Effects of Aromatherapy on Chemotherapy-Induced Nausea and Vomiting: A Control Trial

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1) Protocol Title

Effects of Aromatherapy on Chemotherapy-Induced Nausea and Vomiting: A Control Trial

2) IRB Review History*

Not applicable

3) Objectives*

Primary:

To investigate the effect of aromatherapy inhalation on chemotherapy-induced nausea and vomiting (CINV) and the use of antiemetics among patients with cancer receiving moderate to high emetogenic outpatient chemotherapy regimens.

Secondary:

To investigate the effect of aromatherapy inhalation on resilience, psychological distress symptoms (e.g., stress, anxiety, and depression), and quality of life among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient.

Aims & Hypotheses:

(1) To investigate the effect of aromatherapy inhalation on CINV among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient.
   (a) Outpatient patients with cancer using aromatherapy inhalation will reduce the discomfort associated with their CINV while receiving moderate to high emetogenic chemotherapy.

(2) To investigate the effect of aromatherapy inhalation on the use of antiemetics among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient.
   (a) Outpatient patients with cancer using aromatherapy inhalation will reduce the use of antiemetics while receiving moderate to high emetogenic chemotherapy.

(3) To investigate the effect of aromatherapy inhalation on resilience among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient.
   (a) Outpatient patients with cancer using aromatherapy inhalation will have higher levels of resilience while receiving moderate to high emetogenic chemotherapy.

(4) To investigate the effect of aromatherapy inhalation on psychological distress symptoms of stress, anxiety, and depression among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient.
   (a) Outpatient patients with cancer using aromatherapy inhalation will reduce their psychological distress symptoms of stress, anxiety, and depression while receiving moderate to high emetogenic chemotherapy.

(5) To investigate the effect of aromatherapy inhalation on quality of life among patients with cancer receiving moderate to high emetogenic chemotherapy

regimens outpatient.

(a) Outpatient patients with cancer using aromatherapy inhalation will have a higher level of quality of life while receiving moderate to high emetogenic chemotherapy.

4) **Background***

Forty percent of patients with cancer undergoing moderate to high emetogenic chemotherapy will experience chemotherapy-induced nausea and vomiting (CINV) (Yokoe et al., 2018). Even with medical and treatment advancements, CINV remains a significant clinical challenge for patients undergoing chemotherapy (American Cancer Society, 2020; Escobar et al., 2015). Approximately 71% of breast patients with cancer experienced nausea despite being prescribed antiemetic therapy, and patients consistently ranked nausea over vomiting as the worst side effect associated with chemotherapy (Aapro, 2018; Escobar et al., 2015). However, healthcare providers frequently underestimate the prevalence of acute and delayed CINV, which has left patients' CINV unmanaged.

The American Cancer Society guidelines recommend that patients use antiemetic medicine at the first sign of nausea to prevent vomiting (Hesketh et al., 2017). However, physiology and risk factors that contribute to nausea are not understood clearly, and many of the antiemetic agents currently available do not relieve patients' CINV and may produce additional adverse side effects (Aapro, 2018; Herz, 2005). Previous CINV research has been conducted in patients who received highly emetogenic chemotherapy (e.g., cisplatin, doxorubicin plus cyclophosphamide, epirubicin plus cyclophosphamide, and anthracycline-cyclophosphamide (AC) treatments) (Escobar et al., 2015), and few studies have been conducted with moderately emetogenic chemotherapy (e.g., carboplatin, irinotecan, and oxaliplatin) (Nam, 2018). Additionally, research has indicated that patients' and healthcare providers' have misperceptions (e.g., cultural difference and level of understanding) of nausea and vomiting (Molassiotis et al., 2007; Yamaguchi et al., 2009). The patients' and healthcare providers' misperceptions may increase CINV, highlighting the need for a patient self-reporting mechanism (Escobar et al., 2015; Grunberg et al., 2004).

Literature suggests that essential oil aromatherapy (e.g., peppermint, lemon, and lavender) can alleviate nausea and vomiting in a variety of patient populations (e.g., oncology, pregnant, and postoperative patients) (Eghbali, Varaei, Yekaninelad, Mohammadxadeh, & Shahi, 2017; Howard & Hughes, 2008; Kia, Safajou, Shahnazi, & Nazemiyeh, 2014; Louis & Kowalski, 2002; Lua & Zakaria, 2012). A recent study showed that the use of aromatherapy, in addition to antiemetic therapy, can reduce CINV during the acute phase of chemotherapy (Farahani et al., 2019). Additionally, aromatherapy is recommended as a complementary treatment for postoperative nausea and vomiting due to its safe and rapid onset, ease of administration, minimal drug interaction, and side effects that have shown to reduce anxiety and depression and increase patients well-being (Duff, 2009; Louis & Kowalski, 2002).

The use of aromatherapy in a controlled environment can prevent or reduce patients' CINV and psychological distress symptoms after cancer

chemotherapy without utilizing antiemetic medications (Eghbali et al., 2017; Herz, 2005; Hodge, McCarthy, & Pierce, 2014). Similar to aromatherapy, resilience, a person's ability to cope positively and adapt to their cancer diagnosis and treatment has shown to reduce symptoms such as anxiety and depression and increase the patient's well-being (Matzka et al., 2016). This study aims to investigate the effect of aromatherapy inhalation as a complimentary non-pharmaceutical intervention on CINV, resilience, and the use of antiemetics among patients with cancer receiving moderate to high emetogenic chemotherapy regimens outpatient. The study team used the National Comprehensive Cancer Network (NCCN) guidelines (NCCN,2020) to identify moderate and high emetogenic chemotherapy regimens.

5) Inclusion and Exclusion Criteria*

Inclusion includes:

- 18 years of age or older
- able to read and speak English or Spanish
- able to and willing to give informed consent
- currently undergoing moderate and high emetogenic chemotherapy (adjuvant or neoadjuvant)
- receiving three or more remaining cycles of chemotherapy
- symptoms of nausea or vomiting after the first chemotherapy infusion

Exclusion includes:

- unable or unwilling to give informed consent
- sensitivity to essential oils*
- olfactory disorders
- receiving chemotherapy for the first time
- undergoing low emetogenic chemotherapy regimens
- patients with hormone-sensitive cancers
- timely request of treating provider
- presently participating in an ongoing research study

(*) sensitivity to essential oils will be assessed when the study team members screen and recruit a potential participant.

6) Number of Subjects*

The total single-site sample size is 100.

7) Study-Wide Recruitment Methods*

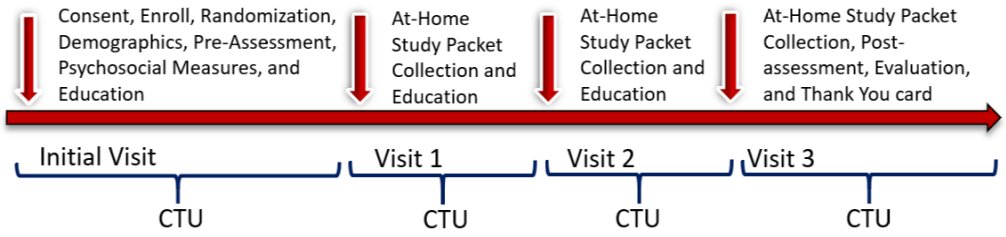
Not applicable, for study’s single site recruitment methods see section #24.

8) Study Timelines*

This research study can feasibly be completed in a proposed two-year time frame.

The duration period per participant will vary depending on their prescribed chemotherapy regimen, ranging from four to 12 weeks. If a participant is admitted to an SCCC's inpatient unit or has their chemotherapy temporally held during their study period, the study procedures will be postponed until their next scheduled outpatient CTU visit, see Table 1. The study will recruit 100 patients from a wide variety of racial and ethnic groups, gender, and over the age of 18.

Table 1. *Participant Study Duration*



Study Endpoints*

a) Primary Outcome
   a) **Outcome Measure Title**: Reduction in severity of CINV
   b) **Outcome Measure Description**: Assessed by the mean score of the Antiemesis (MAT) tool, which measures acute and delayed CINV across patients' chemotherapy regimens.
   c) **Outcome Measure Timeframe**: Data tool collected during study visits 1, 2, 3, and 4.

b) Secondary Outcome
   a) **Outcome Measure Title**: Reduction in Antiemetic Use
   b) **Outcome Measure Description**: Assessed by the mean score of antiemetics diary, which measures the usage frequency (date and time) and type (name) of antiemetic medications.
   c) **Outcome Measure Timeframe**: Data diary collected during study visits 1, 2, 3, and 4.

c) Exploratory Outcome
   a) **Outcome Measure Title**: Improved Resilience
   b) **Outcome Measure Description**: Assessed by the mean score of the Connor-Davidson Resilience Scale (CD-RISC), which measures the participants' resilience pre and post the intervention.
   c) **Outcome Measure Timeframe**: Data collected at baseline and final visit.

d) Exploratory Outcome
   a) **Outcome Measure Title**: Reduction in Psychological Distress Symptoms
   b) **Outcome Measure Description**: Assessed by the mean score of the psychological distress symptoms visual analog scale the patients' anxiety, stress, and depression at pre-and post-assessment.
   c) **Outcome Measure Timeframe**: Data collected at baseline and final visit.

e) Exploratory Outcome
   a) **Outcome Measure Title**: Improved Quality of Life
   b) **Outcome Measure Description**: Assessed by the mean score of Functional Assessment of Chronic Illness Therapy General (FACIT-G), which measures the

patients' quality of life and well-being at pre-and post-assessment.

c) **Outcome Measure Timeframe**: Data collected at baseline and final visit.

The study objectives and endpoints were selected because (a) more research is necessary to understand the effects of aromatherapy on moderate and high emetogenic chemotherapy regimens in an outpatient setting; (b) the literature suggests that CINV has a relationship with decreased quality of life and increased antiemetic usage and psychological distress symptoms; (c) the relationship between CINV and resilience has not been established. However, literature has shown a relationship between resilience and a reduction in psychological distress symptoms and improved quality of life.

9) Procedures Involved*

The study will continue as follows:

Initial visit

The study's initial visit will occur while patients are in the CTU or fast-track area as they get ready for treatment. The entire study will be explained to the patient when they are preparing for their chemotherapy regimen in a comfortable area provided by the SCCC. After answering the potential participants' questions, the study team member will go through the study's informed consent process if the participant is interested and willing to consent. The potential participants will have time to review and discuss informed consent. After the patient signs the informed consent, the participant will be randomized to the control or the intervention arm.

On the same day, the study team member will meet the participant in the CTU while they receive their infusion and provide both the control and intervention groups, access to complete, via iPad or laptop, the electronic pre-assessment and demographic form, psychological distress VAS, resilience scale, FACIT-G, and a study packet that includes the Antiemesis (MAT) tool, antiemetic diary or antiemetic/aromatherapy diary. The study packet will be completed and returned to the study team member on the participants' next scheduled chemotherapy infusion. The study team member will explain to the participants how to use the MAT tool and how to fill the antiemetic diary or antiemetic/aromatherapy diary. The study team member will go through the instructions to ensure that they understand the forms and how to complete them.

Arm 1 - Control group:

Participants in the control group will receive standard medical care, consisting of antiemetic medicine at the first sign of CINV on a schedule as prescribed by the healthcare provider. The study team member will review with the participant how to use the weekly study packet (e.g., MAT tool and antiemetic diary) and explain that a study team member will collect the packet on their next scheduled chemotherapy infusion.

Arm 2 - Intervention group:

Participants in the intervention group will receive an aromatherapy inhaler for complementary use with their antiemetic medication. Participants will be encouraged to use the aromatherapy inhaler at the first sign of CINV before taking their antiemetic medications that are labeled “as needed”. The interventional group will be instructed that one normal inhale is equivalent to one dose of aromatherapy and must report essential oils sensitivity to a study team

member. The participant will be withdrawn from the study if essential oils sensitivity is identified. Aromatherapy will be used as often as needed or whenever CINV is encountered. Participants are advised to take their prescribed antiemetic medications that are labeled “as needed” as directed by their healthcare provider if they find insufficient comfort change in their CINV after using the aromatherapy. The study team member will explain to the participants that they will need to fill out the MAT tool and antiemetic/aromatherapy diary. And study team member will collect the packet on their next scheduled chemotherapy infusion.

Visit 1: Participants' visit one will take place on their next scheduled chemotherapy infusion – i.e., the participants' first chemotherapy cycle during their study period.

Arm 1 - Control group:
A study team member and participant will meet during the participant's scheduled CTU appointment to collect their MAT tool and antiemetic diary. During this interaction, the study team member will reinforce instructions and answer any participant's questions, concerns, or confusion regarding the MAT tool and antiemetic diary. A new study packet will be provided to the participants.

Arm 2 - Interventional group:
A study team member and participant will meet during the participant's scheduled CTU appointment to collect their MAT tool and antiemetic/aromatherapy diary. During this interaction, the study team member will reinforce instructions and answer any participant's questions, concerns, or confusion regarding the aromatherapy inhaler, MAT tool, and antiemetic/aromatherapy diary. A new study packet and an aromatherapy inhaler, if necessary, will be provided to the participants.

Visit 2: Participants' visit two will take place on their next scheduled chemotherapy infusion – i.e., the participants' second chemotherapy cycle during their study period.

Arm 1 - Control group:
A study team member and participant will meet during the participant's scheduled CTU appointment to collect their MAT tool and antiemetic diary. During this interaction, the study team member will reinforce instructions and answer any participant's questions, concerns, or confusion regarding the MAT tool and antiemetic diary. A new study packet will be provided to the participants.

Arm 2 - Interventional group:
A study team member and participant will meet during the participant's scheduled CTU appointment to collect their MAT tool and antiemetic/aromatherapy diary. During this interaction, the study team member will reinforce instructions and answer any participant's questions, concerns, or confusion regarding the aromatherapy inhaler, MAT tool, and antiemetic/aromatherapy diary. A new study packet and an aromatherapy inhaler, if necessary, will be provided to the participants.

Visit 3: Participants' visit three will take part on their next scheduled chemotherapy infusion – i.e., the participants' third chemotherapy cycle during their study period. A study team member

will give the participant access to complete the following assessments via iPad or laptop: post-assessment and demographic form, psychological distress VAS, resilience scale, and FACIT-G.

Arm 1 - Control group:

A study team member and participant will meet during the participants' scheduled CTU appointment to collect their final MAT tool and antiemetic diary. During this interaction, the study team member will assess the participant's study experience and provide the participant with a thank you card appreciation for their study participation.

Arm 2 - Interventional group:

A study team member and participant will meet during the participants' scheduled CTU appointment to collect their final MAT tool and antiemetic/aromatherapy diary. During this interaction, the study team member will assess the participant's study experience and provide the participant with a thank you card appreciation for their study participation.

If a participant is admitted to an SCCC's inpatient unit or has their chemotherapy temporally held during their study period, the study procedures will be postponed until their next regularly scheduled outpatient CTU visit. Participants' known admissions will be noted in the respective participant's study notes.

Table 2

Participant's Study Period and Associated Assessments

Timepoints	**1**	**2**	**3**	**4**
Visits	Initial	1	2	3 (Final)
Assessments collected on:				
Demographic	X*			
Pre-assessment	X*			
Psychological distress symptoms (VAS)	X*			X*
Resilience	X*			X*
FACIT-G	X*			X*
MAT tool		X	X	X
Antiemetic diary		X	X	X
Antiemetic/Aromatherapy diary (intervention group only)		X	X	X
Post-assessment				X*

Note: (*) indicates measures where data are entered directly in REDCap.

Interventions and Assessment Instruments:

Pre-Assessment and Demographic Checklist:

The participants will complete a pre-assessment and demographic checklist that assesses their demographic information (e.g., race, ethnicity, age, and education level), essential oils sensitivity, and risk factors of CINV. The pre-assessment demographic checklist will provide the descriptive characteristics of the study's sample population.

- Additional data, such as medical history (e.g., diagnoses, allergies, medications, cancer history, and treatment regimen), family history, and recent outpatient and inpatient clinic or hospital visits, will be extracted from the electronic health record.

Aromatherapy Inhaler (Arm 2 – Intervention Only):

The study's aromatherapy inhaler can be used when participants' have their first sign of CINV and as needed. The aromatherapy inhaler contains a proprietary blend of peppermint, spearmint, lavender, and ginger essential oils that can last up to 6 months. Participants will twist open the cap, hold the inhaler below their nose, and take deep breaths to activate the aromatherapy inhaler. Once the participant is done, they will close the aromatherapy inhaler to turn it off. The aromatherapy vapors can be safely inhaled for as long as it takes to provide comfort and relief for the patient. There are no "limits" or duration restrictions for any essential oils in the blend. The aromatherapy inhalation amount can vary from brief intermittent use to continuous inhalation over several minutes. The aromatherapy inhaler has unlimited uses with no time limits. One inhalation of aromatherapy is equivalent to one dose. There are no known contraindications. At each study visit, the study team member will offer the participant a replacement aromatherapy inhalation device.

Antiemetic/Aromatherapy Diary (Arm 2 - Intervention Only):

The antiemetic/aromatherapy diary will allow the participants to record their weekly usage (date and time) of aromatherapy and antiemetic uses and evaluate the aromatherapy and type (name) of antiemetic medications. The evaluation will assess the effects of the aromatherapy on CINV by capturing the number of inhalations per nausea episode and asking the participants, 'Did the aromatherapy take away your nausea?' answers include: 'it took away my nausea completely' to 'it had no effect on my nausea.' If the participants cannot get relief from the aromatherapy, the participants will take the prescribed antiemetic, and the participants will document the type of antiemetic medication they needed.
Additionally, there is a space to name other complementary methods used to relieve CINV and describe how the CINV was controlled in the antiemetic/aromatherapy diary.

MAT Tool:

The Antiemesis (MAT) tool created by the Multinational Association of Supportive Care in Cancer (Dranisaris et al., 2017) is a user-friendly and reliable tool designed to measure acute and delayed CINV across patients entire chemotherapy regimen. The MAT tool is available in English and Spanish languages. The MAT tool consists of eight items that assess participants' CINV (i.e., occurrence, duration, and frequency). Four items assess the participants' acute phase (i.e., first 24 hours after receiving chemotherapy), and the last four items assess the delayed phase (i.e., day 2 to day 4 after chemotherapy treatment). The MAT tool has been used as a communication tool to facilitate discussions about their CINV to their healthcare providers (Alafafsheh & Ahmad, 2016; Molassiotis et al., 2007; Yamaguchi et al., 2009). This MAT tool has shown good reliability and validity, with Cronbach alpha of 0.77-0.97 in 1200 patients with cancer (Alafafsheh & Ahmad, 2016; Dranisaris et al., 2017; Molassiotis et al., 2007; Yamaguchi et al., 2009).

Antiemetic Diary (Arm 1 - Control Only):

The antiemetic diary allows the participants to record their usage (date and time) and type (name) of antiemetic medications. Additionally, there is a space to name other

complementary methods used to relieve CINV and describe how the CINV was controlled in the antiemetic diary.

Resilience Scale:

The Connor-Davidson Resilience Scale (CD-RISC) will assess the participants' resilience pre and post the intervention (Burns & Anstey, 2010). For this study, we will use the 10-item questionnaire that includes questions such as: are you 'able to adapt to change,' 'can (you) deal with whatever comes,' to 'can handle unpleasant feelings.' This scale has shown good reliability and validity, with Cronbach alpha of 0.88 in 343 patients with cancer and 122 breast patients with cancer (Matzka, Mayer, Köck-Hódi, Moses-Passini, Dubey, Jahn, … & Eicher, 2016; Scali, Gandubert, Ritchie, Soulier, Ancelin, Chaudieu, & Uddin, 2012).

Psychological Distress Symptoms:

A visual analog scale will be used to assess the patients' psychological distress symptoms of anxiety, stress, and depression at pre and post-assessment. Three individual visual analog scales of anxiety, stress, and depression will be measured on a 0 to 10 scale over the past 7-days (Benedetto, & Sheehan, 2014; Labaste et al., 2019; Lesage, Berjot, & Deschamps, 2012). The scale ranged from "0" (no anxiety, stress, and depression) to "10" (worst anxiety, stress, and depression). Visual analog scale is an accurate and sensitive tool to rate subjective symptoms. The visual analog scale has been found to be less burdensome for research participants. Studies have demonstrated that visual analog scale ratings were a reliable and validated instrument used to assess anxiety, stress, depression, and other symptoms, in a variety of patient populations (Benedetto, & Sheehan, 2014; Labaste et al., 2019; Lesage, Berjot, & Deschamps, 2012).

Quality of life:

Functional Assessment of Chronic Illness Therapy General (FACIT-G) measures patients' quality of life and well-being on a 27-item, four dimensions of health: physical, functional, social, and emotional well-being (Cella et al., 1993). The study will assess the patients' quality of life and well-being at pre and post-assessment timepoints. Questions range from 'I am forced to spend time in bed,' 'I feel close to my friends,' 'I worry about dying,' to 'I am able to enjoy life.' FACIT-G is a reliable and psychometric sound instrument with a Cronbach alpha of >0.89 that has been used in a variety of patients with cancer (Cella, 2012; Kin-Fong Cheng, 2006; Thomas, Pendey, Ramdas, Sebastian, & Nair, 2004).

Post-Assessment Questionnaire:

The participants will complete a post-assessment questionnaire on their final chemotherapy infusion. The post-assessment will evaluate the study and its instruments/tools. Questions range from 'Was the MAT tool easy to use,' 'Was the antiemetic diary easy to use,' to 'How likely are you to continue using aromatherapy.' The intervention group will be asked additional evaluation questions about the inhaler, the effects of the aromatherapy, and comments/suggestions.

10) Data and Specimen Banking*

☒ This section is not applicable. This research is not banking data or specimens for future use.

11) Data Management*

Data will be stored and managed in REDCap and SPSS. The data file on the shared Box (a password-protected digital encrypted shared drive, a part of the University of Miami) will be used for analysis purposes so that all research team members have access to the most recent version of the file.

All data will be collected using study participant de-identified ID numbers to protect the confidentiality of participants. All participants will be assigned unique alphanumeric numbers as they enroll in the study. No personal identifying information will appear on any questionnaires or other material. All participant information will be de-identified at the Sylvester location. Likewise, information matching the participant number to a name or other identifying information will be kept in a password-protected shared Box folder that the study's PI and Co-PI can only access. All other participants' assessment data will be scanned into a password-protected shared Box folder labeled only with participants' ID numbers and will be entered into REDCap. REDCap database system will be used to help input participant demographics and study-related information.

Standard operating procedures specifying the rules, methods, and procedures to follow will be used and checked by the study team member. The research team members will be in weekly contact with the PI to review any data (i.e., missing data) and ensure data integrity. The Co-PI will also review all consent forms to ensure that they are complete.

Descriptive analysis will be conducted on demographic (e.g., age and gender) variables to report the characteristics of the sample. Pre- and post-assessments will be analyzed using paired t-tests for normally distributed continuous data and Wilcoxon signed-rank for non-normal continuous data. Chi-Square test of independence will be used for categorical data. Additionally, descriptive statistics and qualitative content analysis will be used to analyze data regarding ease of study.

1. General Approach

All endpoints will be evaluated using parametric analysis to examine the difference between the two conditions across the 3-time points for primary endpoints (CINV and Use of Antiemetics) and 2-time points for secondary endpoints (resilience, psychological distress, and quality of life). The analysis will be conducted using SPSS Version 26. For binary outcomes (CINV), logistic regression will be used. For continuous outcomes (antiemetic use, resilience, psychological distress, and quality of life) a Mixed ANOVA will be used with condition as the between-subjects variable and change over time on the outcome as the within-subjects variable. Sphericity and homogeneity of variance assumptions will be tested prior to interpretation of the results, and the

Greenhouse-Geisser correction will be implemented if Sphericity is violated. A type I error rate of .05 will be used to determine significance for all analyses.

Outcome	Measure	Type of measurement
CINV	MAT	Binary
Use of antiemetics	Antiemetic Diary	Continuous
Resilience	CD-RISC	Continuous
Psychological Distress	Visual Analog Scale	Continuous
Quality of Life	FACIT-G	Continuous

2. Analysis of the Primary Endpoint(s)

   For CINV, logistic regression will be used to determine whether the use of aromatherapy decreases the risk for any of the following outcomes: acute nausea, delayed nausea, acute vomiting, or delated vomiting. For use of antiemetic medication, a Mixed ANOVA will be used to evaluate differences between conditions (aromatherapy group vs. treatment as usual) across the 3-time points (Visit 1, Visit 2, and Visit 3). Time x treatment effects will be evaluated as well as main effects.
3. Analysis of the Secondary Endpoint(s)

   For resilience, psychological distress, and quality of life, a Mixed ANOVA will be used to evaluate differences between conditions (aromatherapy group vs. treatment as usual) across the 2-time points (Initial visit and final visit). Time x treatment effects will be evaluated as well as main effects
4. Baseline Descriptive Statistics

   Participant demographic characteristics will be analyzed using descriptive statistics. Specifically, frequencies and percentages will be reported for categorical variables, and means and standard deviations will be reported for continuous variables.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects*

This section is not applicable. The risks of this study are minimal.

13) Withdrawal of Subjects*

The Study's intervention group uses an aromatherapy inhaler, leading to a potential sensitivity to essential oils. Participants will be informed that in the case they have a sensitivity to essential oils, they need to stop using the inhaler and contact the Study PI immediately. The participant will be withdrawn from the Study and encouraged to see their healthcare provider.

There are no foreseeable participant risks or inconveniences related to participation in the research. The participants are free to withdraw at any time, and their decision to participate, refuse, or withdraw will have no impact on their treatment or any other relationship with SCCC. There is no economic burden for the participants.

The participant will be considered “lost to follow-up” if they stop communicating with the study team. The participant will also be considered “lost

to follow-up" if the participant's oncologist withdraws them from IV moderate to high emetogenic chemotherapy.

14) Risks to Subjects*

Quality assurance will follow the University of Miami School of Nursing and Health Sciences quality assurance guidelines. These include minimizing potential harm for the participants.

The study measures include questions regarding well-being, some of which may cause emotional distress or discomfort. Participants will be informed that they may refuse to answer any question if they do not feel comfortable answering it. If a participant expresses or demonstrates emotional distress, the participant will be encouraged to contact the Sylvester Comprehensive Cancer Center (SCCC) Cancer Support Services for an appointment at 305-243-4129 or 305-243-8204.

The study's intervention group uses an aromatherapy inhaler, leading to a potential sensitivity to essential oils. Participants will be informed that in the case they have a sensitivity to essential oils, they need to immediately stop using the inhaler and contact the PI of the study, Dr. Anglade. The participant will be withdrawn from the study and encouraged to see their healthcare provider.

There are no foreseeable participant risks or inconveniences related to participation in the research. The participants are free to withdraw at any time, and their decision to participate, refuse, or withdraw will have no impact on their treatment or any other relationship with SCCC. There is no economic burden for the participants.

Unanticipated Problems (Adverse Events and Serious Adverse Events)

a) Definition of Unanticipated Problems

(1) The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

b) Unanticipated Problem Reporting: The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) as per institutional guidelines.

c) This study poses a low risk to study participants. However, psychological distress, aromatherapy inhaler sensitivity to essential oils, or a breach of confidentiality would constitute an adverse event.

(1) The psychological risk could be experienced if the participants believe that they are at high risk of breakdown or other stressors.

(a) Participants will be informed of their freedom to withdraw from the study at any time.

(i) If psychological distress is experienced: The PI will be notified, and study participants will be encouraged to contact the Sylvester Courtelis Center for Psychosocial Oncology and be given the appointment line for an appointment with a psychologist or psychiatrist.

(2) The study's intervention group uses an aromatherapy inhaler, leading to a potential sensitivity to essential oils.

(a) Participants will be informed that in the case they have a sensitivity to essential oils, they need to immediately stop using the inhaler and contact the PI of the study, Dr. Anglade.

(i) The participant will be withdrawn from the study and encouraged to see their healthcare provider.

d) The adverse event will be documented using the form HSR-4A: Internal non-serious adverse event log sheet.

(1) If a confidentiality breach occurs, the research team member will notify the PI immediately.

(2) The principal investigator will investigate all AE & SAE.

(a) If the AE/SAE is 1) unexpected, 2) possibly related to the study, and 3) is a greater risk to the participant or others or serious, the PI will notify the IRB within 5 business days.

(b) Only Grade 3 or higher AE/SAEs that are considered ‘definite, probable, or possibly related’ to the intervention (i.e., aromatherapy inhaler) will be captured.

15) Potential Benefits to Subjects*

No direct benefit is anticipated for the participants in the control arm. The intervention group may experience some relief from the discomfort associated with CINV.

16) Vulnerable Populations*

This study will not include neonates, prisoners, children, or cognitively impaired adults. Pregnant women will not be excluded from this study; however, the study will not search for pregnant women. If a pregnant woman meets the

inclusion criteria, she will be allowed to participate if she so chooses. Pregnant participants may withdraw from the study at any time.

17) Multi-Site Research*

Not applicable.

18) Community-Based Participatory Research*

Not applicable.

19) Sharing of Results with Subjects*

This study will not share results with participants.

20) Setting

The study will be conducted at the SCCC's outpatient CTU located in South Florida. The study will include 100 oncology patients over 18 receiving moderate to high emetogenic chemotherapy regimens from various cancer diagnoses and stages.

Setting site:

1. Sylvester Main Medical Campus

   1475 NW 12th Ave, Miami, FL 33136

21) Resources Available

Principal Investigator, Dr. Debbie Anglade, will oversee the study's management and manage communications with the IRB. Dr. Anglade is a seasoned principal investigator and serves as Assistant Professor of Clinical at the University of Miami School of Nursing and Health Studies. Dr. Anglade and the Co-PI will train the research team members to administer informed consent, self-reported questionnaires, and data management. She will assist with participant screening, consenting, data collection, and data management.

Co-Investigator, Caterine Diaz, is a registered nurse with more than 17 years of experience specializing in oncology patient care. She has participated in creating and developing nursing research studies for the past five years. She will take part in screening, making schedules, guiding patients through informed consent, and meeting patients to collect and process data.

Sub-Investigator, Dr. Joseph Pizzolato is a triple board-certified hematologist and oncologist at Sylvester Comprehensive Cancer Center. He earned his medical degree from Icahn School of Medicine at Mount Sinai, New York. Dr. He completed his residency in internal medicine at Columbia-

Presbyterian Hospital, New York, and his fellowship in medical oncology/hematology at Memorial Sloan-Kettering Cancer Center. He has extensive clinical research experience and interests. He currently serves as the medical director of the Comprehensive Therapeutic Unit and Medical Director Sylvester Comprehensive Cancer Center Aventura Satellite.

Study Statistician, Dr. Karina Gattamorta, is a Research Associate Professor at the University of Miami School of Nursing and Health Studies. Her training is in methodology, statistics, and measurement. She will oversee the data management and data analysis of this study.

Research Assistant Roberto L. Roman Laporte, DNP, RN, CMSRN, EBP-C is a Ph.D. student at the University of Miami School of Nursing and Health Studies. Dr. Roman Laporte is a registered nurse with over 10 years of nursing experience in medical-surgical nursing, oncology, progressive care, and ambulatory surgery. He is a seasoned nurse scientist with experience in the creation and development of research studies for over 8 years.

Stephanie Klein, RN, BSN, OCN, BMTCN is a research infusion nurse at the University of Miami Sylvester Comprehensive Cancer Center in the Phase 1 clinical trials department. She will be assisting with patient screening, patient education, consenting process, and data entry.

Ana Muriel BSN, RN, is an experienced oncology and research infusion nurse at the University of Miami Sylvester Comprehensive Cancer Center phase 1 clinical trial department. She will be assisting with patient screening, patient education, consenting process, and data entry.

Hoyan NG-Chen Pharm.D., BCPS., is the Pharmacy Manager and Interim Director of Pharmacy at the University of Miami/Sylvester Comprehensive Cancer Center in South Florida. She manages chemotherapy plan order verifications, compounding preparations, operations/workflow management, and various patient/family education programs. She will be assisting with patient screening and chemotherapy regimen verification for the study.

Angelina Meza-Suarez BSN, CHRN, RN, has been a nurse at the University of Miami since 1994. Angelina is a Hyperbaric Safety Director for 15 years. She will be assisting with patient screening, patient education, consenting process, and data entry.

Junet Alvarez, BSN, RN, CCRC, is a registered nurse with extensive clinical research coordinator experience. She will be assisting with patient screening, patient education, consenting process, and data entry.

Yhenifer Diaz-Granados, RN, is a bilingual oncology nurse at the University of Miami Sylvester Comprehensive Cancer Center with extensive experience in

administering chemotherapy and biological therapy for over 9 years. She has served as a charge nurse in the CTU area for the last 4 years. She will be assisting with patient screening, patient education, consenting process, and data entry.

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22) Prior Approvals

The study team received approval for using the CD-RISC, FACT-G questionnaires, and the Soothing Scents Company's QueaseEASE aromatherapy inhaler product (see associated documents). All other instruments are open to the public and are free to use.

23) Recruitment Methods

This two-arm control trial study will be conducted at the Sylvester Comprehensive Cancer Center (SCCC) main, campus in the Comprehensive Treatment Unit (CTU). The study will identify cancer patients that are undergoing moderate to high emetogenic chemotherapy regimens by screening upcoming patients scheduled chemotherapy visits. The study team members will review potential participants' daily schedule notes to screen the potential participants by the study inclusion criteria. If the potential participant meets the inclusion criteria for the study, the study team member will verify and meet the potential participants on their next treatment appointment in the CTU.

i. Recruitment flyers will be posted at the SCCC main campus. The recruitment flyers will provide information about the study, eligibility criteria, and contact information. If a potential participant calls the contact person on the recruitment flyer, the study team member will explain the study to them. If the participant is interested and meets the eligibility criteria, the study team member will verify the next scheduled chemotherapy infusion visit and confirm the visit with the potential participant. At this time, the study team member will explain that the informed consent process will take place on their next scheduled chemotherapy infusion.

ii. Potential participants will be identified using the weekly SCCC's CTU schedule notes, displaying patients' chemotherapy regimen summary (e.g., chemotherapy drug type, dosage, and frequency). The study team member will identify patients undergoing moderate to high emetogenic chemotherapy (adjuvant or neoadjuvant). Identified patients will be screened for eligibility criteria by reviewing the patients' medical records. If a patient meets all eligibility criteria, a study team member will approach the patient during their regular outpatient CTU visit and screen for essential oils sensitivity. In case the potential participant is interested and willing to consent immediately, the study team member will review the study's informed consent. Once the informed consent is

signed, the participant will receive a copy of the informed consent form. If the potential participant needs additional time to think about the study, the study team member will follow up with the patient at their next scheduled chemotherapy infusion visit. At this time, if the potential participant is interested and still meets the eligibility criteria, the study team member will explain the study and review the informed consent process.

24) Local Number of Subjects

The total single-site sample size is 100 participants.

25) Confidentiality

All participants will be assigned a unique study ID number. Identifying information will be stored separately from other study data in a password-protected, encrypted Excel file. All data will be stored on secure servers at the University of Miami, Box. Additionally, the REDCap software will be utilized during the study to maximize data security. Only authorized study personnel will have access to identifying information throughout the study.

Choose the statements below that are applicable to this research:

26(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☒ Yes (If checked go to 26(b))

☐ No (If checked, go to Section 27)

26(b). Check the box next to the correct statement below

☐ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☒ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB

26(c). How will the research store the data?

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☒ On a cloud-based storage system that is approved by the University of Miami

☐ On the secured JHS SharePoint environment

☐ Other, specify: Click here to enter text.

26(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed

in the instructions for Section 26 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

26(e) Additional requirement for Jackson Health System Data:

☒ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☐ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

27. Biospecimens

☒ Not applicable. No biospecimens will be collected

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☐ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

26) Provisions to Protect the Privacy Interests of Subjects

The study team member will take steps to ensure that the participants' privacy is protected. The study team member will introduce, explain, and answer any questions

related to the study. The study team member will explain that medical information will be de-identified for the study. All participant demographic information and collected data will be encoded for confidentiality in REDCap. Participants will be assigned a number that will be utilized to track their data throughout the study. No participant personal identifying information will be utilized to share data among personnel or to analyze results from assessments. The PI and Co-PI will be responsible for assigning participant codes for data tracking and randomization. This will be done utilizing an online pseudo-random number randomizer (https://www.randomizer.org/) (Urbaniak & Plaus, 2013).

27) Compensation for Research-Related Injury

This section is not applicable. The risks of this study are minimal.

28) Economic Burden to Subjects

This section is not applicable. There is no cost to the participants.

29) Consent Process

All participants are required to provide informed consent before the beginning of study procedures. The informed consent will occur at the SCCC's outpatient CTU on the patients' chemotherapy infusion visit in their quiet, comfortable setting. The consent, all study procedures, and materials will be available and completed in the participant's preferred language (English or Spanish) by a study team member fluent in the preferred language (English or Spanish). Potential participants will receive a full explanation of the study, including the study's purpose, procedure, and risks/benefits. The study team member will also explain that participation is voluntary at no cost; all study information is kept confidential, and that they may withdraw from the project without penalty or any monetary loss. Potential participants will have ample time to ask any pertinent questions related to the study. After answering all their questions, and the potential participant understands the study information, a study team member will go through the informed consent process in the participant's preferred language. The study team member will allow the participant to decide whether they want to participate. Once the informed consent is signed in REDCap, a copy will be provided to the participant, the signed consent will be uploaded to the participant's electronic medical record, and sent via encrypted email to the treating oncologist notifying them of the patient's consent to participate in the study. The study team member will provide the study's contact information should the participant have any additional questions during the study.

Non-English-Speaking Subjects

The consent, all study procedures, and materials will be available and completed in the participant's preferred language (English or Spanish) by a study team member fluent in the preferred language (English or Spanish).

30) Process to Document Consent in Writing

All recruited participants will sign the informed consent before receiving the study's instructions, assessments, and packet. The consent and data will be stored in the password-protected University of Miami's secure server, REDCap.

31) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Type of Request:

☒ Waiver of Authorization for access to medical record for subject identification/recruitment.

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.

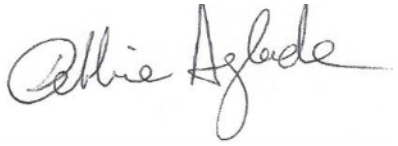
☒ ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

☒Not applicable. This research will not collect data from JHS record under a waiver of authorization

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).



12/10/21

PI Signature Date

32) Drugs or Devices

Upon the FDA's review of the study protocol, on October 18, 2021, the FDA exercised enforcement discretion to allow this study to proceed without an IND and therefore is not expected to comply with IND reporting requirements.

Soothing Scents QueaseEase aromatherapy inhalers will be stored in a cool, dry place according to the manufacturer's recommendations. The QueaseEase inhalers will be stored in a central location in the Principal Investigator's locked office at SCCC, distributed to the satellite locations, and kept in a secured office. The inhalers will be accessible to the study team only. The distribution of the inhalers to each intervention arm randomized participant will be documented in the participant log by the research nurse.