Ketamine for Acute Pain after Trauma: KAPT Trial

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Protocol Title:	Ketamine for Acute Pain after Trauma: KAPT Trial
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Population:	Adult trauma patients admitted to the Surgical Intermediate Unit (SIMU) and Shock Trauma Intensive Care Unit (STICU) at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC)
Number of Sites:	Single center, MHH-TMC
Study Duration:	Two years (tentatively)
Subject Duration:	Time while hospitalized and six month follow up

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General Information

Intravenous infusions of ketamine at sub-dissociative doses have gained popularity as the drug in low doses is thought to decrease pain and opioid exposure after elective surgery. However, evidence supporting ketamine in trauma patients is mixed. With the current opioid epidemic ravaging the United States, providers are increasingly searching for effective non-opioid medications to manage acute pain after injury. Trauma patients are a particularly vulnerable population. Approximately one-third of trauma patients admitted to the Red Duke Trauma Institute (RDTI) at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC) are at moderate to high risk for opioid abuse. While regional anesthetic techniques are extremely useful in the management of acute pain, trauma patients often have more than one body system injured limiting the effectiveness of such techniques. The proposed project is a comparative effectiveness study in which acutely injured trauma patients will be randomized to one of two acute pain interventions: 1) ketamine drip + usual care or 2) usual care. The primary outcome will be opioid exposure during hospitalization. Additionally, we plan to perform an exploratory analysis on how best to describe a patient's pain experience after injury.

Background

Effective pain relief after trauma is essential to allow for patient mobilization, improve functional status, and minimize post-injury emotional stress.(1-4) Opioids continue to be a mainstay in acute pain management following injury. Even today, guidelines recommend opioids as first line therapy for critically ill patients.(5) However, opioid prescribing practices after traumatic injuries and surgeries substantially drive the current opioid epidemic.(6)

Trauma patients are a particularly vulnerable population. Approximately one-third are at moderate to high risk for opioid abuse (*Lane S, unpublished data*) and 13% progress to persistent opioid use after injury *(Baker, RC unpublished data)*. *The RDTI has taken great strides to minimize opioid exposure in trauma patients, but additional strategies are needed.*

The Red Duke Trauma Institute (RDTI) at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC) has a long history of implementing and testing the use of multimodal pain regimens (MMPR), whereby non-opioid medications are given in a scheduled fashion with opioids available on an as needed basis (https://med.uth.edu/surgery/acute-trauma-pain-multimodal-therapy/). While our MMPR has dramatically reduced the in-hospital opioid exposure of injured patients, injury results in substantial pain and opioids are often still needed (*Wei S, unpublished data*). This is especially true in the first few days after injury. To further reduce opioid exposure, we need additional treatment strategies in addition to the current of an MMPR to further reduce opioid exposure by trauma patients during this critical period.

A promising intervention for acute pain is intravenous ketamine given at a sub-dissociative dose. Ketamine is a phencyclidine analog and dissociate anesthetic. The use of sub-dissociative doses of ketamine have greatly increased in recent years despite somewhat varying literature supporting its use. In one of the most recent clinical trials of ketamine in patients with rib fractures, a sub-dissociative dose of ketamine did not significantly reduce opioid exposure in 91 patients, though a significant reduction was seen in the more severely injured sub-population.(3) The most recent guidelines published by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine,

and the American Society of Anesthesiologists recommend sub-dissociative ketamine infusions for patients undergoing painful surgery.(4)

Ketamine has a relatively wide therapeutic window. It is commonly used at higher doses for procedural sedation and perioperative anesthesia. Higher doses, however, can precipitate the classically associated psychometric properties and induce hypertension and tachycardia. There are few known contra-indications for ketamine at sub-dissociative doses, but the following are relative contraindications:(4)

1) Pregnancy
2) Poorly controlled cardiovascular disease, including unstable coronary artery disease and hypertension
3) Severe hepatic dysfunction (cirrhosis)

For the remainder of this proposal, the sub-dissociative dose of intravenous ketamine (0.25 mg/kg/hr) will simply be referred to as ketamine.

Lastly, clinical researchers have struggled to fully describe the pain experiences of patients across levels of care. For example, pain levels in intubated and non-verbal patients have been assessed using visual clues. At the RDTI, the Behavioral Pain Score (BPS) is used in non-verbal patients. The BPS is a three domain tool with 4 scores in each domain for a possible score range of 3-12. In contrast, patients who can verbalize are asked to report subjective levels of pain. At the RDTI, the Numeric Rating Scale (NRS) is used in verbal patients; the NRS is an 11 point scale with a range from 0-11. These scales measure the same thing – pain – but with differing values representing different assessments. As the two tools are not interchangeable, the longitudinal interpretation of both pain tools over time in the same patient is not currently possible. These scoring systems, however, are done universally by nursing staff and remain the ubiquitous source of pain data. Other methods of pain testing in clinical research, such as sensory testing, are simply not feasible in large, longitudinal, population-based studies.

Hypothesis and Specific Aims:

The overall hypothesis of the grant is that intravenous ketamine in addition to usual care (UC) will result in a lower opioid exposure than UC alone.

Specific Aims:

1) **To perform a randomized controlled trial of intravenous ketamine/UC to UC alone.** The infusion will begin as early as possible and continue for a minimum of 24 hours and a maximum of 72 hours after admission. Additionally, the infusion will begin again after each subsequent major surgery. The primary outcome will be in-hospital opioid exposure (measured as Morphine Milligram Equivalents [MME]). Secondary outcomes will be pain scores, complications, and patient-centered outcomes. Heterogeneity of treatment effect will be assessed by performing both confirmatory and hypothesis-generating subgroup analyses to identify moderators of the effect of the different treatment strategies.
2) **To longitudinally quantify the pain experience of a patient during hospitalization** by incorporating all of the ubiquitous nursing-collected pain scores. This exploratory and novel method will require the standardization of the NRS and BPS pain tools and compare the global

pain experience quantified by the two to opioid exposure, self-reported health status, and self-reported patient experience.

Study Design

Setting: This randomized, clinical trial will occur at the RDTI at MHH-TMC.

Trial Arms: Treatment Strategies

Group	Ketamine	Control
Drug dose	*Bolus:* 0.35 mg/kg *Infusion:* start 0.15 mg/kg/hr; titration range is 0.1–0.25 mg/kg/hr	None
Duration	*24 (minimum) to 72 (maximum) hours after admission and each subsequent major surgery*	n/a
Usual Care	• Acetaminophen 1,000 mg PO q6 hours • Naproxen 500 mg PO q12 hours • Gabapentin 300 mg PO q8 hours • Lidocaine patches Opioids as needed for additional pain control	• Acetaminophen 1,000 mg PO q6 hours • Naproxen 500 mg PO q12 hours • Gabapentin 300 mg PO q8 hours • Lidocaine patches Opioids as needed for additional pain control
Timing	Ketamine drip to begin as early as possible: • Hemodynamically stable patients – start immediately (ideally in ED prior to CT scan) • Hemodynamically unstable patients – start once stabilized	
Notes:	**At current, ketamine is only possible in the SIMU and STICU. One of the clinical tangents of the trial is that we will work with nursing to allow patients who have been stable on a ketamine drip in the SIMU or STICU to be transferred to the floor without discontinuing the infusion.*	**Patients who fail UC may transition to a ketamine drip*

Study Population:

Inclusion Criteria	Exclusion Criteria
• Adult trauma patients (≥16 years) • Admission to Surgical Intermediate Unit (SIMU) and/or Shock Trauma Intensive Care Unit (STICU) • Randomization within 12 hours of arrival	• Patient not expected to survive/moribund • Contraindication to ketamine: ○ Allergy ○ Poorly controlled hypertension ○ Cardiac arrhythmias disorders (including atrial fibrillation) ○ Congestive heart failure (diastolic or systolic) ○ Unstable coronary artery disease or recent myocardial infarction (<6 months) ○ Cirrhosis

	○ Seizure disorder ○ In patients with an unknown past medical history, patients will be excluded if: ▪ They have a median sternotomy scar ▪ Mechanism of injury is fall from standing ▪ Age >65 years ▪ Any arrhythmia on EKG • Pregnancy • Prisoners (defined as those arriving from a correctional facility) • History of dementia or movement disorder (e.g. Parkinson's)

Screening: All adult trauma patients (≥ 16 years) arriving to the trauma center and admitted to the trauma service will be screened for eligibility by the clinical research staff. The research staff is available 24/7 and will screen, randomize, and collect data. Once it is determined that the patient is eligible, the research staff will randomize the patient into one of the two study treatment groups and will notify the clinical physician team of the randomization allocation.

Randomization: Randomization will be blocked and stratified by unit of admission. An independent statistician will determine the randomization sequence. REDCap will be utilized for the randomization.

Consent:

Effective pain control should begin as early as possible. Often, in the Emergency Department, opioids are the first line of acute pain control because they are ubiquitous and well known. Ketamine is commonly used in the Emergency Department as well, but at higher doses for moderate sedation during procedures (fracture reduction and splinting, tube thoracostomy, etc…). The fundamental change this trial addresses is the provision of lower doses of ketamine earlier in the patient's emergency care.

We request a waiver of consent to randomize patients as:

- The intervention is minimal risk; the ketamine dosing proposed is already being used by prehospital personnel, emergency room physicians, and trauma surgeons at similar or higher doses. It is widely considered a safe drug with a wide therapeutic window.
- The research could not be practicably carried out without the waiver; due to the acute clinical status of the trauma patient population (intubation, intoxication, severe pain, emotional stress), *truly informed* consent cannot be obtained in the vast majority of patients (or their legally authorized representative [LAR]) before the ketamine would be given.
- The waiver would not adversely affect the rights and welfare of the subjects; patients often receive opioids and/or ketamine in the Emergency Department acutely without their knowledge or written consent, they simply want pain control. We will be providing pain control and rescue opioids would not be withheld from the intervention group.

Once the patient is randomized, a member of the trauma research team will make attempts to contact either the patient or LAR to obtain consent for using Protected Health Information (PHI), to return to perform discharge surveys, and to contact after discharge for post-discharge surveys. Consents will be obtained by trained research personnel. Once appropriate to approach the patient for consent, a study team member will explain the study, its implications for the patient, and give the patient written study

information. If, after 5 days, the patient remains unable to self-consent and no LAR is available to consent, the consent will be waived and data included. Additionally, if the subject does not survive following the traumatic injury or is discharged from the hospital before the study team is able to obtain consent, their information will be included in the data analysis.

Additionally, an educational pamphlet on safe opioid use will be given to the patient.

If the subject consents to participation, they will sign the consent document. If the subject refuses, data collection will stop at time of refusal.

In a previous acute pain trial (Multi-modal Analgesic Strategies for Trauma [MAST] Trial) of 1,616 patients using a similar methodology for consent, 1,207 (75%) patients signed consent, 35 (2%) were waived due to death prior to consent, 178 (11%) were waived as the patient was discharged prior to consent, 141 (9%) were waived due to 5 days of attempts elapsing, and 55 (3%) patients declined participation.

Data Collection

Data collection will occur by one of two methods: manual entry or automatic capture of data. Data points to be collected are detailed in Appendix 1. Appendix 1 also indicates the manner by which data points will be collected – manually, from National Trauma Data Base registry, or automatic capture from the electronic medical record. A RedCap database will be utilized to securely store all data.

In addition to the in-hospital data collection, the research staff will contact the subject 6 months following hospital admission to complete the Euro-QOL EQ-5D-3L and PTSD Screening Tool assessments and collect information regarding pain level and opioid use.

Data Analysis

Outcomes:

Primary outcome: average MME per day.

Secondary outcomes:

- In-hospital:
  - Pain scores
  - Morbidity:
    - Delirium
    - Unplanned intubation
    - Unplanned admission to an intensive care unit
  - Ketamine:
    - Time to ketamine drip starting
    - Time on ketamine drip
    - Patient request to discontinue for any complaint
  - Use of other pain control adjuncts: regional anesthesia, lidocaine drip
  - Lengths of stay: ventilator-/hospital-/ICU-free days
- Discharge:
  - Discharge from the hospital with an opioid prescription (type and number)
  - Discharge Euro-QOL EQ-5D-3L (Appendix 2)
  - Discharge PTSD Screening Tool (PC-PTSD-5) (Appendix 3)
  - Discharge Opioid Risk Tool (ORT) (Appendix 4) (may be obtained from medical records)

- 6 month follow up:
  - Euro-QOL EQ-5D-3L (Appendix 2)
  - Presence of continued post-traumatic pain (Yes/No)
  - Persistent opioid use (Yes/No)
  - PTSD Screening Tool (PC-PTSD-5) (Appendix 3)

Sample Size and Feasibility:

Given the uncertainty of an exact treatment effect of ketamine in our patient population and the potential for contamination of the control group if the trial is continued for a prolonged length of time, we recommend performing the largest feasible study over 18 months with a Bayesian analysis of the primary and secondary outcomes.

Treatment effect: Though not exactly generalizable to our population, the previous ketamine trial in trauma patients reported a 20% reduction in MME over the first two days after admission.

Feasibility: Over the last 6 months (November 2018 – April 2019), manual review of admission to the trauma service revealed 302 potentially eligible patients. This is equivalent to 906 patients potentially eligible patients over the 18-month trial period. Given the emergent nature of the intervention and general difficulties enrolling severely injured patients, we conservatively estimate enrolling 40% of potentially eligible patients.

Sample size and power: We therefore anticipate recruiting approximately N = 395 into the current trial. Based on its skewed distribution we posit that MME's per day will be Gamma distributed (MME's need not be integer values). Using the 50^{th} and 75^{th} percentiles, MME = 45 and 67 respectively, from our previous data we estimate the control condition as following the distribution ~Gamma(shape = 2.7784923, scale = 18.343307). Further, assuming that the ketamine condition results in a 20% decrease in MME's (50^{th} and 75^{th} percentiles MME = 36 and 53.6 respectively) we assume the observed data for this condition is distributed ~Gamma (shape = 2.7784923, scale = 14.674646). We assume that clustering within unit induces a substantial ICC = 0.2. Finally, we stipulated that a 75% chance that the ketamine treatment reduces MME's by at least 15% relative to treatment as usual would constitute sufficient evidence to warrant a larger clinical trial. Assuming the previously stated sample size, effect, ICC and decision rule, K = 1000 Monte Carlo simulations suggest there is a > 99% chance of observing this effect.

General Data Analytic Plan:

The data analytic strategy will use Bayesian inference, applying generalized linear multilevel modeling with level-two random effects or fixed effects (depending on model convergence) to account for clustering of participants within department and, where applicable, observations within participants. Modeling will use R v. 3.4 and Stan v. 1.10.(9, 10) Initial analyses will examine group differences for baseline variables and examination of correlations between baseline variables and specified outcomes. For the purposes of evaluating the comparability of groups, a posterior probability that a difference/correlation exists of $\geq$ 95% will constitute evidence for statistically reliable differences. Potential confounders, so identified, will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not.(11, 12) This will permit determination of the degree to which any group differences might confound conclusions regarding treatment. All analyses will use intention-to-treat principles. Bayesian approaches will implement joint modeling of observed outcomes and the missing data which is robust to ignorable missingness (i.e., MCAR and MAR).(13) Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.(14)

Convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will be assessed via graphical (Gelman-Rubin Plots) and quantitative (Gelman-Rubin Diagnostics and Effective Sample Size) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear multilevel models, priors for regression coefficients will be specified as ~Normal (μ=0, σ^2=1000) on the identity or log-scale depending upon the model, level one error variances will be specified as ~Half-T (df = 3, mean = 0, standard deviation = 100). Prior distribution for level two variances will use ~Half-T (df = 3, mean = 0, standard deviation = 1000). Priors for the comparison of proportions will be specified as ~Beta (α=0.5, β=0.5). For all subgroup analyses using multilevel models the approach will follow that used in Tyson, et al.(15)

One of the major limitations in the conduct of clinical trials on acute pain is the difficulty interpreting patients' pain experience in the hospital. While the NRS pain scores are ubiquitous, easy to use, and compliance is high, the scores are subjective and relative to a patient's expectations, pain tolerance, and immediate context. The BPS is a validated tool for measuring pain in non-verbal patients and is more objective. However, it has not been scaled to allow for use in conjunction with the NRS to fully describe a patient's pain experience.

In addition to the above limitations, both the NRS and BPS are measurements of a patient's pain at one time point. Pain is dynamic. The amount of time a patient spends at a given pain level is likely more reflective of their global pain experience than single measures.

To attempt to address the pain score limitation noted in the Background section, we plan an exploratory analysis whereby we will:

1) Create a scale to standardize the two measurements (See Table 1)
2) Use the date and time of each measure to model the trajectory of pain assessments and the time for which a patient stays at those pain levels
3) Use the area under the curve to quantify the global pain experience of the patient
4) Compare varying levels of this area under the curve to different outcomes, including:
    - Euro-QOL EQ-5D-3L at discharge (Appendix 2)
    - Euro-QOL EQ-5D-3L at 6 months (Appendix 2)
    - Presence of continued post-traumatic pain (Yes/No)
    - Persistent opioid use (Yes/No)
    - PTSD Screening Tool (PC-PTSD-5) (Appendix 3) at discharge
    - PTSD Screening Tool (PC-PTSD-F) (Appendix 3) at discharge
    - ORT Screening Tool (Appendix 4) at discharge

Example:

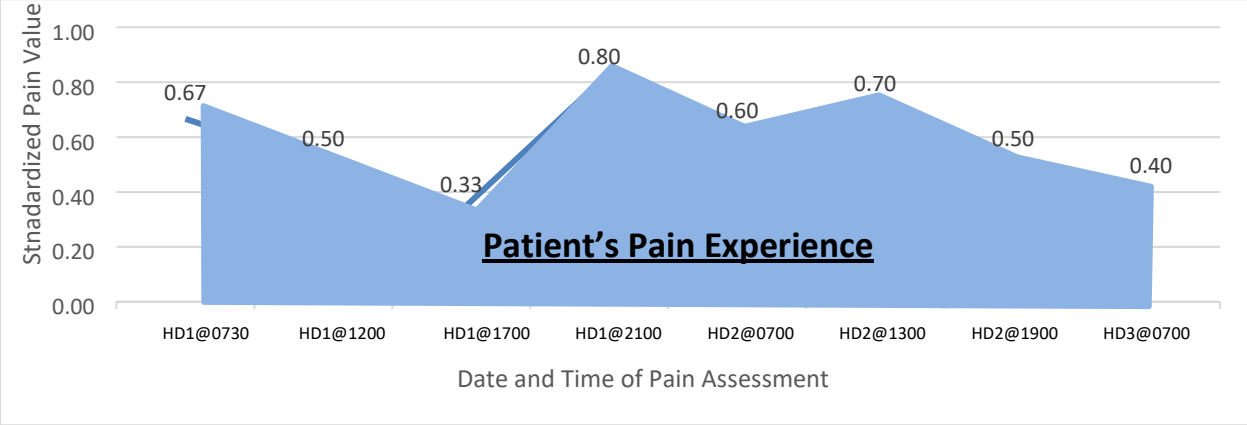
Table 3. Recorded Pain Scores

Date/Time	Pain Score	Standardized Score
Patient admitted to STICU intubated		
HD 1 @ 0730	BPS = 8 (3/3/2)	0.67
HD 1 @ 1200	BPS = 6 (2/2/2)	0.50
HD1 @ 1700	BPS = 4 (1/2/1)	0.33
Patient extubated		
HD1 @ 2100	NRS = 8	0.80

HD2 @ 0700	NRS = 6	0.60
HD2 @ 1300	NRS = 7	0.70
HD2 @ 1900	NRS = 5	0.50
HD3 @ 0700	NRS = 4	0.40
Patient discharged		

Traditionally reported pain scores are listed as to the left (Table 3). This, however, neglects the amount of time spent at said pain levels. To try and address this limitation, we will model pain and time, as below (Figure Two). In this model, the area under the curve would quantify both the level and duration of acute pain, representing a global assessment of a patient's pain experience.

Figure Two



Statistical Plan:

Multilevel generalized linear or generalized additive models will fit functional forms to pain scores. Random effects will permit each participant to have individualized functional forms. Comparison of different functional forms will use the AIC or AIC_c. Having estimated the functional form for each participant's pain-score curve we will estimate the area under each curve using appropriate methods of integration. The resulting AUC's will serve as summary measures of each participant's pain experience. Multilevel generalized linear models will then evaluate the Euro-QOL EQ-5D-3L at discharge, patient satisfaction with pain management at discharge, Euro-QOL EQ-5D-3L at 6 month, presence of continued post-traumatic pain (Yes/No), persistent opioid use (Yes/No), PTSD Screening Tool (PC-PTSD-5) each as a function of pain AUC.

Quality Control and Assurance

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Bi-weekly audits of data will be performed by both clinical investigators and research assistants.

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Appendix One: Data

Variable	Manual extraction	From Registry/NTDB	Electronic Data Withdrawal
In-hospital	Demographics • Age • Sex • Race • Prior opioid use Injury characteristics • Mechanism of injury • Specific injuries: - Total number ribs with a fracture (0-24) (two or more fractures in a single rib counts as 1) - Flail chest - Long bone fracture (radius, ulna, humerus, femur, tibia, fibula) - Vertebral body fracture - Laparotomy - Thoracotomy - Amputation - Any pelvis/acetabular fracture Complications • Ketamine specific complications	Injury Characteristics • AIS values • ISS Complications • Cardiac arrest • Unplanned admission to ICU • Unplanned intubation Outcomes • Hospital length of stay • ICU length of stay • Ventilator days • Mortality	• Daily morphine milligram equivalents • Pain scores • Costs
Discharge	• Discharge opioid status • Regional anesthetic used • Euro-QOL EQ-5D-3L		
Follow up	• Euro-QOL EQ-5D-3L • Presence of continued post-traumatic pain (Yes/No) • Persistent opioid use (Yes/No) • PTSD Screening Tool (PC-PTSD-5)		

Appendix Two: Euro-QOL EQ-5D-3L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑

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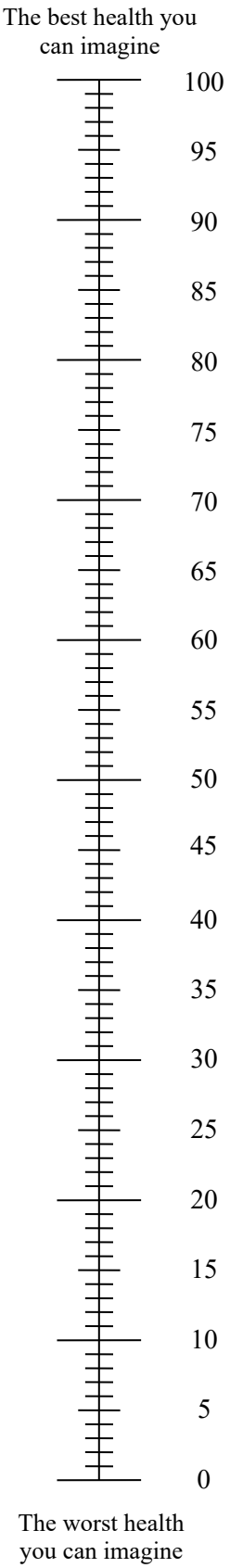
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY = ☐

- Now, please write the number you marked on the scale in the box below.



IRB NUMBER: HSC-MS-19-0726
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Appendix Three: PTSD Screening Tool (PC-PTSD-5)

ID # _____

PC-PTSD-5

Sometimes things happen to people that are unusually or especially frightening, horrible, or traumatic. For example:

- a serious accident or fire
- a physical or sexual assault or abuse
- an earthquake or flood
- a war
- seeing someone be killed or seriously injured
- having a loved one die through homicide or suicide.

Have you ever experienced this kind of event?

YES NO

If no, screen total = 0. Please stop here.

If yes, please answer the questions below.

In the past month, have you…

1. had nightmares about the event(s) or thought about the event(s) when you did not want to?

   YES NO

2. tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)?

   YES NO

3. been constantly on guard, watchful, or easily startled?

   YES NO

4. felt numb or detached from people, activities, or your surroundings?

   YES NO

5. felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused?

   YES NO

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Appendix Four: Opioid Risk Tool (ORT)

1. **Do you have a family history of substance abuse?**
   (Substance abuse means having problems from using a substance too much or too often)

	Yes	No	Did not respond
Alcohol			
Illegal Drugs *(e.g., marijuana, cocaine, methamphetamine, heroin)*			
Prescription Drugs *(e.g., Xanax, hydrocodone, Vicodin)*			

2. **Have you had a personal history of substance abuse?**
   (Substance abuse means having problems from using a substance too much or too often)

	Yes	No	Did not respond
Alcohol			
Illegal Drugs *(e.g., marijuana, cocaine, methamphetamine, heroin)*			
Prescription Drugs *(e.g., Xanax, hydrocodone, Vicodin)*			

3. **Age** ☐
   (Mark box if 16 – 45 years old)

4. **Do you have a history of preadolescent sexual abuse?**
   (This means unwanted sexual contact by an adult before you were age 13)

5. **Do you have any psychological disorders or diseases?**

   ADD (Attention Deficit Disorder)
   OCD (Obsessive Compulsive Disorder)
   Bipolar Disorder
   Schizophrenia
   Depression