Study Title: Intraoperative aromatherapy versus placebo for Port-a-Cath placement under Monitored Anesthesia Care. A randomized controlled trial

Principal Investigator (PI): Neil Bailard MD

Co-Investigator(s) (Co-I): Juan P. Cata MD

Collaborator(s): Carin Hagberg MD, Jeffrey Cerny MD, Spencer Kee MD, Katy French MD, Alicia Kowalski MD, Elizabeth Rebello MD

Statistician: Lei Feng

Sponsor Name: BEEKLEY CORPORATION

SUMMARY TABLE

Title	**Intraoperative aromatherapy versus placebo for Port-a-Cath placement under Monitored Anesthesia Care (MAC). A randomized controlled trial.**
Study Population Size (# of patients)	70
Study Design	This is a prospective, controlled, randomized trial.
Primary Objective	To compare the time to readiness for discharge (minutes) from Post-Anesthesia Care Unit (PACU) after Port-a-Cath placement surgery between patients who are randomized to receive intraoperative aromatherapy versus placebo
Secondary Objectives	To evaluate the following secondary outcomes: 1) Anxiety score (HADS) in preoperative holding area 2) Midazolam use intraoperatively (mg) 3) Intraoperative opioid use (morphine equivalents) 4) Intraoperative anti-emetic use 5) Time to first occurrence of postoperative nausea or vomiting (PONV) in PACU 6) Rate and intensity of PONV in PACU 7) Antiemetic use in PACU 8) Opioid use in PACU (morphine equivalents) 9) Pain intensity in PACU (0-10 numerical rating scale) 10) Patient satisfaction in PACU
Inclusion Criteria	• Adult patients (≥ 18 years old) • Undergoing Port-a-Cath placement surgery under Monitored Anesthesia Care

	• Signed Informed Consent form
Exclusion Criteria	• Patients undergoing other surgical procedures during Port-a-Cath placement (including explantation of a Port-a-Cath or other previous vascular access device) • Patients requiring general anesthesia or those not eligible for MAC • Patients allergic or sensitive to plants, essential oils, or any of the medications used in this study • Patients with history of G6PD deficiency • Patients with history of atrial fibrillation • Patients unable to complete study questionnaires • Patients who are completely anosmic or who have history of intolerance to aromatherapy. • Patients who have been taking any opioid daily for 90 days or more • Patients who have been taking any benzodiazepine daily for 30 days or more
Study Procedures	
Pretreatment Evaluation	Eligible subjects will be identified from within the patient population of the study site. There will be no advertisements for study subjects.
On-Study Visits	All study procedures and data collection will occur on the day of surgery.
Follow-up Visits	None
End of Study Visit	None

Brief Analysis Plan	We will summarize continuous demographics and clinical variables using means, standard deviations, medians and ranges. Categorical demographic variables and clinical variables will be summarized through frequencies and percentages. Fisher's exact test or Chi-square test will be used to evaluate the association between two categorical variables of interest. Wilcoxon-rank sum test or t-test will be used to compare continuous outcomes between treatment groups. Linear/logistic regression model may be fitted to assess the effect of important covariates on the primary/secondary endpoints.

1. OBJECTIVES

The primary objective is to compare the time to readiness for discharge from PACU (minutes) after Port-a-Cath placement surgery between patients who are randomized to receive intraoperative aromatherapy versus placebo

Secondary Objectives are to evaluate the following secondary outcomes:

1. Anxiety score (HADS) in preoperative holding area
2. Midazolam use intraoperatively (mg)
3. Intraoperative opioid use (morphine equivalents)
4. Intraoperative anti-emetic use
5. Time to first occurrence of postoperative nausea or vomiting in PACU
6. Rate and intensity of PONV in PACU
7. Antiemetic use in PACU
8. Opioid use in PACU (morphine equivalents)
9. Pain intensity in PACU (0-10 numerical rating scale)
10. Patient satisfaction in PACU

2. BACKGROUND

2.1. Porta-Catheter placement

A Porta-Catheter (Port-a-Cath) is a vascular access device placed completely under the skin on either side of the chest. The device is routinely placed to deliver chemotherapy treatments, obtain blood draws or infuse fluids intravenously. Port-a-Cath placement may be performed under general anesthesia or sedation (Monitored Anesthesia Care, MAC) depending on patient health factors and preference. Intraoperative anxiety is a common problem when MAC instead of general anesthesia is used during minor surgical procedures such as Port-a-Cath placement. Johansson et al. reported that 60% of the patients felt "unpleasant" during Port-a-Cath insertion under local anesthesia. Intraoperative anxiety is associated with a negative influence on pain perception, increased use of sedatives like benzodiazepines (i.e., midazolam) and opioids, prolonged recovery after surgery and unnecessary postprocedural hospitalization. Benzodiazepines such as midazolam produce calming effects via binding to $GABA_A$ receptors. Fatigue, confusion, respiratory depression, and restlessness are undesirable adverse effects of midazolam and opioids which limit patients' ability to actively participate in their intra- and postoperative care. Furthermore, Chang et al. found that the use of benzodiazepines does not improve patient's satisfaction during Port-a-Cath placement. Non-benzodiazepines drugs such as dexmedetomidine can also been used to provide procedural anxiolysis. Intraoperative sedation with i.v. dexmedetomidine has demonstrated significant reduction in the postoperative opioid consumption and prolongation of postoperative analgesia when general anesthesia is avoided, as reported by Giordano et al. However, dexmedetomidine can cause hypotension and bradycardia and prolonged sedation. As a result of the potential adverse of benzodiazepines and dexmedetomidine, and opioids, non-pharmacological therapies have been studied to limit their excessive use intraoperatively.

Music, a non-pharmacological intervention, has been studied to reduce anxiety in minor surgery. While Schaal et al. indicated that perioperative music did not reduce anxiety or cortisol levels during Port-a-Cath placement, McDaniel et al. reported that music via headphones (though not via loudspeakers) resulted in significantly lower anxiety after the procedure compared to the beginning. However, a major deficiency in McDaniel's study was the lack of randomization to the studied interventions and that musical therapy can interfere

with the patients' ability to follow commands. Therefore, it is important to examine other non-pharmacological intraoperative interventions which may be able to reduce anxiety and the use of excessive doses of midazolam and opioids, as well as improve recovery after Port-a-Cath placement.

2.2 Aromatherapy

Essential oils have a long tradition in pharmaceutical sciences as natural products with pharmacological applications. Aromatherapy, the therapeutic use of essential oils extracted from aromatic plants, may offer a simple, low-risk and cost-effective method of managing intraoperative anxiety. Aromatherapy is fast-acting, noninvasive, has minimal side effects, and can be applied in multiple forms including aromatabs. It has been demonstrated that inhalation aromatherapy molecules act on olfactory receptors located in primary olfactory neurons. Upon activation of olfactory neurons, an action potential is generated and propagated via the olfactory tract which projects from the lateral olfactory stria to the amygdala, a key structure of the limbic system involved in behavior and emotions. Lv et al. suggested that anti-anxiolytic mechanisms included interaction with NMDA or $GABA_A$ receptors, voltage-dependent sodium channels, voltage-dependent calcium channels, and glutamatergic and cholinergic neurotransmission.

Various essential oils have been studied to reduce anxiety. Linalyl acetate and linalool are molecules found in lavender. The former has narcotic actions while linalool is considered a sedative, an NMDA antagonist and an inhibitor of serotoninergic targets. Yuan et al. proposed that both molecules also exert anti-inflammatory effects by inhibiting activation of NF-kB and the release of pro-inflammatory cytokines (i.e., TNF-a, IL-1B and PGE2). The sedative effects of lavender aromatherapy have been studied in multiple clinical studies. A meta-analysis by Perry et al. showed a lack of conclusive evidence to indicate aromatherapy for the treatment of preoperative anxiety. However, more recent studies have shown promising results. For instance, Wotman et al. demonstrated a reduction in preoperative anxiety in ambulatory surgery patients treated with aromatherapy undergoing procedures in general otolaryngology. A major limitation of the study was the lack of a placebo-controlled arm. Comparable results were reported by Jaruzel et al. in a pilot observational study in breast cancer patients and by Beyliklioğlu et al. in a randomized controlled trial. Kim et al. in a study of acupuncture needle

insertion found that subjects who inhaled a lavender oil for 5 minutes demonstrated a decrease in anxiety, less needle insertion pain, and Bispectral Index (processed EEG) changes suggestive of sedation.

Peppermint oil has long been valued for its antinausea effect. Grigoleit et al. found that menthol and menthone, the main constituents of peppermint oil, appear to act as smooth muscle relaxants through calcium channel blockade when the oil is orally ingested. As an inhaled vapor, peppermint oil likely acts through another mechanism, such as by influencing neurotransmitter release at the chemoreceptor trigger zone of the medulla. Hines et al., in a systematic review, found that aromatherapy appeared to be no better than placebo in preventing nausea, although there was some evidence that patients who had received aromatherapy required fewer antiemetic medications. Hines et al. rated the quality of the included studies as moderate to very low by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria, however. More recently, Ahmadi et al. found peppermint oil aromatherapy to be effective in reducing nausea after abdominal surgery. Maghami et al. found that peppermint oil aromatherapy was effective in reducing nausea after open-heart surgery, although the peppermint oil was delivered via in-line nebulizer in patients who remained intubated, limiting the study's generalizability.

Because the existing literature is equivocal for both lavender and peppermint aromatherapy, we believe that a well-designed placebo-controlled trial may help to resolve some of the uncertainty as to their clinical effectiveness in the ambulatory perioperative setting. As well, to our knowledge there have been no studies of aromatherapy conducted on subjects undergoing surgery performed under Monitored Anesthesia Care (versus general anesthesia).

Our primary hypothesis is that preoperative and intraoperative placement of an active lavender-peppermint patch (vs. placebo patch) will result in a shorter time to discharge-readiness in the post-anesthesia care unit (PACU). Secondary hypotheses are that subjects randomized to active aromatherapy patch will have lower midazolam use intraoperatively (mg), lower intraoperative opioid use (morphine equivalents), lower supplemental intraoperative antiemetic use, longer time to first occurrence of PONV, lower rate and intensity of post-operative nausea or vomiting in PACU, lower rate of rescue antiemetic use in PACU, lower maximum pain intensity in PACU (0-10 numerical rating scale), and higher patient satisfaction in PACU (Likert scale).

3. Background Device Information

Aromatabs® are inhalational aromatherapy patches intended to self-adhere to a patient's gown or clothing and release pleasant odors over several hours (up to 8 hours, per manufacturer). The essential oils themselves do not contact with the patient's skin, since the patch is contained in a plastic envelope, and it is this plastic envelope that is affixed to the patient's gown or clothing. https://beekley.com/product-details/elequil-aromatabs-lavender-peppermint-373

The Aromatabs® patches will be stored in a secured cabinet in the study team office, following storage guidelines from the manufacturer. Each patch will be labeled in accordance with FDA regulations and institutional policies before use. Detailed records of receipt, use or disposition will be maintained by the Principal Investigator in accordance to FDA regulations and institutional policies.

This is study is not intended to promote nor market Aromatabs®.

4. Study Design

This is a prospective randomized controlled trial.

5. Discussion of Study Population

5.1 Study Characteristics

Number of Subjects: This study will enroll 70 patients. We anticipate that we will have at least 62 eligible and treated patients.

5.2 Inclusion and Exclusion Criteria

a) Inclusion Criteria

- Adult patients (≥ 18 years old)

- Port-a-Cath placement under Monitored Anesthesia Care
- Signed informed consent

b) Exclusion Criteria

- Patients undergoing other surgical procedures during Port-a-Cath placement (including explantation of a Port-a-Cath or other previous vascular access device)
- Patients requiring general anesthesia or those not eligible for MAC
- Patients allergic or sensitive to plants, essential oils, or any of the medications used in this study
- Patients with history of G6PD deficiency
- Patients with history of atrial fibrillation
- Patients unable to complete study questionnaires
- Patients who are completely anosmic or who have history of intolerance to aromatherapy
- Patients who have been taking any opioid daily for 90 days or more
- Patients who have been taking any benzodiazepine daily for 30 days or more

6. Subject Identification, Recruitment and Consent

6.1 Method of Subject Identification and Recruitment

Eligible subjects will be identified from within the patient population of the study site by members of the research team. Advertisements for study subjects are not anticipated.

6.2 Consent Process

Subjects deemed eligible to participate in the study will be explained in detail the purpose, nature, and procedures of the study, as well as the potential risks, benefits, and alternatives. They will be given a consent form to read and if they so choose, to discuss with friends, family, and other clinicians. They will be invited to ask questions and, after all questions are answered to their satisfaction, invited to sign the consent form. The Principal Investigator or another member of the research team will participate in the consenting process to ensure the subject

has full understanding of the procedure and risks. No study-specific procedure will be performed before the consent form is signed.

A separate consent document for the port-a-cath will be explained by your surgery team.

All consents will be signed electronically within the medical record on a MD Anderson Cancer Center password protected computer.

6.3 Costs to the Subject

None

6.4 Payment for Participation

There will be no payments for participation in the study.

6.5 Return of Individual Research Results

Individual research results will not be provided back to the subject.

7. Methods and Study Procedures

7.1 Pretreatment Evaluation

The PI/Co-PI/research coordinator of the study will evaluate the inclusion/exclusion criteria. Patients will be approached while in the preoperative area to discuss participation in the study. The PI/Co-PI/research coordinator will ensure that patients are properly informed about the study. All study related data will only be collected after the PI or Co-PI approves patient enrollment in the study and the patient has signed the consent.

7.2 Procedure

Prior to surgery, subjects will be randomized to either a lavender/peppermint patch (Elequis Aromatabs®, Beekley Corporation (https://beekley.com/aromatherapy/elequil-

aromatabs-aromatherapy-designed-for-the-clinical-setting) or a matching placebo patch. The assigned Aromatab® will be activated in the preoperative holding area by opening the outer plastic envelope and then affixed to a folded towel placed aside the subject's head, contralateral to the side of the planned surgery. The towel and Aromatab® will be transferred to the operating table with the subject as they arrive in the operative suite and maintained beside the subject's head throughout the surgery.

All subjects will have standard physiologic monitors placed on arrival to the operating room as per American Society of Anesthesiologists standards. They will have a nasal oxygen cannula or face mask placed to maintain adequate oxygenation. An anesthesia provider (Certified Registered Nurse Anesthetist and/or Physician Anesthesiologist) will be present with them continuously from the time they leave the preoperative holding area until the time that they reach the PACU, and a handoff is given to the receiving PACU nurse. Patients will be eligible to receive a maximum dose of 2 mg midazolam i.v. in the preoperative holding area just before transporting to the operative suite (standard of care, depending on patient's age, physiologic condition, and preference). The anesthesia provider will administer intraoperative doses of midazolam i.v. and opioid i.v. as needed, titrating to the desired level of sedation. The towel and Aromatab® will be discarded when the subject leaves the operating room. Prophylactic antiemetics will be administered per anesthesiologist clinical judgment, as Port-a-Cath placement is not known to carry a high risk of postoperative nausea and vomiting (PONV), and general anesthesia is not being administered. Further, midazolam itself is known to have an antiemetic effect, as reported by Grant et al. If subjects report experience nausea or vomiting during the procedure, rescue emetics will be administered as necessary and per standard of care.

Postoperatively, all subjects will be taken to the PACU and cared for by a PACU nurse in standard fashion until they are discharged. Under the current standard of care, the surgeon injects local anesthetic around the surgical wound, thus very few current outpatient Port-a-Cath patients require postoperative opioids. If subjects have breakthrough pain, postoperative opioids or other analgesics will be administered as necessary and per standard of care. If the subjects experience postoperative nausea or vomiting in PACU, rescue emetics will be administered as necessary and per standard of care. In the PACU, a research coordinator, research fellow, collaborator, or other member of the research team will assess patient's nausea/vomiting, pain intensity and satisfaction.

7.3 Training of Clinical Site Personnel

The PI will conduct a training session with all anesthesia collaborators. The anesthesia collaborators will view a video demonstrating preparation and positioning of the aromatherapy patch/placebo patch on a folded towel, and placement of that towel next to the patient's head.

7.4 Data Collected from EMR

- Demographics (e.g., BMI, age, gender, and ethnicity)
- Comorbidities (Charlson score)
- Dosing and type of preoperative, intraoperative, and postoperative medications
- Information regarding sedation management intraoperatively
- Sedation times (sedation start from placement of aromatab or placebo to procedure end)
- Procedure times (procedure start to procedure end)

7.5 Additional Data Collected by Research Coordinator

- Hospital Anxiety and Depression Score (HADS) recorded in preoperative holding area after subject has given consent
- Aldrete Parsap recovery scores, recorded every 15 minutes in PACU from patient arrival (Anesthesia End timepoint) until a Parsap score of 18 or higher
- Time in minutes from Anesthesia End to Aldrete Parsap score of 18 or higher
- Pain intensity using the Verbal Numeric Rating Scale (0: no pain and 10 worst pain ever) every 15 minutes from procedure end until a Parsap score of 18 or more is reached
- Nausea intensity using the Verbal Numeric Rating Scale (0: no nausea and 10 worst nausea ever) every 15 minutes from procedure end until a Parsap score of 18 or more is reached.

- Vomiting: The number of episodes of vomiting will be recorded every 15 minutes from procedure end until a Parsap score of 18 or more is reached.
- Patient satisfaction (Patient-Reported Outcome, Likert scale), assessed as soon as a Parsap score of 18 or more has been reached.
- Apfel Post-Operative Nausea and Vomiting Risk Score

8. Subject Withdrawals

Subjects may be withdrawn from the study for the following reasons:

1) Subject non-compliance with study procedures
2) Unacceptable adverse events (safety or tolerability)
3) The subject may withdraw from the study at any time and for any reason
4) Clinician decision that it is in the best interest of the subject to withdraw from the study

9. Safety and Reportable Events

9.1 Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to investigational product. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being. An Adverse Event that is related to the investigational device may be referred to as an Adverse Device Effect (ADE).

Unanticipated Adverse Device Effect (UADE): Any device related adverse event, the nature or severity of which is not consistent with or listed in the applicable product information (e.g., instructions for use, subject informed consent document, subject information brochure [if applicable], promotional literature) or any other unanticipated serious problem associated

with a device that relates to the rights, safety, or welfare of subjects. These are dichotomous outcomes.

Expected Adverse Events

The experimental treatment is generally recognized as safe. No adverse events are expected.

9.2 Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires medical or surgical intervention to prevent permanent impairment or damage

9.3 Recording Adverse Events

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of procedure through end of the study. Th PI will immediately conduct an evaluation of any unanticipated adverse device effect.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. All reported AEs must be recorded in the database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study treatment and the study procedure. This protocol will use common

terminology criteria for adverse events (CTCAE) version 4.0. For the AEs not characterized in the CTACE, the following definitions for rating severity of AEs will be used:

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate:	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe:	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported.

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction post-surgery, or are associated with customary, standard care of patients undergoing these procedures:

- Early post-operative pain (within 48hours post-index procedure) at the incision site and/or related to position on procedure table
- Post-anesthesia emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Electrolyte imbalance without clinical sequalea following endoscopic procedure, even if requiring correction

- Low grade temperature increase (≤38.3°C/≤101°F)
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

9.4 Responsibilities for Reporting Serious Adverse Events

The Investigator should record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable. The study period for reporting serious adverse events (e.g., from the time of signing consent to final study visit) should be indicated, who needs to be notified and the time frame for notification. If there are any specific reporting forms to be completed, this should be indicated here. The Investigator will comply with regulations and institutional review board (IRB) policy regarding the reporting of adverse events.

If the PI determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, the PI will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the PI makes this determination and the manufacturer shall be informed of any malfunctions or adverse device effects within 15 working days of PI acknowledgement of the event. PI may not resume a terminated investigation without IRB and FDA approval.

10. Risk/Benefit Assessment

10.1 Potential Risks

- Skin or eye irritation from the aromatic oils or other components of the patch

10.2 Protection Against Risks

- Appropriate patient selection
- Continual monitoring of the patient throughout the perioperative period
- Affixing of the aromatherapy patch to a towel placed next to the patient's head, rather than to the patient's gown or to their skin
- No direct contact with the oils themselves (safely contained in the plastic envelope of the Aromatab® patch itself)

10.3 Potential Benefits to Subjects

- Decreased sedation or drowsiness
- Less post-operative nausea
- Reduction in time spent in the PACU, more rapid fitness for discharge

10.4 Alternatives to Participation

- The patient may decline to participate, in which case standard of care Monitored Anesthesia Care will be provided

11. Confidentiality of Data and Information Storage

All study participants will be assigned a study number. The PI will maintain the key to the study number and medical record number in a password locked MD Anderson computer. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient data will be entered into a password protected electronic spreadsheet and online database (i.e., REDCap). Only the investigators, who have been invited to participate in the study and who are registered with the IRB, as well as have documented completion of all IRB and HIPAA regulations will have access to patient data, but not the medical record key.

Electronic records will be stored for 5 years after study conclusion on the institution's

password protected computer, after which time they will be deleted. If there is a breach in confidentiality or violation of IRB and HIPAA regulations, the IRB will be notified in a timely manner (within 7 days) and appropriate actions taken thereafter. All data used in the analysis and reporting of this investigation will be de-identified. Any photography shall be done in a discrete manner. Should images run the risk of enabling patient identification, identifying characteristics will be obscured electronically prior to publication.

In order to ensure compliance with the Health Insurance Portability and Accountability Act (HIPAA), all subjects enrolled in the study will be required to provide authorization to disclose Protected Health Information (PHI). This authorization will be included in the informed consent document as required by the IRB. In all study reports and in any resulting publications, subjects will not be referred to by their initials and/or study identification number.

12. Sample Determination and Data Analysis

12.1 Randomization

Once patients meet all inclusion criteria and after consenting, they will be randomized to receive either Aromatab® patch or placebo patch with a 1:1 allocation ratio. Concealment of treatment will occur until two hours prior to surgery. Patients and O.R. caregivers will not be blinded as to their study group (not feasible).

12.2 Sample Size Determination

This is a randomized controlled trial to compare the time to readiness for discharge from PACU (minutes) after Port-a-Cath placement surgery between the patients who are randomized to receive intraoperative aromatherapy (Aromatab® patch) versus placebo. We will enroll 70 patients, and we anticipate that we will have at least 62 eligible and treated patients. Patients will be randomized to receive either Aromatab® patch or placebo patch with a 1:1 allocation ratio. The primary objective of the study is to determine if patients randomized to receive Aromatab® patch will have a significantly shorter time to readiness

for discharge from PACU (minutes) after surgery when compared to patients who receive a placebo patch. The primary endpoint, time to readiness for discharge from PACU after surgery, is defined as the time interval in minutes, from the end of surgery to the time when a patient is evaluated as ready to be discharged from PACU. We observed from previous data on the patients treated with standard of care (same as placebo) that the mean PACU duration was 66.5 minutes with a standard deviation of 20.7. The study with 31 patients in each treatment arm will have 80% power to detect a difference of 15 minutes in mean time to readiness for discharge from PACU after surgery between 66.5 minutes for the placebo arm and 51.5 minutes for the aromatherapy arm assuming a common standard deviation of 20.7 using a two group t-test with a two-sided type I error rate of 0.05 (nQuery+nTerim 4.0).

12.3 Planned Statistical Analysis

We will summarize continuous demographics and clinical variables, such as age, surgery time, anesthesia time, amount of medication, time in PACU, and pain score, using means, standard deviations, medians, and ranges. Categorical demographic variables and clinical variables, such as gender, incidence, and intensity of PONV, incidence of antiemetic use in PACU, will be summarized through frequencies and percentages. Fisher's exact test or Chi-square test will be used to evaluate the association between two categorical variables of interest. Wilcoxon-rank sum test or t-test will be used to compare continuous outcomes such as time to readiness for discharge from PACU (minutes) after surgery between treatment groups. Linear/logistic regression model may be fitted to assess the effect of important covariates on the primary/secondary endpoints.

12.4 Data Collection and Management

All study data will either be collected on a paper case report form (CRF) (which will be entered into a computer database) or will be extracted directly from the EMR to the REDCap database. Each subject will be assigned a random number code and the key linking the code and the subject identifier will be stored on an MD Anderson password protected computer. All changes to the CRF will follow Good Clinical Practice guidelines. The

Research Manager is responsible for auditing the consistency of the data transcribed from the paper CRF to the computer. A protocol violation log will be maintained, and all protocol violations will be reported to the IRB.

Members of the research team are responsible for transferring the information to the appropriate CRFs. The PI is responsible for ensuring the forms are accurately completed at the time of, or as soon as possible after, the subject procedure or the availability of test results. The PI is required to sign the CRF on the appropriate page(s) to verify that she has reviewed the recorded data. Upon PI approval, CRFs will be entered into the password protected REDCap database for analysis.

The PI will not share any of the data collected in this study with the Sponsor.

13. References

1. Johansson E, Engervall P, Björvell H, Hast R, Björkholm M. Patients' perceptions of having a central venous catheter or a totally implantable subcutaneous port system-results from a randomised study in acute leukaemia. Support Care Cancer. 2009 Feb;17(2):137-43.
2. Giordano C, Pini Prato A, Casciaro R, Simonini A (2018) Dexmedetomidine Infusion Perioperative to Control Agitation in Non-intubated Young Patient with Cystic Fibrosis Undergoing Upper Arm Ultrasound Guided Totally Implantable Port-A-Cath Placement: A Case Report. Analg Resusc: Curr Res 7:1.
3. Chang DH, Hiss S, Herich L, Becker I, Mammadov K, Franke M, Mpotsaris A, Kleinert R, Persigehl T, Maintz D, Bangard C. Implantation of venous access devices under local anesthesia: patients' satisfaction with oral lorazepam. Patient Prefer Adherence. 2015 Jul 7;9:943-9.
4. Schaal NK, Brückner J, Wolf OT, Ruckhäberle E, Fehm T, Hepp P. The effects of a music intervention during port catheter placement on anxiety and stress. Sci Rep. 2021 Mar 11;11(1):5807.
5. McDaniel C, Burkett AM, Cormier M, Duvall J, Davis S, Gabriel L et al. PICC, The Music and Travel to the Port of Relaxation: The Effects of Music on Perceived Pain and Anxiety in Patients Receiving PICCs and Port-A-Caths. J Radiol Nurs, 28(1), 32-34.
6. Lv XN, Liu ZJ, Zhang HJ, Tzeng CM. Aromatherapy and the central nerve system (CNS): therapeutic mechanism and its associated genes. Curr Drug Targets. 2013 Jul;14(8):872-9.
7. Yuan R, Zhang D, Yang J, Wu Z, Luo C, Han L et al. Review of aromatherapy essential oils and their mechanism of action against migraines. J Ethnopharmacol. 2021 Jan 30;265:113326
8. Perry R, Terry R, Watson LK, Ernst E. Is lavender an anxiolytic drug? A systematic review of randomised clinical trials. Phytomedicine. 2012 Jun 15;19(8-9):825-35.
9. Wotman M, Levinger J, Leung L, Kallush A, Mauer E, Kacker A. The Efficacy of Lavender Aromatherapy in Reducing Preoperative Anxiety in Ambulatory Surgery

Patients Undergoing Procedures in General Otolaryngology. Laryngoscope Investig Otolaryngol. 2017 Nov 8;2(6):437-441.

10. Jaruzel CB, Gregoski M, Mueller M, Faircloth A, Kelechi T. Aromatherapy for Preoperative Anxiety: A Pilot Study. J Perianesth Nurs. 2019 Apr;34(2):259-264.
11. Beyliklioğlu A, Arslan S. Effect of Lavender Oil on the Anxiety of Patients Before Breast Surgery. J Perianesth Nurs. 2019 Jun;34(3):587-593.
12. Kim S, Kim HJ, Yeo JS, Hong SJ, Lee JM, Jeon Y. The effect of lavender oil on stress, bispectral index values, and needle insertion pain in volunteers. J Altern Complement Med. 2011 Sep;17(9):823-6.
13. Grigoleit HG, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. Phytomedicine. 2005 Aug;12(8):612-6.
14. Hines S, Steels E, Chang A, Gibbons K. Aromatherapy for treatment of postoperative nausea and vomiting. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD007598. DOI: 10.1002/14651858.CD007598.pub3. Accessed 27 September 2021.
15. Ahmadi Y, Rezaei J, Rezaei M, Khatony A. Comparison of the Effect of Inhalation Aromatherapy with 10% and 30% Peppermint Essential Oils on the Severity of Nausea in Abdominal Surgery Patients. Evid Based Complement Alternat Med. 2020 Apr 20;2020:5897465.
16. Maghami M, Afazel MR, Azizi-Fini I, Maghami M. The effect of aromatherapy with peppermint essential oil on nausea and vomiting after cardiac surgery: A randomized clinical trial. Complement Ther Clin Pract. 2020 Aug;40:101199.
17. Grant MC, Kim J, Page AJ, Hobson D, Wick E, Wu CL. The Effect of Intravenous Midazolam on Postoperative Nausea and Vomiting: A Meta-Analysis. Anesth Analg. 2016 Mar;122(3):656-663.
18. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg. 1970 Nov-Dec;49(6):924-34.
19. Aldrete JA. Modifications to the postanesthesia score for use in ambulatory surgery. J Perianesth Nurs. 1998 Jun;13(3):148-55.
20. Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, Zhang K, Cakmakkaya OS. Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth. 2012 Nov;109(5):742-53.

14. Appendixes

Calendar of Events

Data collection forms

Appendix 1: Calendar of Events

Visit Window	Screening	Intra-op	Post-op
Subject Recruitment	x		
Enrollment/Pt education	x		
Medical Record Documentation	x	x	x
CRF completion		x	x

Appendix 2: Data Collection Forms

ELIGIBILITY

Study #: _____
MRN: _____

Inclusion criteria

- Adult patients (≥18 years old) Yes / No
- Undergoing Port-a-Cath placement surgery under Monitored Anesthesia Care Yes / No
- Signed informed consent form Yes / No

Exclusion criteria

- Patients undergoing other surgical procedures during Port-a-Cath placement (including explantation of a Port-a-Cath or other previous vascular access device) Yes / No
- Patients requiring general anesthesia or those not eligible for MAC Yes / No
- Patients allergic or sensitive to plants, essential oils, or any of the medications used in this study Yes / No
- Patients with history of G6PD deficiency Yes / No
- Patients with history of atrial fibrillation Yes / No
- Patients unable to complete study questionnaires Yes / No
- Patients who are completely anosmic or who have history of intolerance to aromatherapy Yes / No
- Patients who have been taking any opioid daily for 90 days or more Yes / No
- Patients who have been taking any benzodiazepine daily for 30 days or more Yes / No

DEMOGRAPHIC AND PREOPERATIVE DATA

Study #: _____

MRN: _____

Age: _____

Sex: Female/Male

Ethnicity: (Circle all that applies)

Caucasian Black Hispanic Asian. Other

Height (cm): _____ Weight (kg): _____

Body Mass Index (BMI) _____

ASA (Circle one): 1 2 3 4

CURRENT CANCER (Circle all that applies)

Breast Malignant bone tumor Lung Urological Gastrointestinal Head and Neck Genitourinary Skin Central nervous system Lymphoma Leukemia Myeloma Other Unknown

MEDICAL HISTORY

Oncology History (other than primary) Yes/No

If yes, please circle all that applies:

Breast Malignant bone tumor Lung Urological Gastrointestinal Head and Neck Genitourinary Skin Central nervous system Lymphoma Leukemia Myeloma Other Unknown

Charlson Comorbidities

Myocardial infarction (+1)

Congestive heart failure (+1)

Peripheral vascular disease (+1)

Cerebrovascular disease (except hemiplegia) (+1)

Dementia (+1)

Chronic pulmonary disease (+1)

Connective tissue disease (+1)

Ulcer disease (+1)

Mild liver disease (+1)

Diabetes (without complications) (+1)

Diabetes with end-organ damage (+2)

Hemiplegia (+2)

Moderate or severe renal disease (+2)

Solid tumor (non-metastatic) (+2)

Leukemia (+2)

Lymphoma, multiple myeloma (+2)

Moderate or severe liver disease (+3)

Metastatic solid tumor (+6)

AIDS (+6)

(Check all that apply)

Comorbidity Score

_____

Please select a patient age range 50 - 59 (+1)

60 - 69 (+2)

70 - 79 (+3)

80 - 89 (+4)

90 - 99 (+5)

Age Score

_____

Total Charlson Comorbidities Score

_____

History of Smoking (Please check appropriate box.)

□ Current smoker

□ Quit smoking: within 30 days of surgery

□ Quit smoking: 1 month to 1 year before surgery

□ Quit smoking: more than 1 year before surgery

□ Never smoked

PREOPERATIVE ANALGESIA

Pain Intensity (Circle one): 0 1 2 3 4 5 6 7 8 9 10 N/A

(Verbal numeric rating scale: 0: no pain – 10: worst pain possible)

Preoperative Opioids Yes_____No_____ Prescribed since when?_____

Fentanyl amount/day (mcg) _____ (Please enter 0 if not taking)

Hydrocodone amount/day (mg) _____ (Please enter 0 if not taking)

Hydromorphone amount/day (mg) _____(Please enter 0 if not taking)

Methadone amount/day (mg) _____ (Please enter 0 if not taking)

Morphine amount/day (mg) _____ (Please enter 0 if not taking)

Oxycodone amount/day (mg) _____ (Please enter 0 if not taking)

Oxymorphone amount/day (mg) _____ (Please enter 0 if not taking)

Tramadol amount/day (mg) _____ (Please enter 0 if not taking)

Codeine amount/day (mg) _____ (Please enter 0 if not taking)

Other Opioids (Write name and dose) _____

Preoperative Morphine Equivalent Daily Dose:_____

Preoperative NSAIDs Yes_____No_____(Check all that apply)

Ibuprofen amount/day (mg) _____ (Please enter 0 if not taking)

Naproxen amount/day (mg) _____ (Please enter 0 if not taking)

Meloxicam amount/day (mg) _____ (Please enter 0 if not taking)

Ketorolac amount/day (mg) _____ (Please enter 0 if not taking)

Diclofenac amount/day (mg) _____ (Please enter 0 if not taking)

Celecoxib amount/day (mg) _____ (Please enter 0 if not taking)

Other preoperative NSAID (Write name and dose)

_____

Preoperative Gabapentinoids Yes_____No_____(Check all that apply)

Gabapentin amount/day (mg) _____ (Please enter 0 if not taking)

Pregabalin amount/day (mg) _____ (Please enter 0 if not taking)

Preoperative Acetaminophen Yes_____No_____
If yes, amount/day (mg)_____

Preoperative benzodiazepines Yes_____No_____ Prescribed since when?_____
Diazepam amount/day (mg) _____ (Please enter 0 if not taking)
Alprazolam amount/day (mg) _____ (Please enter 0 if not taking)
Triazolam amount/day (mg) _____ (Please enter 0 if not taking)
Lorazepam amount/day (mg) _____ (Please enter 0 if not taking)
Clonazepam amount/day (mg) _____ (Please enter 0 if not taking)
Midazolam amount/day (mg)_____(Please enter 0 if not taking)

Preoperative antiemetics
Ondansetron amount/day (mg) _____ (Please enter 0 if not taking)
Granisetron amount/day (mg) _____ (Please enter 0 if not taking)
Aprepitant amount/day (mg) _____(Please enter 0 if not taking)
Promethazine amount/day (mg) _____ (Please enter 0 if not taking)
Droperidol amount/day (mg) _____ (Please enter 0 if not taking)
Metoclopramide amount/day (mg) _____ (Please enter 0 if not taking)
Scopolamine patch amount/day (mg) _____ (Please enter 0 if not taking)

Apfel-Score for PONV

Gender	Male 0 / Female: +1
Smoking status	Smoker 0 / Non-smoker +1
History of motion sickness or PONV	No 0 / Yes +1
Use of postoperative Opioids	No: 0 / Yes +1

Total points:_____

HOSPITAL ANXIETY AND DEPRESSION SCALE

Study#: _____

MRN: _____

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

1. I feel tense or 'wound up'
    - Not at all
    - From time to time, occasionally
    - A lot of the time
    - Most of the time
2. I get a sort of frightened feeling as if something awful is about to happen.
    - Not at all
    - A little but it doesn't worry me
    - Yes, but not too badly
    - Very definitely and quite badly
3. Worrying thoughts go through my mind
    - Only occasionally
    - From time to time, but not too often
    - A lot of the time
    - A great deal of the time
4. I can sit at ease and feel relaxed
    - Definitely
    - Usually
    - Not Often
    - Not at all
5. I get a sort of frightened feeling like 'butterflies' in the stomach.
    - Not at all
    - Occasionally
    - Quite Often
    - Very Often
6. I feel restless as I have to be on the move.
    - Not at all
    - Not very much
    - Quite a lot
    - Very much indeed
7. I get sudden feelings of panic.
    - Not at all
    - Not very often
    - Quite often

- Very often indeed

8. I still enjoy the things I used to enjoy.
   - Definitely as much
   - Not quite as much
   - Only a little
   - Hardly at all
9. I can laugh and see the funny side of things as much as I always could.
   - Not quite so much now
   - Definitely not so much now
   - Not at all
10. I feel cheerful.
   - Most of the time
   - Sometimes
   - Not often
   - Not at all
11. I feel as if I am slowed down.
   - Not at all
   - Sometimes
   - Very often
   - Nearly all the time
12. I have lost interest in my appearance.
   - I take just as much care as ever
   - I may not take quite as much care
   - I don't take as much care as I should
   - Definitely
13. I look forward with enjoyment to things.
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all
14. I can enjoy a good book or radio or TV program.
   - Often
   - Sometimes
   - Not often
   - Very seldom

SEDATION AND INTRAOPERATIVE DATA

Study #: _____
MRN: _____

Randomization: Active treatment / placebo

Date of Surgery. ____/____/____
Procedure Start Time: _____:_____. Procedure End Time: _____:_____.
Duration of Surgery (min): _____.

Sedation
Sedation Start Time (placement of patch): _____:_____.
Sedation End Time (removal of patch): _____:_____.
Duration of sedation (min): _____.

Midazolam given: Yes / No If yes: total dose (mg): _____

Analgesia
Intraoperative Acetaminophen: Yes / No If yes: total dose (mg): _____
Intraoperative Opioids
Fentanyl: Yes / No If yes: total dose (mg): _____
Hydromorphone: Yes / No If yes: total dose (mg): _____
Other (Name and dose): _____

Rescue antiemetics
Dexamethasone: Yes / No If yes: total dose (mg): _____
Ondansetron: Yes / No If yes: total dose (mg): _____.
Granisetron: Yes / No If yes: total dose (mg): _____
Promethazine: Yes / No If yes: total dose (mg): _____
Propofol: Yes / No If yes: total dose (mg): _____

Any AE/SAE: _____

POSTOPERATIV DATA – PACU

Study #: _____
MRN: _____

Time of admission to PACU: _____/_____
Time of discharge from PACU: _____/_____

Verbal numerical Pain Score, Aldrete Parsap Recovery Score, nausea intensity and the number of vomiting episodes are recorded every 15 minutes from Anesthesia end until a Parsap Score ≥ 18 is reached. Patient Satisfaction is assessed as soon as a Parsap Score ≥ 18 has been reached.

Aldrete Parsap Recovery Score

Indices	Task	Score
Activity	Able to move four extremities voluntarily or on command Able to move two extremities voluntarily or on command Unable to move extremities voluntarily or on command	2 1 0
Respiration	Able to breathe deeply and cough freely Dyspnea, limited breathing or tachypnea Apneic or on mechanical ventilator	2 1 0
Circulation	BP ± 20% of pre-anesthetic level BP ± 20 - 49% of pre-anesthetic level BP ± 50% of pre-anesthetic level	2 1 0
Consciousness	Fully awake Arousable on calling Not responding	2 1 0
O_2 Saturation	Able to maintain O_2 saturation > 92% on room air Needs O_2 inhalation to maintain O_2 saturation > 90% O_2 saturation <90% even with O_2 supplement	2 1 0
Dressing	Dry and clean Wet but marked and not increasing Growing area of wetness	2 1 0
Pain	Pain free Mild pain handled by oral medication Severe pain requiring parenteral medication	2 1 0
Ambulation	Able to stand up and walk straight Vertigo when erect Dizziness when supine	2 1 0
Fasting-Feeding	Able to drink fluids Nauseated Nausea and vomiting	2 1 0
Urine Output	Has voided Unable to void but comfortable Unable to void and uncomfortable	2 1 0

T1: _____/_____ Score: _____
T2: _____/_____ Score: _____ if patient is still admitted to PACU
T3: _____/_____ Score: _____ if patient is still admitted to PACU
T4: _____/_____ Score: _____ if patient is still admitted to PACU
T5: _____/_____ Score: _____ if patient is still admitted to PACU
T6: _____/_____ Score: _____ if patient is still admitted to PACU
T7: _____/_____ Score: _____ if patient is still admitted to PACU
T8: _____/_____ Score: _____ if patient is still admitted to PACU
T9: _____/_____ Score: _____ if patient is still admitted to PACU
T10: _____/_____ Score: _____ if patient is still admitted to PACU

Pain intensity (VNRS, 0: no pain – 10: worst pain possible)
T1: _____/_____ Score: _____
T2: _____/_____ Score: _____ if patient is still admitted to PACU
T3: _____/_____ Score: _____ if patient is still admitted to PACU
T4: _____/_____ Score: _____ if patient is still admitted to PACU
T5: _____/_____ Score: _____ if patient is still admitted to PACU
T6: _____/_____ Score: _____ if patient is still admitted to PACU
T7: _____/_____ Score: _____ if patient is still admitted to PACU
T8: _____/_____ Score: _____ if patient is still admitted to PACU
T9: _____/_____ Score: _____ if patient is still admitted to PACU
T10: _____/_____ Score: _____ if patient is still admitted to PACU

Postoperative Analgesics
Acetaminophen: Yes / No If yes dose (mg)_____ route: po/iv

NSAIDs
Celecoxib: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Ketorolac: Yes / No If yes dose (mg)_____ route: po/iv

Ibuprofen: Yes / No If yes dose (mg)_____ route: po/iv

Naproxen: Yes / No If yes dose (mg)_____ route: po/iv

Other: Yes / No If yes dose (mg)_____ route: po/iv

Postoperative Opioids
Fentanyl: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Hydromorphone: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Morphine: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Hydrocodone: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Tramadol: Yes / No If yes dose (mg)_____ route: po/iv____time first dose:____:____

Oxycodone: Yes / No If yes dose (mg)_____ route: po/iv___time first dose:___:___

Codeine: Yes / No If yes dose (mg)_____ route: po/iv___time first dose:___:___

Other: Yes / No If yes dose (mg)_____ route: po/iv___time first dose:___:___

Nausea intensity (VNRS, 0: no nausea – 10: worst nausea possible)
T1: _____/_____ Score: _____
T2: _____/_____ Score: _____ if patient is still admitted to PACU
T3: _____/_____ Score: _____ if patient is still admitted to PACU
T4: _____/_____ Score: _____ if patient is still admitted to PACU
T5: _____/_____ Score: _____ if patient is still admitted to PACU
T6: _____/_____ Score: _____ if patient is still admitted to PACU
T7: _____/_____ Score: _____ if patient is still admitted to PACU
T8: _____/_____ Score: _____ if patient is still admitted to PACU
T9: _____/_____ Score: _____ if patient is still admitted to PACU
T10: _____/_____ Score: _____ if patient is still admitted to PACU

Vomiting: Yes / No Time of first occurrence of vomiting. _____:_____
Vomiting episodes
T1: _____/_____ Number: _____
T2: _____/_____ Number: _____ if patient is still admitted to PACU
T3: _____/_____ Number: _____ if patient is still admitted to PACU
T4: _____/_____ Number: _____ if patient is still admitted to PACU
T5: _____/_____ Number: _____ if patient is still admitted to PACU
T6: _____/_____ Number: _____ if patient is still admitted to PACU
T7: _____/_____ Number: _____ if patient is still admitted to PACU
T8: _____/_____ Number: _____ if patient is still admitted to PACU
T9: _____/_____ Number: _____ if patient is still admitted to PACU
T10: _____/_____Number: _____ if patient is still admitted to PACU

Ondansetron: Yes / No If yes: dose (mg)_____ route: po/iv___time first dose:___:___
Granisetron: Yes / No If yes: dose (mg)_____ route: po/iv___time first dose:___:___
Promethazine: Yes / No If yes: dose (mg)_____ route: po/iv___time first dose:___:___
Other:_____ Yes / No If yes: dose (mg)_____ route: po/iv___time firstdose:___:___

Likert Scale for patient satisfaction (circle one)

Satisfaction level	Score
Very much satisfied	5
Somewhat satisfied	4
Undecided	3
Not really satisfied	2
Not at all satisfied	1

There are no screening tests or blood draws require to enter the study.

We expect 70 patients here at MD Anderson Cancer Center to agree and participate in the study.

Prior to surgery, subjects will be randomized 1:1 to either a lavender/peppermint patch of Elequis Aromatabs®, or a matching placebo patch.