A Prospective, Randomized, Single-Blind, Active Control Trial to Compare Safety and Effectiveness Of Liposomal Bupivacaine (Exparel) to Standard bupivacaine HCl with epinephrine (Marcaine) for Pain Management in Patients Undergoing Video-Assisted Thoracoscopic Lobectomy (BEMP study)

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1. INTRODUCTION

1.1. Background and rationale

Background

The US government has made the historic declaration of the current opioid crisis as a public health emergency. And though this action will allow for expanded access to telemedicine services and reallocate funding for abuse programming, it remains the responsibility of researchers to propose clinical solutions that can improve patient outcomes. From 2014 to 2015 the death rate from synthetic opioids, such as fentanyl, increased by 72.2%. While all of Illinois was distinguished among other states with a significant increase in drug overdose death rates from 2013-2015 by the Center for Disease Control (CDC) and Illinois Department of Public Health (IDPH), people living in rural communities are more likely to overdose on prescription pain medications than people in cities. This poses an obstacle for all clinicians, and particularly those charged with pain management following surgery. Thoracic surgery requiring thoracotomy is widely recognized as one of the most painful surgical procedures, and is associated with extended hospital length of stay, respiratory morbidity, and delayed post-surgical return of function. Intercostal nerve damage and muscular trauma are considered the principal causes of postoperative pain after thoracotomy. Medical management of postoperative pain utilizing opioids and NSAIDs has become the standard approach for post thoracotomy analgesia; whereby de minimis opioid use is a requirement for patient discharge conversely contributing to increased hospital length of stay.

Over the last 3 decades clinicians have levied increasing emphasis on minimally invasive surgical techniques, reducing the risk of intraoperative complications in surgery by demonstrably reliable improvements in postoperative outcomes. Video-assisted thoracoscopic surgery (VATS) is a minimally invasive technique which eliminates the necessity of rib retraction and shrinks the incision size, reducing intercostal nerve and muscular trauma to preserved pulmonary function. This methods relies on visualization of the mediastinal anatomy and surgical apparatus using a camera. Further advancement over the last decade has broadened the indications for VATS utilization to encompass more complex procedures, marginalizing the need for open thoracotomy practices.

Though VATS shows comparable benefits to open thoracotomy being a safer alternative for elderly patients, low postoperative pulmonary complications, decreased trauma, no rib spreading, lower hospitalization, and a faster recovery, patients still risk moderately severe acute postoperative pain. Successful management of postoperative pain after VATS is indicative of adequate post-surgical recovery as suboptimal postoperative pain management may lead to chronic pain, which may be or become neuropathic in nature. Thoracotomy is suspected to induce chronic pain at 57% percent of patients surviving a year after surgery, where pain was severe in 8% of those cases. 30-50% of patients were shown by one study to have postoperative pain at the thoracotomy site after 2 months which can be credited by a considerable amount to intercostal nerve injury with a neuropathic origin. And though some patients in this study found post-thoracotomy pain

after 1-year, some of those same patients did not report any pain symptoms at 6 months. Long term follow-ups for pain management after thoracotomy are not standard care per common practices. Additionally, though there is a treasure trove of evidence connecting VATS to chronic pain, very little has been done to conclusively detail the relationship between post-thoracoscopy chronic pain and opioid dependence which may arrive later in a patients' medical history. The gravity of the transpiring American public health emergency has inspired the research community to ardently consider this issue. Minimally invasive procedures like VATS are incomplete solutions to post-operative pain management where chronic pain and drug dependence require greater consideration.

Increasing utilization of non-opioid medications as surrogate opioid management for post-thoracotomy pain could potentially diminish the medical reliance on and incipient patient risks incurred as a result of opioid use for VATS procedures. Comparisons of different analgesic methods reveal reduced incidence and intensity of long-term procedural pain. Bupivacaine HCl, marketed under the names Marcaine, Sensorcaine, and Vivacaine-- is the current non-opioid drug of choice for thoracic epidural analgesia in 89.7 percent of surgical cases. Marcaine behaves as the amino-amide anesthetic *1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide* achieving moderate inhibition of Na (+) ion transduction across the neuronal membrane by decreasing the membrane permeability and consequently inhibiting the excitation of neurons to depress the pain response. Amino-amide anesthetics are commonly associated with hypotension and can enhance the hypotensive effects of a number of antihypertensive drugs. Other adverse reactions like cardiac arrest, bradycardia, apnea, and hypoventilation have also been associated with Amino-amide local anesthetics. Marcaine is approved for localized analgesia and regional blocking by the Food and Drug Administration under Hospira, Inc. and has since received wide recognition in thoracic surgery for postoperative pain management following thoracotomy. Contrarily, Marcaine reports only a duration of action of < 6 hours per dose administration. Continuous local administration of bupivacaine has been shown to reduce pain, cytokine levels, and opioid requirements postoperatively. This limitation pressures anesthesiologist, surgeons, and nursing staff through inordinate surveillance of a consistent need for analgesia to coordinate additional measures for pain management such as the administration of NSAIDS and narcotics. Ancillary support of bupivacaine HCl infusion utilizing epinephrine and/or perineural catheters come short of remediation to the limited duration of action. The potential to increase the duration of adequate local analgesia by other novel means may have an effect on dosing requirements, and offer a way to reduce the blood concentration of bupivacaine. A 2015 study by the University of Texas Medical School of 85 participants undergoing open thoracotomy comparing the use of the liposomal bupivacaine formulation known as Exparel as an intercostal nerve block to their current thoracic epidural standard resulted in significant pain control postoperatively.

The liposomal version of bupivacaine marketed by Pacira Pharmaceuticals in 2011, is indicated for single-dose post-surgical administration into surgical site to produce local analgesia. Vesicular encapsulation has been confirmed as a novel method of extending

delivery of anesthesia and, as a multi-vesicle liposome formulation of bupivacaine, Exparel provides an extended duration of action reporting > 72 hours of post injection analgesia. Liposomes are loaded with bupivacaine by an ammonium sulfate gradient established at an appropriate pH for complete saturation of the vesicles with bupivacaine. The drug is released gradually after dispensation to provide steady analgesia to the affected area. Exparel was initially approved by the FDA for treatment of patients undergoing bunionectomies or hemorrhoidectomies. The FDA has since broadened the indication of Exparel to "administration into surgical site to produce postsurgical analgesia."

While assessing whether use of a higher fidelity analgesia will affect the requirement for narcotic administration for postoperative pain and the risk of opioid dependence and abuse observed when postoperative pain is treated with a longer, steady release of anesthesia over time, this study aims to consider outcomes related to patient hospital costs as well as short and long term pain assessment after hospital discharge.

Hospital costs associated with VATS anesthesia narcotic use in rural Illinois community has not been subjected to the due scrutiny necessary to understand the effect of the opioid crisis; the Council of Economic Advisors report on this insurgence estimates the overall national cost in 2015 at nearly $504.0 billion and climbing. IDPH semiannual report on opioid trends in hospitalizations and emergency department visits show continued increase annually since the 2016 and an overall upward trend since 2013. A report by SIU School of Medicine places estimated direct medical costs in 2009 at $2.2 billion. Ad caveat-- these estimates includes long term data collected on downstream effects of opioid abuse, which has been unfortunately and indelibly correlated to prescriptions for anesthesia during surgery, including the rise in healthcare resources utilized over time by opioid abusers as compared to their non-addicted peers, costs to the criminal justice system, and fatality costs of lost potential earnings. This study does not intend to assess the impact on other downstream economic factors, though by collecting comparison data on healthcare charges as a result of narcotic requirements from use of local administration of Exparel and Marcaine for VATS, the preferred surgical technique for lung diseases by SIU Medicine Cardiothoracic surgeons, we can increase our understanding of the disparity that opioid crisis plagues on the bottom line of our hospital and the pockets of its patrons. Though both of these drugs provide a non-opioid analgesic and are available and indicated for the intended use, the gross differences in their durations of activity underscore a potentially significant difference in the necessity of narcotic use for post-thoracotomy pain which we plan to further describe in the proposed research. To be able to efficaciously distinguish between the two drugs is in the best interest of our patients.

Currently, there is very little published data representing these outcomes in consort. Growing preference for local analgesia and intercostal nerve blocking with Exparel for pain after thoracotomy presents a unique opportunity to study the effects on cost, length of hospital stay, and primarily the comparative downstream effect on narcotic

requirements pain management. Per our own query, 1 clinical trial currently registered with clinicaltrials.gov compares Exparel and Marcaine prospectively for post-operative pain management following lung surgery. No other study currently intends to analyze chronic neuropathic pain, opioid usage, and hospital cost data. In our current clinical setting, the use of Marcaine versus Exparel is based purely on physician preference.

2. STUDY OBJECTIVES

The hypothesis is the possibility of liposomal bupivacaine providing more relief with less need of narcotics when compared to standard bupivacaine. To compare pain management following local infiltration of liposomal bupivacaine (Exparel®) versus standard bupivacaine HCl with epinephrine (Marcaine®) after VATS (video-assisted thoracoscopic surgery)-lobectomy. This will be accomplished by evaluating total opioid usage and patient reported pain scores.

2.1. Efficacy Outcomes Measured

2.1.1. Primary Outcomes

i. Total morphine equivalents consumed during 72 hours post-op

2.1.2. Secondary Outcomes

i. Patient self-reported pain visual analog scale score
ii. Narcotic or pain medications consumed throughout hospitalization and during first 30 days, 6 months and 1 year post-lobectomy
iii. Incidence of Paresthesia
iv. Time until first opioid usage
v. Anti-emetic usage
vi. Length of hospital stay
vii. Postoperative complications (e.g. pneumonia, pulmonary complications, wound infections etc.)
viii. Time to ambulation
ix. Time to first bowel movement
x. Time to chest tube removal
xi. Peak expiratory flow measurements
xii. Intraoperative versus postoperative pain management costs
xiii. Overall Hospital Cost

2.2. Safety Outcomes Measured

i. Adverse events, serious adverse events (SAEs),

ii. Suspected adverse drug reactions

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a prospective, randomized, single-blind, active control trial for patients undergoing elective lobectomy. Subjects will be randomly assigned to receive either liposomal bupivacaine (Exparel, test group A) or standard bupivacaine HCl with epinephrine (Marcaine, active comparator group B) during surgery. Pain management will be monitored via opioid usage and visual pain assessment throughout the hospital stay and at postoperative day 30, 6 month and 1 year follow up visits. Overall study schema is described in Figure 1 at the end of this document

3.2. Clinical Setting:

Study will be conducted at SIU-Medicine Clinics and Memorial Medical Center.

3.3. Patient population

Study population includes patients undergoing elective standard of care lobectomy. Based on our power analysis, 150 subjects (75 in each randomized group) need to be included (see *Section 5, Statistical Analyses*). Taking into consideration a potential loss of 50 patients due to withdrawal, lost to follow up or other reasons, 200 patients will initially be enrolled and randomized to attain 150 evaluable subjects at the end of study (1-year follow up). We estimate this study will take up to three years to complete our enrollment.

3.3.1. Inclusion Criteria

1. Adult at least 18 years of age
2. Subject needs elective lobectomy for NSCLC
3. Willing to comply with all aspects of protocol, including providing information about opioid usage for post-surgical pain and signed informed consent

3.3.1. Exclusion Criteria:

1. < 18 years of age, > 80 years of age
2. Inability or unwillingness to consent
3. Emergency surgery

4. Previous ipsilateral thoracic surgery
5. Need for operative pleurectomy or pleurodesis as the primary operation
6. Chronic Narcotic use for 6 or more months
7. Any extensive narcotic use in the 1 month period prior to screening with an exception for the use of narcotics commensurate with standard care diagnostic procedures for VATS Lobectomy
8. Allergies to bupivacaine or other local anesthetics, narcotics, NSAIDs or acetaminophen
9. Moderate to severe hepatic impairment (ALT or AST) value greater than 3 times the upper limit of normal.
10. Severe renal impairment or end stage renal failure disease (creatinine greater than 2.0 mg/dl).
11. History of peptic ulcerative disease
12. Severe chronic obstructive pulmonary disease (COPD) due to LVRS (lung-volume reduction surgery).
13. Pregnancy
14. Need for conversion from a Video-Assisted Thoracic Surgery procedure to an open thoracotomy
15. Subjects who are incarcerated
16. Subject has been treated with an experimental device within 30 days or received an experimental agent within the longer of 30 days or five half-lives. Or subject is current enrolled in another clinical trial.
17. Unable to follow protocol directions due to organic brain or psychiatric disease.
18. History of alcoholism or any other substance abuse, which, in the opinion of the investigator, would affect compliance with the protocol.

3.4. Study procedures

3.4.1. Summary

All patients scheduled for surgical consult with Cardiothoracic Surgery for possible VATS lobectomy will be prescreened for initial eligibility criteria. Subjects who elect to go forward with surgery will be presented with the opportunity to participate in the study. Informed consent form will be discussed in detail at the clinic or MMC (for in-patient potential subjects) by authorized study personnel. Patient will be given time to review the informed consent with family if so desired. After the patient voluntarily agrees to participate (sign ICF), their inclusion/exclusion criteria will be reviewed again

based on SOC testing to ensure continued eligibility. Patient data such as vitals, physical examination (PE), medications, and medical and surgical history will be recorded or obtained from the EHR. Subjects will be randomized to one of two groups, test (A) and active control (B), Night or morning of scheduled surgery. At the end of surgery, study drug will be administered as described in details below per the standard FDA guidelines. Outcomes will be measured during post-operative hospital stay and until 1 year after surgery for extended follow up which is the standard protocol with CT surgery. A schedule for all assessments throughout the study is described in table 1 at the end of this document.

3.4.2. Informed consent

All participants will be required to provide written informed consent. The study staff will introduce the study to potentially eligible patients. The principal or co-investigators and/or study coordinators will review the informed consent document with the subject. The subject will be provided information related to the study purpose, procedures, potential risks and benefits to participation, voluntary nature of their potential participation and provide them an opportunity to ask and have all questions answered prior to obtaining any signature. A study investigator will be available to answer any questions. Subjects will not be compensated for participation and there are no additional research-related costs to subjects for participation in the study. Both medications and the surgery are standard of care and will be billed accordingly.

3.4.3. Treatments to Be Administered

(1) Prescribing information

- Bupivacine- epinephrine 0.25%, 1:200,000 (Marcaine): See Drug Insert (submitted)
    i. 0.25% concentration up to 225mg with epinephrine administered as an subcutaneous injection at the port site
        - Final dosing will be determined by the physician based on patient weight and is individualized on a case by case basis.
        - Maximum dosage : 400 mg/24 hours

- Bupivacine liposomal 1.3% (Exparel): See Drug Insert (submitted)
    i. Up to 266 mg (20 mL) administered as a subcutaneous injection at the port site, diluted to a final concentration of 2.22mg/mL with 100mL normal saline (0.9%).

- Final dosing will be determined by the physician based on patient weight and is individualized on a case by case basis.
- Maximum dosage: 266 mg (20 ml)

(2) Labeling of Investigational Products

Pharmacy will dispense the investigational drug per randomization assignment and labelled per hospital standards. These are FDA-approved products that are both used as standard of care.

(3) Storage of Investigational Products

Investigational products will be stored in the Memorial Medical Center Pharmacy per hospital guidelines. Accountability for Investigational Products

Accountability of the investigational products will be achieved per Memorial Medical Center guidelines by MMC staff as done per standard protocol

3.4.4. Method of treatment assignment/Randomization

(1) Subject Numbering

Subjects will be assigned a unique consecutive subject number, 3 digits. Preceding the digits will be the letters EM (Exparel/Marcaine) to identify the study. For example, subject numbers will be EM001, EM002, etc., in consecutive order. Subject numbers, once assigned, will not be reused.

(2) Randomization

A randomization schema will be performed by a secondary statistician at the Centers for Clinical Research for all 200 patients and will be listed on one list that will be provided to MMC pharmacy and will also be stored by the Research Coordinators for reference. The patient ID and randomization assignment will be sent to the pharmacy along with screening weight of the subject. The subject(s) and study statistician(s) will remain blinded to the treatment assignments throughout the course of the study while the surgical team and coordinators will not be blinded. Data will be analyzed by the blinded statistician(s) to ensure minimal bias.

(3) Administration and timing of Study drug

Study drug will be administered by the investigator surgeon or members of surgical team under supervision of the investigator surgeon as described below:

Test group A: At the end of the surgical procedure patients in group A will receive injections of liposomal bupivacaine (Exparel, standard dose based on patient's screening weight) delivered via a 25 gauge needle into the surrounding cutaneous and deep tissue including the periosteum around the thoracoscopic port incision sites after closure.

Active Comparator Group B: At the end of the surgical procedure patients in group B will receive, injections of standard bupivacaine HCl with epinephrine 0.25% delivered via 25 gauge needle into the surrounding cutaneous and deep tissue including the periosteum around the thoracoscopic port incision sites after closure.

- *Rationale for Selection of Doses*

Dose will be calculated by the physician based on the screening weight of each randomized patient as is done in the standard way. This will provide reasonable comparison of standard dose of each drug that would have been given for any individual patient.

(4) Treatment compliance

Treatment compliance will be measured in terms of the subject receiving an injection of either Exparel® or Marcaine with epinephrine® from the study personnel. No other forms of compliance will be measured.

Reasons for any deviation from the administration of less than 100% of the investigational products dose must be recorded in the subject's medical records.

3.4.5. Assessment periods and associated observations and measurements

Described in schedule of assessments in Table 1

3.4.6. Concomitant Medications during the Study

(1) Prohibited Concomitant Medications Prior to Study Treatment:

Any chronic/habitual use of narcotics or within one period before consent and screening will be exclusionary. Any use of narcotics between screening and operative day, will be classified as screen failure (if not randomized) or withdrawn (if randomization has been done).

(2) Concomitant Medications during the Study

Details of all home medications, pain management medications, and anti-nausea medications will be recorded.

4. STUDY VARIABLES

4.1. Efficacy

Percentage of subjects with one or more components of a major morbidity. (up to Day 30 post operation). Components of morbidity:

a. **MED usage** (Morphine Equivalent Dose, the amount of morphine an opioid dose is equal to using http://clincalc.com/Opioids/)
b. **VAS** for Pain (Visual Analog Scale)

4.2. Safety

The following safety variables will be assessed in this study per the DSMP (Data Safety Monitoring Plain:

a. Adverse events, serious adverse events (SAEs), and discontinuations due to AEs.

b. Physical examination

c. Vital signs.

4.3. Clinical

a. **Postoperative mortality** (defined as the deaths occurring during primary hospital stay or prior to 30th postoperative day).

b. **Additional surgical intervention** (defined as having to reenter the operating room because of bleeding, pneumothorax, prolonged air leak, or any other complication associated with primary surgery).

c. **Prolonged mechanical ventilation** (defined as mechanical ventilation that exceeds 24 hours from closure until extubation).

d. **Prolonged air leak (**defined by the STS Thoracic Surgery Database as an air leak that persists for greater than 5 post-operative days).

e. **Complications** including cardiac such as cardiac tamponade, atrial fibrillation, or cardiac herniation.

f. **Infection** (defined as presence of surgical incision infection, abscesses, pneumonia, or blood stream infections or sepsis. This could be patients who are treated with antibiotics, or show a positive culture.

g. **Stroke** (defined as neurological deficits of abrupt onset made by clinical diagnosis that were caused by a disruption of cerebral blood flow).

h. **Prolonged hospital stay** defined as 5 days post operatively

i. **Prolonged ICU stay** defined as ICU stay longer than 24 hours post operatively, or reentering the ICU before 30-day post-operative follow up.

5. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Based on the results of the Parascondola et al study, a power analysis was performed to determine the necessary sample size in the 2 treatment arms for the proposed study. While the Parascondola study only examined inpatient narcotic use for the first 72 hours post-op, we plan to include all narcotic usage in this time period as the primary outcome of the proposed study. The estimated difference between the groups at 72 hours produced an effect size of d=0.862. This effect size would only require a sample size of 31 in each group to achieve a power of .90 to detect a statistically significant difference for alpha=0.05. Given the attrition in the Parascondola study, it would seem advisable to view this effect size as having a certain degree of unreliability associated with it. Therefore, we also examined the magnitude of the difference in treatment groups which was observed at the 60 hour time point (d=0.503). Using the mid-point of d=0.6825, 49 subjects per group would be required to have statistical power=0.90 for alpha=0.05. Even if the underlying effect size were d=0.5, a sample size of 75 per group would have power=0.84 with alpha=0.05. This sample size (n=75/group) should also provide reasonable power to detect significant differences for the secondary outcomes of pain assessment at 24, 48 and 72 hours, as well as the cumulative pain score at 72 hours (area under the curve - AUC_{72}). Sample size determination was made using G*Power 3.1.9.2. (Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41, 1149-1160.)

Statistical Methods

Descriptive statistics including means (standard deviations), medians (interquartile ranges – IQRs) and frequencies (counts / percentages) will be used to present the baseline characteristics for the 2 groups. Independent group's t-tests, Wilcoxon rank-

sum tests and chi-squared tests of independence (or exact tests as appropriate) will be used to compare baseline characteristics of the 2 groups to assess effectiveness of randomization. Wilcoxon rank-sum tests will also be used to test for differences between the groups on the primary outcome measure, cumulative narcotic use over the first 72 hours post-op, as well as secondary outcomes including pain scores, length of stay and cost. Chi-squared tests, or Fisher's exact tests will be used to compare the proportions of patients in the 2 groups experiencing complications or using opioids at 6 and 12 months.

6. DATA MANAGEMENT AND CONFIDENTIALITY

Study coordinators will be responsible for data collection and will ensure that forms are completed and signed. Protected Health Information (PHI) will be recorded for tracking the subjects through the course of the study. Subjects may be assigned IDs for unbiased analysis, however these IDs will be linked to PHI separately. Data will be collected on data collection forms (appendix 1, including AE and medication logs) and subsequently entered into RedCAP for statistical analysis. Original signed consent forms, data collection forms and any relevant source documentation will be maintained for the duration of the study in locked file cabinets inside Cardiothoracic Surgery office suites. Electronic data will be stored on a secure server accessible via password-protected computer. Only authorized study personnel will have access to the study data. After completion of data analysis and final manuscript(s) approval, all non-electronic records will be sent to SIU-Records Management for extended storage. Records will be stored for such a period after study completion as dictated by SIU regulations.

7. ASSESSEMENT OF SAFETY

Stopping rules and attributes of seriousness, unexpectedness, severity and causality will be assigned by the investigators and further reviewed during monthly meetings, or as needed based on urgency, as part of the data and safety monitoring plan (DSMP).

Summary: Screening eligibility will be reviewed based on standard of care testing done for the elective index procedure. Adverse events (AE) will be monitored and recorded daily throughout the subjects' hospital stay and again at their post-surgical follow-up visits (30 day) and at 6 month and 1 year (part of standard of care) either in person or through review of subjects' EHRs and phone interviews. These will be reviewed individually by the PI and co-investigators and reported by study personnel. An adverse event log will be created for this study. Regularly scheduled meetings of study personnel will take place to review study progress, procedures, AEs and safety considerations. Real time management of AEs will be done per standard of care by the subjects' health care providers. Any serious AE or unanticipated problems will be reported to the Springfield

Committee for Research Involving Human Subjects (SCRIHS) in accordance with SCRIHS policy.

Specification of Safety Parameters: Safety of exparel and marcaine will be evaluated in this study. Safety endpoints will include:

(1) Adverse events including serious adverse events (SAEs), suspected ADRs, and discontinuations due to AEs
(2) Physical examination
(3) Vital signs

Table 1: Schedule of study assessments

Assessment	Baseline/ Screening	Pre-op (D0)	OP (D0)	Each POD	hospital discharge	F/UP (D30 ± 7d)	F/UP (6m)	F/UP (12m)
Inclusion/exclusion	X	X						
ICF	X							
Vitals	X		X	X	X	X	X	X
PE (done as standard of care by any authorized clinical team member)	X		X	X	X	X	X	X
Medical/Surgical History	X							
Concomitant medications (excluding pain Rx)	X	X	X	X	X	X	X	X
Pain/opioid medication log	X	X	X	X	X	X	X	X
Randomization		X						
Study drug administration			X					
Pain-VAS	X		X	X*	X*	X	X	X
Incentive spirometry (done at bedside)			X	X	X			
MEQ**			X	X	X	X	X	X
Complications			X	X	X	X	X	X

*On POD1 and later, pain assessment will be done as is standard of care by hospital staff until discharge.

** Calculation of MEQ using http://clincalc.com/Opioids/

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