter (8mm) facilitates easy insertion into the mouth, and the swab is made of durable polymer which withstands chewing. If sample volume is limited, biomarker assessment will be done in the following order of priority: CRP, IL-6, IL-10, cholinesterase, cortisol, IL-1 beta. Collected samples will be kept in a freezer of the MDACC PCU in a biosafety bag and transported daily in a small portable cooler to the UT School of Nursing Bioscience Laboratory (SON 510-520) just across the street by a research assistant. Samples will be stored in -80oC freezer until batch assayed. The Bioscience Laboratory is fully equipped with all necessary equipment and a trained laboratory person will run the assays. Salivary biomarkers will be assessed using specific immunoassay kits from Salimetrics, LLC (State College, PA). All biomarker kits have shown high sensitivity and high precision, and these types of assays are routinely performed in this laboratory. The cost of bioassays will be covered by Dr. Kang.

Scientific Rationale: Added procedure for saliva collection, storage and transfer to Dr. Kang at the UT School of Nursing Bioscience Laboratory.

»»» Revised Text # 12

Document: Abstract

Section: Statistical Considerations

Paragraph: 2

Page: 10

Old Text (if applicable):

Data Analysis: Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

New Text:

Data Analysis: Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (**including biomarkers**) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

Scientific Rationale: added that the biomarkers will also be analyzed in addition to the collected variables

»»» Revised Text # 13

Document: Informed Consent

Section: 3. Description of Study

Paragraph: 6

Page: 4

Old Text (if applicable):

n/a

New Text:

Saliva Samples

While you are in the hospital, saliva samples (about 1/2 a teaspoon) will be collected every day to check for changes in your body's chemical levels. To collect the saliva, a swab will be brushed inside your mouth until enough saliva is gathered on the swab. This should take about 30 seconds to complete.

Scientific Rationale: added saliva sample collection to inform patients that a swab sample will be taken each day until they are discharged.

»»» Revised Text # 14

Document: Informed Consent

Section: **Authorization for Use and Disclosure of Protected Health Information**

Paragraph: 1

Page: 7

Old Text (if applicable):

A. During the course of this study, the research team at MD Anderson will be collecting and using your protected health information. This information may include personal identifying information about you (such as your name, race, date of birth, gender, city, and zip code), your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section D below.

New Text:

A. During the course of this study, the research team at MD Anderson will be collecting and using your protected health information. This information may include personal identifying information about you (such as your name, race, date of birth, gender, city, and zip code), your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and sharing this information is to learn about how the

study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section D below.

Your saliva samples will be sent to the UT School of Nursing Bioscience Laboratory.

Scientific Rationale: added to inform patients that their saliva samples will be sent to the UT School of Nursing Bioscience Laboratory (Dr. Duck-Hee Kang will facilitate and cover the cost of bioassays).

»»» Revised Text # 15

Document: Protocol

Section: References

Paragraph: all

Page: 9-11

Old Text (if applicable):

1. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized aids patients. *The American Journal of Psychiatry* 1996;153:231-7.
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5. Breitbart W, Alici Y. Agitation and delirium at the end of life: "We couldn't manage him". *JAMA* 2008;300:2898-910, E1.
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9. Candy B, Jackson KC, Jones L, et al. Drug therapy for delirium in terminally ill adult patients. *Cochrane Database Syst Rev* 2012;11:CD004770.
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13. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010;38:419-27.
14. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in icu patients: Reliability and validity of the richmond agitation-sedation scale (rass). *JAMA* 2003;289:2983-91.
15. Fadul N, Kaur G, Zhang T, et al. Evaluation of the memorial delirium assessment scale (mdas) for the screening of delirium by means of simulated cases by palliative care health professionals. *Support*

Care Cancer 2007;15:1271-6.

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19. Grover S, Mattoo SK, Gupta N. Usefulness of atypical antipsychotics and choline esterase inhibitors in delirium: A review. *Pharmacopsychiatry* 2011;44:43-54.
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23. Kraus JW, Desmond PV, Marshall JP, ~~et al.~~ Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978;24:411-9.
24. Pandharipande PP, Pun BT, Herr DL, ~~et al.~~ Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The mends randomized controlled trial. *JAMA* 2007;298:2644-53.
25. Reade MC, O'Sullivan K, Bates S, ~~et al.~~ Dexmedetomidine vs. Haloperidol in delirious, agitated, intubated patients: A randomised open-label trial. *Crit Care* 2009;13:R75.
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New Text:

1. Breitbart W, Marotta R, Platt MM, **Weisman H, Derevenco M, Grau C, Corbera K, Raymond S, Lund S, Jacobson P.** A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized aids patients. *The American Journal of Psychiatry* 1996;153:231-7.
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Scientific Rationale: Updated to include new references as a result of the new additions to the protocol (objectives, rationale, etc) and also completed the references to include all names on the publications.

Edit History:

Vera J. DeLaCruz 4/28/2014 -- Sent
 Vera J. DeLaCruz 04/28/2014 -- Edited
 Vera J. DeLaCruz 4/23/2014 -- Sent
 Vera J. DeLaCruz 04/23/2014 -- Edited
 Vera J. DeLaCruz 04/22/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

5/30/2014 12:27:20 PM

From: Vera J. DeLaCruz

CC: David Hui

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 09

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 09

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input checked="" type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:

Revised Appendix D

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Collaborators Page

Section: Palliative Care and Rehabilitation Medicine

Paragraph: n/a

Page: 1

Old Text (if applicable):

Palliative Care and Rehabilitation Medicine

Akhila S. Reddy* Signed: 05/01/2013 04:01:17 PM*

Donna Zhukovsky* Signed: 05/03/2013 04:24:44 PM*

Eduardo Bruera* Signed: 05/29/2013 11:31:57 AM*

Paul W. Walker* Signed: 05/07/2013 11:55:19 AM*

~~SeongHoon Shin* Signed: 05/02/2013 07:27:11 AM*~~

Sriram Yennu* Signed: 05/01/2013 04:03:43 PM*

New Text:

Palliative Care and Rehabilitation Medicine

Akhila S. Reddy* Signed: 05/01/2013 04:01:17 PM*

Donna Zhukovsky* Signed: 05/03/2013 04:24:44 PM*

Eduardo Bruera* Signed: 05/29/2013 11:31:57 AM*

Paul W. Walker* Signed: 05/07/2013 11:55:19 AM*

Sriram Yennu* Signed: 05/01/2013 04:03:43 PM*

Scientific Rationale: Dr. Shin is no longer with MDACC. Updated per CR contingency memo.

»»» Revised Text # 2

Document: Protocol

Section: Title Page

Paragraph: n/a

Page: 1

Old Text (if applicable):

Supportive Care Co-investigators: Dr. Eduardo Bruera, Dr. Donna Zhukovsky, Dr. Akhila Reddy, Dr. Sriram Yennu, Dr. Paul Walker, ~~Dr. Seong Hoon Shin~~, Ms. Stacy Hall, Dr. Duck-Hee Kang

New Text:

Supportive Care Co-investigators: Dr. Eduardo Bruera, Dr. Donna Zhukovsky, Dr. Akhila Reddy, Dr. Sriram Yennu, Dr. Paul Walker, Ms. Stacy Hall, Dr. Duck-Hee Kang

Scientific Rationale: Dr. Shin is no longer with MDACC. Updated per CR contingency memo.

»»» Revised Text # 3

Document: Appendix D

Section: Table 3

Paragraph: n/a

Page: 1

Old Text (if applicable):

3. Richmond Agitation Sedation Scale (-5 to +4) After Study Medication:

| Date: _____ | | | |
|---|----|------|------|
| Time | RN | RASS | MDAS |
| 0 h (just prior to medication administration) | | | |
| 30 min | | | |
| 60 min | | | |
| 90 min | | | |
| 120 min | | | |
| 3 h | | | |
| 4 h | | | |
| 5 h | | | |
| 6 h | | | |
| 7 h | | | |
| 8 h | | | |

To bedside RN: If you have completed Table 3 (i.e. documented RASS/MDAS for 8 hours after drug administration), please put this form in the delirium study folder on the ICS desk. Otherwise, please keep it in the bedside chart for the next bedside RN. Thanks!!!

New Text:

3. Richmond Agitation Sedation Scale (-5 to +4) After Study Medication:

| Date: _____ | | | | |
|---|----|------|------|------------|
| Time | RN | RASS | MDAS | Resp. Rate |
| 0 h (just prior to medication administration) | | | | |
| 30 min | | | | |
| 60 min | | | | |
| 90 min | | | | |
| 120 min | | | | |
| 3 h | | | | |
| 4 h | | | | |
| 5 h | | | | |
| 6 h | | | | |
| 7 h | | | | |
| 8 h | | | | |

To bedside RN: If you have completed Table 3 (i.e. documented RASS/MDAS for 8 hours after drug administration), please put this form in the delirium study folder on the ICS desk. Otherwise, please keep it in the bedside chart for the next bedside RN. Thanks!!!

Scientific Rationale: Administrative correction to allow source documentation of respiratory rates as stated in the protocol treatment plan.

Edit History:

Vera J. DeLaCruz 5/30/2014 -- Sent
 Vera J. DeLaCruz 05/30/2014 -- Edited
 Vera J. DeLaCruz 05/30/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

6/5/2014 8:23:57 AM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 10

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 10

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: Eligibility (Exclusion)

Paragraph: #2 and #3

Page: 5

Old Text (if applicable):

1. **[Patients]** Life expectancy <3 days (based on clinical signs of impending death)
2. **[Patients]** History of myasthenia gravis, acute narrow angle glaucoma, ~~or~~ hepatic encephalopathy
3. **[Patients]** History of neuroleptic malignant syndrome
4. **[Patients]** History of Parkinson's disease or dementia
5. **[Patients]** History of seizure disorder
6. **[Patients]** History of hypersensitivity to haloperidol or benzodiazepine
7. **[Patients]** On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
8. **[Patients]** Previously documented and persistent QTc prolongation (>500 ms)
9. **[Patients]** Heart failure exacerbation at the time of enrollment

New Text:

1. **[Patients]** Life expectancy <3 days (based on clinical signs of impending death)
2. **[Patients]** History of myasthenia gravis **or** acute narrow angle glaucoma
3. **[Patients]** **Hepatic encephalopathy at the time of screening**
4. **[Patients]** History of neuroleptic malignant syndrome
5. **[Patients]** History of Parkinson's disease or dementia
6. **[Patients]** History of seizure disorder
7. **[Patients]** History of hypersensitivity to haloperidol or benzodiazepine
8. **[Patients]** On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
9. **[Patients]** Previously documented and persistent QTc prolongation (>500 ms)
10. **[Patients]** Heart failure exacerbation at the time of enrollment

Scientific Rationale: We would like to the clarify nature of the exclusion criteria

»»» Revised Text # 2

Document: Abstract

Section: Eligibility

Paragraph: Exclusion

Page: #2 and #3

Old Text (if applicable):

- 1) **[Patients]** Life expectancy <3 days (based on clinical signs of impending death)
- 2) **[Patients]** History of myasthenia gravis, acute narrow angle glaucoma, ~~or~~ hepatic encephalopathy
- 3) **[Patients]** History of neuroleptic malignant syndrome
- 4) **[Patients]** History of Parkinson's disease or dementia
- 5) **[Patients]** History of seizure disorder
- 6) **[Patients]** History of hypersensitivity to haloperidol or benzodiazepine
- 7) **[Patients]** On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 8) **[Patients]** Previously documented and persistent QTc prolongation (>500 ms)
- 9) **[Patients]** Heart failure exacerbation at the time of enrollment

New Text:

- 1) [Patients] Life expectancy <3 days (based on clinical signs of impending death)
- 2) [Patients] History of myasthenia gravis **or** acute narrow angle glaucoma
- 3) **[Patients] Hepatic encephalopathy at the time of screening**
- 4) [Patients] History of neuroleptic malignant syndrome
- 5) [Patients] History of Parkinson's disease or dementia
- 6) [Patients] History of seizure disorder
- 7) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 8) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 9) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 10) [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: We would like to the clarify nature of the exclusion criteria

»»» Revised Text # 3

Document: Appendix A

Section: Exclusion

Paragraph: #2 and #3

Page: 1

Old Text (if applicable):

- | | |
|----|--|
| 1. | [Patients] Life expectancy <3 days |
| 2. | [Patients] History of myasthenia gravis, acute narrow angle glaucoma, or h epatic encephalopathy |
| 3. | [Patients] History of neuroleptic malignant syndrome |
| 4. | [Patients] History of Parkinson's disease or dementia |
| 5. | [Patients] History of seizure disorder |
| 6. | [Patients] History of prolonged QTc interval (>500 ms) |
| 7. | [Patients] History of hypersensitivity to haloperidol or benzodiazepine |
| 8. | [Patients] On regular doses of benzodiazepine or chlorpromazine the past 48 hours |
| 9. | [Patients] Heart failure exacerbation at the time of enrollment |

New Text:

- | | |
|-----|---|
| 1. | [Patients] Life expectancy <3 days |
| 2. | [Patients] History of myasthenia gravis or acute narrow angle glaucoma |
| 3. | [Patients] Hepatic encephalopathy at the time of screening |
| 4. | [Patients] History of neuroleptic malignant syndrome |
| 5. | [Patients] History of Parkinson's disease or dementia |
| 6. | [Patients] History of seizure disorder |
| 7. | [Patients] History of prolonged QTc interval (>500 ms) |
| 8. | [Patients] History of hypersensitivity to haloperidol or benzodiazepine |
| 9. | [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours |
| 10. | [Patients] Heart failure exacerbation at the time of enrollment |

Scientific Rationale: We would like to the clarify nature of the exclusion criteria

Edit History:

Vera J. DeLaCruz 6/5/2014 -- Sent

Vera J. DeLaCruz 06/05/2014 -- Edited

Vera J. DeLaCruz 06/05/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

6/27/2014 1:06:10 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 11

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 11

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:

Clarified in the screening section that a physician will conduct the 2nd step of the consent process

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Abstract/Protocol

Section: Proposed Treatment/Study Plan / C.3. Study screening

Paragraph: 1

Page: 4

Old Text (if applicable):

Screening: Patients identified to be delirious in the APCU will be approached. Informed consent from the legally authorized representative will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

New Text:

Screening: Patients identified to be delirious in the APCU will be approached. Informed consent from the legally authorized representative will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. **If a patient is deemed eligible, the physician will conduct the 2nd step of the consent process to enroll them on the study.** The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

Scientific Rationale: Added clarification that a physician will conduct the 2nd step of the consent process.

Edit History:

Vera J. DeLaCruz 6/27/2014 -- Sent

Vera J. DeLaCruz 06/27/2014 -- Edited

Vera J. DeLaCruz 06/27/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

8/1/2014 3:04:16 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 12

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 12

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: **Table 2. Study Eligibility Criteria**

Paragraph: Exclusion #1

Page: 5

Old Text (if applicable):

- ~~1.~~ ~~[Patients] Life expectancy <3 days (based on clinical signs of impending death)~~
- ~~2.~~ [Patients] History of myasthenia gravis or acute narrow angle glaucoma
- ~~3.~~ [Patients] Hepatic encephalopathy at the time of screening
- ~~4.~~ [Patients] History of neuroleptic malignant syndrome
- ~~5.~~ [Patients] History of Parkinson's disease or dementia
- ~~6.~~ [Patients] History of seizure disorder
- ~~7.~~ [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- ~~8.~~ [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- ~~9.~~ [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- ~~10.~~ [Patients] Heart failure exacerbation at the time of enrollment

New Text:

1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
2. [Patients] Hepatic encephalopathy at the time of screening
3. [Patients] History of neuroleptic malignant syndrome
4. [Patients] History of Parkinson's disease or dementia
5. [Patients] History of seizure disorder
6. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
7. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
8. [Patients] Previously documented and persistent QTc prolongation (>500 ms)
9. [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: It is difficult to predict patients with life expectancy <3 days, and clinicians sometimes exclude patients who have a longer life expectancy. Furthermore, this clinical trial is appropriate for patients with a short life expectancy who have agitated delirium.

»»» Revised Text # 2

Document: Abstract

Section: Eligibility

Paragraph: Exclusion

Page: 4-5

Old Text (if applicable):

- ~~1)~~ ~~[Patients] Life expectancy <3 days (based on clinical signs of impending death)~~
- 2) [Patients] History of myasthenia gravis or acute narrow angle glaucoma
- 3) [Patients] Hepatic encephalopathy at the time of screening
- 4) [Patients] History of neuroleptic malignant syndrome
- 5) [Patients] History of Parkinson's disease or dementia

- 6) [Patients] History of seizure disorder
- 7) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 8) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 9) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 10) [Patients] Heart failure exacerbation at the time of enrollment

New Text:

- 1) [Patients] History of myasthenia gravis or acute narrow angle glaucoma
- 2) [Patients] Hepatic encephalopathy at the time of screening
- 3) [Patients] History of neuroleptic malignant syndrome
- 4) [Patients] History of Parkinson's disease or dementia
- 5) [Patients] History of seizure disorder
- 6) [Patients] History of hypersensitivity to haloperidol or benzodiazepine
- 7) [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
- 8) [Patients] Previously documented and persistent QTc prolongation (>500 ms)
- 9) [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: It is difficult to predict patients with life expectancy <3 days, and clinicians sometimes exclude patients who have a longer life expectancy. Furthermore, this clinical trial is appropriate for patients with a short life expectancy who have agitated delirium.

»»» Revised Text # 3

Document: Appendix A

Section: **Exclusion Criteria**

Paragraph: #1

Page: 1

Old Text (if applicable):

| Exclusion Criteria | |
|--------------------|--|
| 1- | [Patients] Life expectancy <3 days |
| 2- | [Patients] History of myasthenia gravis or acute narrow angle glaucoma |
| 3- | [Patients] Hepatic encephalopathy at the time of screening |

- | | |
|-----|--|
| 4. | [Patients] History of neuroleptic malignant syndrome |
| 5. | [Patients] History of Parkinson's disease or dementia |
| 6. | [Patients] History of seizure disorder |
| 7. | [Patients] History of prolonged QTc interval (>500 ms) |
| 8. | [Patients] History of hypersensitivity to haloperidol or benzodiazepine |
| 9. | [Patients] On regular doses of benzodiazepine or chlorpromazine the past 48 hours |
| 10. | [Patients] Heart failure exacerbation at the time of enrollment |

New Text:

1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
2. [Patients] Hepatic encephalopathy at the time of screening
3. [Patients] History of neuroleptic malignant syndrome
4. [Patients] History of Parkinson's disease or dementia
5. [Patients] History of seizure disorder
6. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
7. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
8. [Patients] Previously documented and persistent QTc prolongation (>500 ms)
9. [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: It is difficult to predict patients with life expectancy <3 days, and clinicians sometimes exclude patients who have a longer life expectancy. Furthermore, this clinical trial is appropriate for patients with a short life expectancy who have agitated delirium. Rearranged order of exclusion criteria on the appendix form to match the protocol and abstract.

Edit History:

Vera J. DeLaCruz 8/1/2014 -- Sent
Vera J. DeLaCruz 08/01/2014 -- Edited
Vera J. DeLaCruz 08/01/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

8/28/2014 12:23:41 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 13

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 13

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
clarified the timing when study medication should be administered

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: **C.7. Study Interventions**

Paragraph: 4

Page: 6

Old Text (if applicable):

Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signs the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

New Text:

Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 1 **and the patient has significant restlessness/agitation/anxiety requiring breakthrough haloperidol**. At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

Scientific Rationale: Some patients have been agitated but did not receive study medication because the threshold has been interpreted variably. We have now clarified the timing when study medication should be administered.

»»» Revised Text # 2

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: Study Interventions (paragraph 4)

Page: 7

Old Text (if applicable):

Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signs the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 2 . At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

New Text:

Because of the fluctuating nature of delirium, the study intervention will be timed based on the occurrence of agitation. After the legally authorized representative signed the consent document, the patient will be monitored every 2 hours with RASS until the RASS score is ≥ 1 **and the patient has significant restlessness/agitation/anxiety requiring breakthrough haloperidol**. At that time, the study will be activated and a dose of haloperidol 2 mg intravenously (IV) will be given along with either lorazepam or placebo.

Scientific Rationale: Some patients have been agitated but did not receive study medication because

the threshold has been interpreted variably. We have now clarified the timing when study medication should be administered.

»»» Revised Text # 3

Document: Appendix D

Section: #2

Paragraph: n/a

Page: 1

Old Text (if applicable):

~~2-~~ Date (MM/DD/YY) and time of study medication administration (HH:MM) ~~ef~~:

New Text:

2. At the FIRST occasion when the patient has significant restlessness/agitation/anxiety necessitating breakthrough haloperidol and RASS 1 or greater, please administer study medication (lorazepam or placebo) concurrently. Date (MM/DD/YY) and time of study medication administration (HH:MM): _____

Scientific Rationale: Some patients have been agitated but did not receive study medication because the threshold has been interpreted variably. We have now clarified the timing when study medication should be administered.

Edit History:

Vera J. DeLaCruz 8/28/2014 -- Sent

Vera J. DeLaCruz 08/28/2014 -- Edited

Vera J. DeLaCruz 08/28/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

10/15/2014 3:55:13 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 14

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 14

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|---|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input checked="" type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input checked="" type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Collaborators Page

Section: Biostatistics

Paragraph: n/a

Page: 1

Old Text (if applicable):

Gary B. Chisholm* Signed: 06/13/2013 03:07:20 PM*

New Text:

Diane Liu Signed: 10/03/2014 12:23:11 PM*

Scientific Rationale: Diane Liu is now the assigned biostatistician for our dept.

»»» Revised Text # 2

Document: Protocol

Section: Title Page

Paragraph: n/a

Page: 1

Old Text (if applicable):

Biostatistics Co-investigator: ~~Mr. Gary Chisholm~~

New Text:

Biostatistics Co-investigator: **Diane Liu**

Scientific Rationale: Diane Liu is now the assigned biostatistician for our dept.

»»» Revised Text # 3

Document: Protocol and Abstract

Section: Statistical Analysis / Statistical Considerations

Paragraph: 1 and 2

Page:

Old Text (if applicable):

D.1. Sample Size Calculation. For between arm comparison (primary objective), 17 patients per arm provides 80% power to detect an effect size as small as 1.0 in RASS between arms when $\alpha=0.5\%$ using two-sided t-tests. ~~Feasibility (secondary objective #2) will be assessed via the proportion of patients completing the study, defined as having the primary outcome (RASS score) available over the first 8 h after medication administration; an observed proportion less than 50% will be a clear indication that future studies based on this methodology are not feasible. The proportion and associated 95% confidence interval (CI) for patients completing the study will be estimated using all 34 patients; a 95% CI for our expected 65% completion rate will be (49%, 81%).~~

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests.

New Text:

D.1. Sample Size Calculation. For between arm comparison (primary objective), 17 patients per arm provides 80% power to detect an effect size as small as 1.0 in **changes of RASS** between arms when $\alpha=0.5\%$ using two-sided t-tests. **In this study, we will continue enrollment until 34 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.**

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests. **Because of the nature of our study population, many patients died or get discharged before requiring the study medication. Thus, we will use per protocol analysis to compare the two study arms among patients who received the medication.**

Scientific Rationale: We have enrolled 29 patients so far onto this study, but only 13 have received the study medication. This is because patients are extremely sick and many died before they were able to receive the study meds (which were only given when they develop an agitation episode). After discussion with our biostatistical team, we decided that we need to enroll 34 evaluable patients instead of just 34 patients, and conduct per protocol analysis.

»»» Revised Text # 4

Document: Abstract

Section: Estimated Accrual

Paragraph: n/a

Page: 10

Old Text (if applicable):

Estimated Accrual:

| | |
|-------------------------------------|--------------|
| Total Accrual at MDACC: | 34-patients |
| Estimated monthly accrual at MDACC: | 2-3 patients |

Accrual Comments:

All patients will be recruited from the acute palliative care unit, and from previous experience, we estimate that we will recruit 2-3 patients a month from this setting.

New Text:

Estimated Accrual:

Total Accrual at MDACC: 60 patients
Estimated monthly accrual at MDACC: 2-3 patients

Accrual Comments:

All patients will be recruited from the acute palliative care unit, and from previous experience, we estimate that we will recruit 2-3 patients a month from this setting. **We will need to enroll approximately 60 patients in order to obtain 34 evaluable patients.**

Scientific Rationale: We have enrolled 29 patients so far onto this study, but only 13 have received the study medication. This is because patients are extremely sick and many died before they were able to receive the study meds (which were only given when they develop an agitation episode). After discussion with our biostatistical team, we decided that we need to enroll 34 evaluable patients instead of just 34 patients, and conduct per protocol analysis. In order to obtain 34 evaluable patients, we will need to enroll approximately 60 patients.

»»» Revised Text # 5

Document: Protocol and Abstract

Section: **A. Study Objectives**

Paragraph: 2

Page: 2

Old Text (if applicable):

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. ~~To determine the feasibility of conducting a study of single dose lorazepam as an adjuvant to haloperidol on delirium in the acute palliative care unit.~~
4. ~~To explore the feasibility of collecting saliva samples and detecting changes in biomarker levels (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) in association with delirium severity.~~

New Text:

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. **To evaluate proportion of patients who consent and are randomized to study however drop out before being treated or before finishing 8-hour RASS assessment; and the reasons of drop-outs will be documented and reported.**
4. To explore the changes in biomarker levels **in saliva samples** (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) **over time and** in association with delirium severity.

Scientific Rationale: We no longer wish to include feasibility as part of our study objectives as

per our statistician, there is no need to estimate feasibility for 34 patients. For the secondary objectives, we are actually interested in knowing the proportion of patients who drop out before getting treatment or before finishing 8-hour RASS assessment, and the reasons. Therefore we removed feasibility from the protocol and abstract.

»»» Revised Text # 6

Document: Protocol / Abstract

Section: C.9. **Secondary** endpoints / Proposed Treatment/Study Plan

Paragraph:

Page: 6

Old Text (if applicable):

C.9. ~~Feasibility~~ endpoints. We will document the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall (if no longer delirious)

New Text:

C.9. **Secondary** endpoints. We will document the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall (if no longer delirious)

Scientific Rationale: We no longer wish to include feasibility as part of our study objectives as per our statistician, there is no need to estimate feasibility for 34 patients. For the secondary objectives, we are actually interested in knowing the proportion of patients who drop out before getting treatment or before finishing 8-hour RASS assessment, and the reasons. Therefore we removed feasibility from the protocol and abstract.

»»» Revised Text # 7

Document: Protocol and Abstract

Section: B4

Paragraph: 3

Page: 4

Old Text (if applicable):

Delirium studies on inflammatory responses have so far produced mixed results when C-reactive protein (CRP) and pro- and anti-inflammatory cytokines (interleukin [IL]-1, -6 and -10) were examined. Speculation for inconsistent findings is that these biomarkers should have been assessed for the pro- to anti-inflammatory balance or interactions with markers of other neuroendocrine systems, not just as

single cytokines (Cerejeira et al., 2011). Concurrent assessments suggest neural-immune interactions between cholinergic activity and cytokine responses in delirium (Cerejeira et al., 2012). Other postoperative delirium studies further suggest that “changes” in these biomarker levels, not just single level, are more informative to understand the risk for developing delirium (Cerejeira, Batista, Nogueira, Vaz-Serra, & Mukaetova-Ladinska, 2013; Plaschke et al., 2010). Taken together, we plan to explore ~~the feasibility of assessing~~ CRP, IL-1beta, IL-6, IL-10, cortisol, and cholinesterase activity from non-invasive biosamples of saliva over time.

New Text:

Delirium studies on inflammatory responses have so far produced mixed results when C-reactive protein (CRP) and pro- and anti-inflammatory cytokines (interleukin [IL]-1, -6 and -10) were examined. Speculation for inconsistent findings is that these biomarkers should have been assessed for the pro- to anti-inflammatory balance or interactions with markers of other neuroendocrine systems, not just as single cytokines (Cerejeira et al., 2011). Concurrent assessments suggest neural-immune interactions between cholinergic activity and cytokine responses in delirium (Cerejeira et al., 2012). Other postoperative delirium studies further suggest that “changes” in these biomarker levels, not just single level, are more informative to understand the risk for developing delirium (Cerejeira, Batista, Nogueira, Vaz-Serra, & Mukaetova-Ladinska, 2013; Plaschke et al., 2010). Taken together, we plan to explore CRP, IL-1beta, IL-6, IL-10, cortisol, and cholinesterase activity from non-invasive biosamples of saliva over time.

Scientific Rationale: We no longer wish to include feasibility as part of our study objectives as per our statistician, there is no need to estimate feasibility for 34 patients. For the secondary objectives, we are actually interested in knowing the proportion of patients who drop out before getting treatment or before finishing 8-hour RASS assessment, and the reasons. Therefore we removed feasibility from the protocol and abstract.

»»» Revised Text # 8

Document: Abstract

Section: Investigational New Drugs

Paragraph: Rationale for Exemption (Paragraph 5)

Page: 12

Old Text (if applicable):

In summary, we are seeking an IND waiver because we will be using an approved agent in approved dosages for delirium instead of other approved in this small feasibility-study.

New Text:

In summary, we are seeking an IND waiver because we will be using an approved agent in approved dosages for delirium instead of other approved in this small study.

Scientific Rationale: We no longer wish to include feasibility as part of our study objectives as per our statistician, there is no need to estimate feasibility for 34 patients. For the secondary objectives, we are actually interested in knowing the proportion of patients who drop out before getting treatment or before finishing 8-hour RASS assessment, and the reasons. Therefore we removed feasibility from the protocol and abstract.

»»» Revised Text # 10

Document: Informed Consent

Section: 3. Description of Study

Paragraph: 12

Page: 3

Old Text (if applicable):

Up to ~~34~~ patients will take part in this study. All will be enrolled at MD Anderson.

New Text:

Up to **60** patients will take part in this study. All will be enrolled at MD Anderson.

Scientific Rationale: We have enrolled 29 patients so far onto this study, but only 13 have received the study medication. This is because patients are extremely sick and many died before they were able to receive the study meds (which were only given when they develop an agitation episode). After discussion with our biostatistical team, we decided that we need to enroll 34 evaluable patients instead of just 34 patients, and conduct per protocol analysis. In order to obtain 34 evaluable patients, we will need to enroll approximately 60 patients.

Edit History:

Vera J. DeLaCruz 10/15/2014 -- Sent

Vera J. DeLaCruz 10/15/2014 -- Edited

Vera J. DeLaCruz 10/8/2014 -- Sent

Vera J. DeLaCruz 10/08/2014 -- Edited

Vera J. DeLaCruz 10/6/2014 -- Sent

Vera J. DeLaCruz 10/06/2014 -- Edited

Vera J. DeLaCruz 10/03/2014 -- Edited

Vera J. DeLaCruz 10/03/2014 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

1/26/2015 3:30:01 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 15

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 15

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
revised Abstract per OPR Grants contingency

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Abstract

Section: Sponsorship and Support Information

Paragraph: n/a

Page: 13

Old Text (if applicable):

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: ~~UTMDACC~~
Support Type: ~~Other: Department Funds~~

This Sponsor/Supporter/Granting Agency will receive data.

New Text:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: **NIH**
Support Type: **Grant Number(s): 1R21CA186000-01A1**

This Sponsor/Supporter/Granting Agency will receive data.

Scientific Rationale: Per OPR Grants contingency to update the Sponsorship information in the Abstract to reflect NIH and Grant #1R21CA186000-01A1.

Edit History:

Vera J. DeLaCruz 1/26/2015 -- Sent

Vera J. DeLaCruz 01/26/2015 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

7/27/2015 8:44:58 AM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 16

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 16

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: C. Experimental Approach

Paragraph: C.3. Study screening

Page: 4

Old Text (if applicable):

C.3. Study screening. Patients identified to be delirious on the APCU will be approached. Informed consent from the legally authorized representative will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. If a patient is deemed eligible, the physician will conduct the 2nd step of the consent process to enroll them on the study. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

New Text:

C.3. Study screening. Patients identified to be delirious on the APCU will be approached. Informed consent from the legally authorized representative (**LAR**) will be obtained by the study staff (**in person or by telephone if the LAR is not present in the APCU when the patient is delirious**) to proceed with screening of patients for eligibility and potential enrollment. If a patient is deemed eligible, the physician will conduct the 2nd step of the consent process (**in person or by telephone**) to enroll them on the study. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

Scientific Rationale: The surrogate decision maker is not always at the bedside when consent is needed for this time-sensitive study. If we obtain consent from the LAR over the telephone, then delays in administering the study medication for agitated delirium could be prevented. After the telephone consent, the LAR ICD signature would be obtained if they return to MDACC.

»»» Revised Text # 2

Document: Abstract

Section: Proposed Treatment/Study Plan

Paragraph: 2

Page: 6

Old Text (if applicable):

Screening: Patients identified to be delirious in the APCU will be approached. Informed consent from the legally authorized representative will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. If a patient is deemed eligible, the physician will conduct the 2nd step of the consent process to enroll them on the study. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

New Text:

Screening. Patients identified to be delirious on the APCU will be approached. Informed consent from the legally authorized representative (**LAR**) will be obtained by the study staff (**in person or by telephone if the LAR is not present in the APCU when the patient is delirious**) to proceed with screening of patients for eligibility and potential enrollment. If a patient is deemed eligible, the physician

will conduct the 2nd step of the consent process **(in person or by telephone)** to enroll them on the study. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the legally authorized representative has signed the informed consent.

Scientific Rationale: The surrogate decision maker is not always at the bedside when consent is needed for this time-sensitive study. If we obtain consent from the LAR over the telephone, then delays in administering the study medication for agitated delirium could be prevented. After the telephone consent, the LAR ICD signature would be obtained if they return to MDACC.

Edit History:

Vera J. DeLaCruz 7/27/2015 -- Sent

Vera J. DeLaCruz 07/27/2015 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

9/4/2015 11:07:09 AM

From: Vera J. DeLaCruz/MDACC

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 17

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 17

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|---|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input checked="" type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input checked="" type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
added objectives, Table 4 (study assessments) revised.

Note to reviewer/IRB Chair: This study is now funded by NCI through an R21 mechanism. We recently discussed the modifications below with the NIH Program officer who approved this round of changes.

All changes in this revision are meant to reconcile the differences between the grant and study protocol. If you have any questions, please do not hesitate to contact Dr. Hui directly. Thank you.

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would Yes No

include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source.

»»» Revised Text # 1

Document: Protocol and Abstract

Section: C10. Study Assessments / Proposed Treatment/Study Plan

Paragraph: Table 4. Summary of Study Assessments

Page: 7

Old Text (if applicable):

⁵ a validated 10 point numeric rating scale that ranges from –5 (unarousable) to +4 (very agitated), where 0 denotes a calm and alert patient. (~~Ely et al. 2003, Sessler et al. 2002~~). This will be assessed by the bedside nurse. ~~As an exploratory outcome, caregivers will also be asked to provide an assessment.~~

New Text:

5 a validated 10 point numeric rating scale that ranges from –5 (unarousable) to +4 (very agitated), where 0 denotes a calm and alert patient. This will be assessed by the bedside nurse. **To determine inter-rater agreement, we will also ask the research staff to provide their rating at the time of study enrollment.**

Scientific Rationale: Removed references from Table 4 in Abstract; One of the NIH R21 panel reviewers asked for more data to be collected on the inter-rater reliability of Richmond Agitation Sedation Scale (RASS) in the palliative care unit. We have thus added this objective.

»»» Revised Text # 2

Document: Protocol and Abstract

Section: A. Study Objectives / Objectives

Paragraph: #1, 2, 4

Page: 2

Old Text (if applicable):

Primary objective:

1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on the intensity of agitation (Richmond Agitation Sedation Scale) over 8 hours.

Secondary objectives:

2. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
3. To evaluate proportion of patients who consent and are randomized to study however drop out

before being treated or before finishing 8-hour RASS assessment; and the reasons of drop-outs will be documented and reported.

4. To explore the changes in biomarker levels in saliva samples (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) over time and in association with delirium severity.

New Text:

Primary objectives:

1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on the intensity of agitation (Richmond Agitation Sedation Scale) over 8 hours.
- 2. To assess the within-arm effect of single-dose lorazepam or placebo, as an adjuvant agent with haloperidol, on agitation intensity (Richmond Agitation Sedation Scale) over 8 hours in patients admitted to an acute palliative care unit.**

Secondary objectives:

1. To compare the effect of single dose lorazepam and placebo as an adjuvant to haloperidol on (1) delirium related distress in nurses and caregivers, (2) delirium duration, (3) need for rescue doses of neuroleptics, (4) delirium recall, (5) symptom expression (Edmonton Symptom Assessment Scale), (6) communicative capacity, (7) adverse effects, (8) discharge outcomes, and (9) survival in cancer patients.
2. To evaluate proportion of patients who consent and are randomized to study however drop out before being treated or before finishing 8-hour RASS assessment; and the reasons of drop-outs will be documented and reported.
3. To explore the changes in biomarker levels in saliva samples (salivary cortisol, cholinesterase, C-reactive protein, interleukin-1 beta, -6, and -10) over time and in association with delirium severity.
- 4. To examine the inter-rater reliability of RASS in the APCU setting between the bedside nurse and the research nurse at the time of study enrollment.**

Scientific Rationale: We submitted this study to NIH for an R21 application over a year ago. After a long re-submission process, this study has finally been approved for funding. Because the R21 has an identical study design but a more conservative study aim, we would like to reconcile the current study protocol and the R21 by adding this objective. We have consulted this with NIH Program officer as well as our biostatistician Dr. Hess. Both endorse these modifications. The resulting larger sample size will adequately address the re-defined objective (see sample size calculation).

»»» Revised Text # 3

Document: Abstract

Section: Estimated Accrual

Paragraph: 1

Page:

Old Text (if applicable):

Estimated Accrual:

| | |
|-------------------------------------|--------------|
| Total Accrual at MDACC: | 60-patients |
| Estimated monthly accrual at MDACC: | 2-3 patients |

Accrual Comments:

All patients will be recruited from the acute palliative care unit, and from previous experience, we estimate that we will recruit 2-3 patients a month from this setting. We will need to enroll approximately 60 patients in order to obtain 34-evaluable patients.

New Text:

Estimated Accrual:

Total Accrual at MDACC: **100** patients
Estimated monthly accrual at MDACC: 2-3 patients

Accrual Comments:

All patients will be recruited from the acute palliative care unit, and from previous experience, we estimate that we will recruit 2-3 patients a month from this setting. We will need to enroll approximately **100** patients in order to obtain **52** evaluable patients.

Scientific Rationale: The larger sample size (52 patients) would allow us have adequate power to address our primary objectives; corrected typo (misspelling)

»»» Revised Text # 4

Document: Appendices A-S

Section: Header and Bottom/end of Appendix Form

Paragraph: n/a

Page: all

Old Text (if applicable):

Patient Initials: _____

Date: _____

MRN: _____

Protocol: 2013-0345

New Text:



(Header)"



Patient Accession Number: _____




Protocol 2013-0345
Revised August 31, 2015
Page X of X



(End or bottom of appendix form):



Research Staff Signature: _____ **Date:** _____



 App. A_Screening Form_8-31-15.docx
  Demographics_Clinical Characteristics_App B_8-31-15.doc


 App. C_Neuroleptics and Benzodiazepines_8-31-15.doc
  2013-0345_App. D_Data Collection Form_8-31-15.docx


 2013-0345_App. E_RASS_8-31-15.doc
  2013-0345_App. F_Delirium Rating Scale_8-31-15.doc
  App. G_MDAS_8-31-15.doc



 2013-0345_App. H_ESAS_8-31-15.doc
  2013-0345_App. I_DEQ Caregiver_Daily_8-31-15.docx



 2013-0345_App. J_DEQ_Nurse_8-31-15.doc
  2013-0345_App. K_Delirium Recall Questionnaire_Patient_8-31-15.doc

 2013-0345_App. L_Adverse Events_NCI CTCAE_8-31-15.doc
  2013-0345_App. M_Adverse Events_UKU Assessment_8-31-15.doc

 2013-0345_App. N_Communication Capacity_Caregivers_8-31-15.doc

 2013-0345_App. O_Communication Capacity_Nurses_8-31-15.doc

 2013-0345_App. P_Clinical Global Impression_Physician_8-31-15.doc
  2013-0345_App. Q_Determination of Haldol EDD_8-31-15.doc

 2013-0345_App. R_Blinding_8-31-15.doc
  2013-0345_App. S_Attrition Record_0-31-15.doc

Scientific Rationale: Revised Headers to remove patient name/initials as these are not needed on the appendices; added accession number, revision date and page number; added signature/date lines for research staff

»»» Revised Text # 5

Document: Collaborator(s) Page

Section: Biostatistics

Paragraph: n/a

Page: 1

Old Text (if applicable):
Biostatistics

Diane Liu* Signed: 10/03/2014 12:23:11 PM*

New Text:
Biostatistics

Diane Liu* Signed: 10/03/2014 12:23:11 PM*

Kenneth Hess _____

Scientific Rationale: Dr. Hess is the senior biostatistician for this grant and protocol.

»»» Revised Text # 6

Document: Protocol and Abstract

Section: D. Statistical Analysis / Statistical Considerations

Paragraph: 1

Page: 8

Old Text (if applicable):

D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect a ~~mean difference of 0.32~~ (0.5 effect size, based on a standard deviation of 0.63) in RASS between arms when alpha=0.5% using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately. For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have ~~95%~~ power to detect an effect size of ~~0.19~~ if the correlation between repeated measures is ~~0.5~~ and ~~84%~~ power if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.

New Text:

D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect an **effect size of 0.79** (0.50 mean difference, based on a **within-group** standard deviation of 0.63) in RASS between arms when alpha=**5%** using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately **using paired t-test (or Wilcoxon signed rank test if data are not normally distributed). Secondary comparisons between arms will be performed using linear mixed models (also known as repeated measures ANOVA).** For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have **90%** power to detect an effect size of **0.186** if the correlation between repeated measures is **0.05** and an **effect size of 0.160** if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.

Scientific Rationale: Per DSMB designee's request on 9/2/15 to consult with our statistical collaborator and revise the statistical plan. We have consulted with Dr. Hess and Ms. Diane Liu and

revised the sample size calculations section.

»»» Revised Text # 7

Document: Protocol

Section: Title Page

Paragraph: n/a

Page: 1

Old Text (if applicable):

Biostatistics Co-investigator: Diane Liu

New Text:

Biostatistics Co-investigator: Dr. Kenneth Hess, Ms. Diane Liu

Scientific Rationale: Dr. Hess is the senior biostatistician for this grant and protocol.

Edit History:

Vera J. DeLaCruz 9/4/2015 -- Sent

Vera J. DeLaCruz 09/04/2015 -- Edited

Vera J. DeLaCruz 9/2/2015 -- Sent

Vera J. DeLaCruz 09/02/2015 -- Edited

Vera J. DeLaCruz 8/31/2015 -- Sent

Vera J. DeLaCruz 08/31/2015 -- Edited

Vera J. DeLaCruz 08/25/2015 -- Edited

Vera J. DeLaCruz 08/25/2015 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

10/06/2015

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 18

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 18

A Previously Submitted Version of this Protocol has Outstanding Contingencies: Version 17

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|---|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input checked="" type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol and Abstract

Section: D. Statistical Analysis / Statistical Considerations

Paragraph: 1 / 1

Page: 8

Old Text (if applicable):

D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect an effect size of 0.79 (0.50 mean difference, based on a within-group standard deviation of 0.63) in RASS between arms when $\alpha=5\%$ using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately using paired t-test (or Wilcoxon signed rank test if data are not normally distributed). Secondary comparisons between arms will be performed using linear mixed models (also known as repeated measures ANOVA). For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have 90% power to detect an effect size of ~~0.486~~ if the correlation between repeated measures is ~~0.05~~ and an effect size of ~~0.460~~ if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.

New Text:

D.1. Sample Size Calculation. For between arm comparison (primary objective), 26 patients per arm provides 80% power to detect an effect size of 0.79 (0.50 mean difference, based on a within-group standard deviation of 0.63) in RASS between arms when $\alpha=5\%$ using two-sided t-tests. We will assess the within-arm effects of lorazepam or placebo over time by examining the change in RASS in each study arm separately using paired t-test (or Wilcoxon signed rank test if data are not normally distributed). Secondary comparisons between arms will be performed using linear mixed models (also known as repeated measures ANOVA). For a one-way, repeated-measures ANOVA with 26 patients per arm (52 patients total) and 11 measurements over time (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours), we will have 90% power to detect an effect size of **0.34** if the correlation between repeated measures is **0.5** and an effect size of **0.28** if the correlation is 0.3 (computed using G*Power 3.1.6). In this study, we will continue enrollment until 52 evaluable patients have been enrolled. Evaluable patients are defined as those who have received the study medication (placebo or lorazepam) and completed the first 8 hours of observation. At the end of the study the percentage of patients who consent and are randomized to study but inevaluable, either not receiving medicine or not having 8-hour measure of RASS, will be provided with 95% confidence interval. The reasons will be documented, summarized and reported.

Scientific Rationale: Revised per IRB contingency to clarify statistical plan.

Edit History:

Vera J. DeLaCruz 10/6/2015 -- Sent

Vera J. DeLaCruz 10/06/2015 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

11/13/2015 1:04:17 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 19

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 19

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
revised DSMB

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Abstract

Section: Data Safety Monitoring Board / DSMB at MDACC

Paragraph: n/a

Page: 11

Old Text (if applicable):

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
~~Independent/Other DSMB~~

New Text:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
MDACC DSMB

Scientific Rationale: The DSMB was inadvertently changed in Version 14. MDACC DSMB will monitor this protocol.

Edit History:

Vera J. DeLaCruz 11/13/2015 -- Sent

Vera J. DeLaCruz 11/13/2015 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

01/28/2016

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 20

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 20

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:

Translated patient and caregiver appendices to Spanish

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol

Section: C. Experimental Approach

Paragraph: Table 2. Study Eligibility Criteria

Page: 5

Old Text (if applicable):

11. [Family Caregivers] Able to communicate in English

New Text:

11. **[Patients and Family Caregivers] Able to communicate in English or Spanish**

Scientific Rationale: We would like to include Spanish-speaking patients and family caregivers as we see Spanish-speaking patients in the Palliative Care Unit

»»» Revised Text # 2

Document: Abstract

Section: Eligibility

Paragraph: Inclusion #11

Page:

Old Text (if applicable):

44) [Family Caregivers] Able to communicate in English

New Text:

11. **[Patients and Family Caregivers] Able to communicate in English or Spanish**

Scientific Rationale: We would like to include Spanish-speaking patients and family caregivers as we see Spanish-speaking patients in the Palliative Care Unit

»»» Revised Text # 3

Document: Appendix A

Section: Inclusion Criteria #11

Paragraph: n/a

Page: 1

Old Text (if applicable):



App. A_Screening Form_8-31-15.docx

- 5. [Patients] On scheduled haloperidol for delirium of ≤ 8 mg in the last 24 hours
- 11) [Family Caregivers] Able to communicate in English

New Text:



App. A_Screening Form_1-28-16.docx

- 5. [Patients] On scheduled haloperidol of ≤ 8 mg in the last 24 hours
- 11. [**Patients and** Family Caregivers] Able to communicate in English **or Spanish**

Scientific Rationale: We would like to include Spanish-speaking patients and family caregivers as we see Spanish-speaking patients in the Palliative Care Unit

»»» Revised Text # 4

Document: Appendix N

Section: n/a

Paragraph: n/a

Page: 1

Old Text (if applicable):

n/a

New Text:



2013-0345 App. N_Communication Capacity_Caregivers_8-31-15_SP.doc M\W_Affidavit_Spanish.pdf

Scientific Rationale: Translated Caregiver questionnaire to Spanish for Spanish-speaking caregivers

»»» Revised Text # 5

Document: Appendix R

Section: n/a

Paragraph: n/a

Page: 1

Old Text (if applicable):

n/a

New Text:



2013-0345 App R_Blinding_8-31-15_SP.doc MW_Affidavit_Spanish.pdf

Scientific Rationale: Translated questionnaire to Spanish for Spanish-speaking caregivers.

»»» Revised Text # 6

Document: Appendix I

Section: n/a

Paragraph: n/a

Page: 1

Old Text (if applicable):

n/a

New Text:



2013-0345_App I_DEQ Caregiver_Daily_8-31-15_SP.docx MW_Affidavit_Spanish.pdf

Scientific Rationale: Translated questionnaire to Spanish for Spanish-speaking caregivers.

»»» Revised Text # 7

Document: Appendix K

Section: n/a

Paragraph: n/a

Page: 1-2

Old Text (if applicable):

n/a

New Text:



2013-0345_App K_Delirium Recall Questionnaire_Patient_8-31-15_SP.doc MW_Affidavit_Spanish.pdf

Scientific Rationale: Translated questionnaire to Spanish for Spanish-speaking patients.

Edit History:

Virginia M Gonzales 02/09/2016 -- Edited

Vera J. DeLaCruz 1/28/2016 -- Sent

Vera J. DeLaCruz 1/28/2016 -- Sent

Vera J. DeLaCruz 01/28/2016 -- Edited

Vera J. DeLaCruz 01/20/2016 -- Edited

Vera J. DeLaCruz 01/20/2016 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

08/05/2016

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 21

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 21

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|--|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input checked="" type="checkbox"/> Change in eligibility | <input type="checkbox"/> Other: |

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol and Abstract

Section: Table 2 Study Eligibility Criteria / Proposed Treatment/Study Plan / Eligibility

Paragraph: Exclusion #2 and #5

Page: 5 /

Old Text (if applicable):

1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
2. ~~[Patients] Hepatic encephalopathy at the time of screening~~
3. [Patients] History of neuroleptic malignant syndrome
4. [Patients] History of Parkinson's disease or dementia
5. ~~[Patients] History of seizure disorder~~
6. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
7. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
8. ~~[Patients] Previously documented and persistent QTc prolongation (>500 ms)~~
9. ~~[Patients] Heart failure exacerbation at the time of enrollment~~

New Text:

1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
2. [Patients] History of neuroleptic malignant syndrome
3. [Patients] History of Parkinson's disease or dementia
4. [Patients] **Uncontrolled** seizure disorder
5. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
6. [Patients] On regular doses of benzodiazepine or chlorpromazine within the past 48 hours
7. [Patients] Previously documented and persistent QTc prolongation (>500 ms)
8. [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: Removed exclusion criterion #2: The target population for this study are patients with terminal delirium. The study medication, Lorazepam, should not cause additional risk for patients with hepatic encephalopathy and may benefit them if the agitated delirium is controlled.

Revised exclusion criterion #4: The target population for this study are patients with terminal delirium who can have a remote history of seizures for wide variety of reasons. The study medication, Lorazepam, should not pose additional risk to this population.

»»» Revised Text # 2

Document: Appendix A

Section: Exclusion Criteria

Paragraph: #2 and #5

Page: 1

Old Text (if applicable):

Exclusion Criteria

- | |
|--|
| <ol style="list-style-type: none">1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma2. [Patients] Hepatic encephalopathy at the time of screening3. [Patients] History of neuroleptic malignant syndrome4. [Patients] History of Parkinson's disease or dementia5. [Patients] History of seizure disorder6. [Patients] History of hypersensitivity to haloperidol or benzodiazepine7. [Patients] On regular doses of benzodiazepine or chlorpromazine |
|--|

the past 48 hours

- 8. [Patients] Previously documented and persistent QTc prolongation (>500ms)
- 9. [Patients] Heart failure exacerbation at the time of enrollment

New Text:

Exclusion Criteria

- 1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
 - 2. [Patients] History of neuroleptic malignant syndrome
 - 3. [Patients] History of Parkinson's disease or dementia
 - 4. [Patients] **Uncontrolled** seizure disorder
 - 5. [Patients] History of hypersensitivity to haloperidol or benzodiazepine
 - 6. [Patients] On regular doses of benzodiazepine or chlorpromazine
- the past 48 hours
- 7. [Patients] Previously documented and persistent QTc prolongation (>500ms)
 - 8. [Patients] Heart failure exacerbation at the time of enrollment

Scientific Rationale: Updated eligibility criteria in the appendix to be consistent with the changes in the Protocol and Abstract.

Edit History:

Vera J. DeLaCruz 8/5/2016 -- Sent

Vera J. DeLaCruz 08/05/2016 -- Edited

Vera J. DeLaCruz 08/05/2016 -- Created

Select a Committee to receive this memo from the list:

To: **IRB**

3/22/2017 5:32:52 PM

From: Vera J. DeLaCruz

CC: David Hui, Susan Frisbee-Hume, Julio A. Allo, Edrea A. Gonzales

Protocol Name: A Preliminary Double-Blind Randomized Controlled Trial of Haloperidol and Lorazepam for Delirium in Patients with Advanced Cancer Admitted to a Palliative Care Unit

MDACC Protocol ID #: 2013-0345

Version: 22

Subject: Resubmission Cover Letter - Protocol 2013-0345, Version 22

The above protocol is being resubmitted to the Office of Protocol Research (IRB).

Please indicate below the reason for re-submission.

- IRB meeting contingencies
- IRB continuing review contingencies
- IRB revision contingencies
- Response/Acceptance of edited informed consent
- Other revisions/amendments

Please indicate the nature of the changes made (select all that apply)

- | | |
|---|---|
| <input type="checkbox"/> Addition of investigational agents | <input type="checkbox"/> Change in patient costs |
| <input type="checkbox"/> Addition of medical procedure or lab or drug | <input type="checkbox"/> Change in research staff |
| <input type="checkbox"/> Addition of new research site | <input type="checkbox"/> Change in sponsor or supporter |
| <input type="checkbox"/> Change in budget | <input checked="" type="checkbox"/> Change in statistical design (i.e. accrual changes) |
| <input type="checkbox"/> Change in dosing or classification | <input type="checkbox"/> Change in use of specimens or data |
| <input type="checkbox"/> Change in drug supplier | <input type="checkbox"/> Removal of medical procedure or lab or drug |
| <input type="checkbox"/> Change in eligibility | <input checked="" type="checkbox"/> Other: |

Please explain the "Other" nature(s) of the changes made:
added new secondary objectives, added references for additional exploratory analyses

Does this resubmission include any revisions to the Consent Documents? Yes No

Does this resubmission impact the Coverage Analysis? Changes would include additions or deletions of items and/or services in the protocol that could affect a patient's bill (ie. Clinic visits, Blood tests, Urine tests, Cardiac tests, Imaging studies, Biopsies, and/or Additional drugs). It could also include a change in the PI and/or funding source. Yes No

»»» Revised Text # 1

Document: Protocol and Abstract

Section: A. Study Objectives / Objectives

Paragraph: Secondary Objectives #5-7

Page: 2

Old Text (if applicable):

n/a

New Text:

5. **To conduct exploratory analyses on RASS as an outcome.**
6. **To examine the proportion of patients enrolled onto the delirium trial who achieved control of agitation and did not require the randomized study medication.**
7. **To identify patient factors associated with control of agitated delirium.**

Scientific Rationale: Objective 5: This exploratory analyses will provide preliminary data to examine RASS-derived metrics for potential use in future trials
Objectives 6 and 7: This would allow us to understand the effect of open-label haloperidol on agitation in the observation period prior to randomized study medication administration.

»»» Revised Text # 2

Document: Protocol and Abstract

Section: D. Statistical Analysis / Statistical Considerations

Paragraph: D.2. Data Analysis (2 and 3)

Page: 9

Old Text (if applicable):

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests. Because of the nature of our study population, many patients died or get discharged before requiring the study medication. Thus, we will use per protocol analysis to compare the two study arms among patients who received the medication. We will determine the inter-rater reliability of RASS between the bedside nurse and the research nurse at the time of study enrollment using kappa statistic.

New Text:

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables (including biomarkers) and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons between arms will be performed using linear mixed models accounting for within patient correlations across time (RASS), t-tests and Mann-Whitney tests. Because of the nature of our study population, many patients died or get discharged before requiring the study medication. Thus, we will use per protocol analysis to compare the two study arms among patients who received the medication. We will determine the inter-rater reliability of RASS between the bedside nurse and the research nurse at the time of study enrollment using kappa statistic.

To address objective 5, we will be examining multiple variations of RASS-derived metrics as outcome variables and how they behave within each study arm and between study arms, such as

- Time to achieve RASS within target range for several consecutive readings, where the target range may be either 0 to -2 or 0 to -3, the number of consecutive readings may vary between 2 and 6

- The proportion of patients who achieved RASS within target range for a defined % of time within the first 8 hours, where the target range may be either 0 to -2 or 0 to -3, the defined % of time may vary between 50-100%

- We will also be examining how these RASS-derived metrics correlate with the magnitude of RASS reduction

To address objectives 6 and 7, we will estimate the proportion of patients enrolled onto the delirium trial who achieved control of agitation and did not require study medication, with 95% confidence interval. We will summarize the demographic/clinical characteristics separately for the patients who achieved control of agitation and did not require study medication and for those that developed agitation and received treatment for agitation. We will evaluate the time from registration to agitation in which patients who never developed agitation before discharge will be censored at discharge. Any death before charge without the development of agitation will be considered as a competing risk. The cumulative incidence of agitation will be estimated using the competing risk analysis and can be compared between different patient groups using Gray's test [Pintilie M 2006; Gray RJ Ann Stat 1988]. To assess the effects of covariates on the cumulative incidence function for agitation, we will use the univariate and multivariate proportional hazards models of Fine and Gray [Fine J Am Stat Assoc 1999]. Other statistical methods may be employed when appropriate.

Scientific Rationale: Objective 5: This exploratory analyses will provide preliminary data to examine RASS-derived metrics for potential use in future trials

Objectives 6 and 7: This would allow us to understand the effect of open-label haloperidol on agitation in the observation period prior to randomized study medication administration.

This study is CNPE. We do not plan on enrolling any new patients.

»»» Revised Text # 3

Document: Protocol

Section: F. References

Paragraph: n/a

Page: 13

Old Text (if applicable):

New Text:

Additional References:

1. Pintilie M (2006) Competing risks: a practical perspective. Wiley, Hoboken.
2. Gray RJ (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 3:1141–1154.
3. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509

Scientific Rationale: Added references for additional exploratory analyses

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