Protocol

Increasing Physical Activity among Breast Cancer Survivors with Depression

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Principal Investigator(s): Chad D. Rethorst, Ph.D.
UT Southwestern Medical Center - Center for Depression Research and Clinical Care (CDRCC)
6363 Forest Park Rd, Dallas, TX 75235
Phone: (214) 648-0153
Email: Chad.Rethorst@utsouthwestern.edu

Sub-Investigator(s): Madhukar Trivedi, MD Psychiatry
Tracy Greer, Ph.D. Psychiatry

Biostatistician: Thomas Carmody, Ph.D.
UT Southwestern Medical Center
6363 Forest Park Rd., Dallas, TX 75235

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UT Southwestern Medical Center (UTSW)
Center for Depression Research and Clinical Care (CDRCC)
6363 Forest Park Rd., BL 13.100
Dallas, TX 75235

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CDRCC	Center for Depression Research and Clinical Care
ERC	Ethics Review Committee
GCP	Good Clinical Practice
IRB	Institutional Review Board
MDD	Major Depressive Disorder
MOST	Multi-Phase Optimization Strategy
MVPA	Moderate-to-Vigorous Physical Activity
SAE	Serious Adverse Event

STUDY SUMMARY

Title	Increasing Physical Activity among Breast Cancer Survivors with Depression
Short Title	Physical Activity in Breast Cancer Survivors with Depression
Protocol Number	122015-072
Phase	N/A
Methodology	Pilot study of a physical activity intervention among breast cancer survivors with depression
Study Duration	25 weeks
Study Center(s)	Single-center, UT Southwestern Center for Depression Research and Clinical Care
Objectives	Evaluate the feasibility of implementing a multi-component physical activity intervention in breast cancer survivors with significant depressive symptoms.
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Eligible breast cancer survivors between 3 months and 5 years post-treatment. 1) Positive depression screen (PHQ-9 score > 8) or current antidepressant treatment 2) Report <150 minutes of weekly moderate-to-vigorous physical activity (MVPA) on the GPAQ 3) Physically able to engage in physical activity 4) Written and verbal fluency in English.
Statistical Methodology	A total of 50 patients will be enrolled in this pilot study. The primary objective of this study is to determine the feasibility of implementing a multi-component physical activity intervention among breast cancer survivors with depression. A preliminary analysis of changes in physical activity and depressive symptoms will be conducted following the physical activity intervention.

1.0 BACKGROUND

The over 2.9 million breast cancer survivors in the United States face significant post-treatment health burdens. Five-year recurrence rates for Stage I-III breast cancer survivors range from 7-13%[1] and a subset of breast cancer survivors (e.g., BRCA1/2 mutation carriers) may also have increased risks for other cancers.[2] Breast cancer survivors have significant medical comorbidities, symptom burdens, and late effects that decrease quality of life and affect prognosis.[3] Substantial gaps remain in our understanding of how to improve prognosis for this rapidly growing population. Depression and physical inactivity are inter-related, but modifiable, risk factors associated with prognosis among breast cancer survivors. The proposed pilot project will assess the implementation of evidence-based strategies for increasing physical activity among breast cancer survivors. **Successful completion of project aims will result in crucial pilot data to support future grant applications to identify optimal strategies for increasing physical activity in breast cancer survivors.**

Depression and Cancer Prognosis. **Depression is a common comorbidity in breast cancer survivors and an important factor associated with poor prognosis.** Individual studies estimate the prevalence of Major Depressive Disorder (MDD) in breast cancer survivors to range from 10-30%.[4] When including dysthymia and minor depression, the rates of mood disorders in breast cancer survivors are estimated to be as high as 50%.[5,6] **More importantly, depressive symptoms are linked to higher rates of mortality among breast cancer survivors.** A recent meta-analysis integrated 76 prospective studies, including those in which depression was assessed prior to cancer diagnosis and those that assessed depression after diagnosis. Results indicated an 18% increase in mortality for breast cancer patients with depression.[7] Conversely alleviation of depressive symptoms in breast cancer patients is associated with longer survival,[8] suggesting the importance of evidence-based interventions targeting depression.

Physical Activity and Cancer Prognosis. **Evidence links physical activity and survival in following breast cancer but the role of inflammatory biomarkers in this relationship has not been adequately examined.**[9] The largest longitudinal studies[10-14] report consistent decreased risk of breast cancer mortality (ranging from 39% to 51%) among physically active breast cancer survivors. These studies also find physical activity associated with a reduced risk of all-cause mortality, ranging from 27% to 56%.

Physical Activity and Depression. **Numerous trials, including our own work described in Section (3.3.2), have assessed the efficacy of aerobic exercise as a treatment for depression.** Meta-analyses summarizing these studies have reported effect sizes ranging from 0.83 to 1.39 which are comparable to effects of antidepressant medications.[15] The effects of exercise on depression specifically among cancer survivors have also been widely examined. A recent meta-analysis[16] identified 15 RCTs that have examined the effect of exercise on depressive symptoms in cancer survivors. This meta-analysis estimated an effect size (Cohen's d) of 0.22, suggesting a small-to-moderate effect of exercise on depressive symptoms in cancer survivors.

2.0 STUDY OBJECTIVES

2.1 Although multiple strategies for increasing physical activity have proven efficacious, little is known about the optimal intervention strategies for breast cancer survivors or how those interventions can be effectively implemented in real-world settings. The proposed pilot project will assess the implementation of evidence based strategies for increasing physical activity among breast cancer survivors. Results from this pilot project will support future grant applications. These future studies will utilize multi-phase optimization strategy (MOST) to identify the optimal combination of intervention strategies to increase physical activity among breast cancer survivors.

Aim 1. Evaluate the feasibility of screening and subject recruitment through targeted mailings to breast cancer survivors using the UT Southwestern cancer registries.
Aim 1A. Assess the percentage of contacted survivors completing online questionnaires.
Aim 1B. Assess the percentage of respondents meeting eligibility criteria (< 150 minutes of physical activity per week and ≥ 8 on the PHQ-9).
Aim 1C. Assess the percentage of eligible respondents enrolled in the physical activity intervention.

Aim 2. Evaluate the feasibility of implementing a multi-component physical activity intervention in breast cancer survivors with significant depressive symptoms.

Aim 2A. Physical activity program compliance.

Aim 2A.a. Assess the percentage of physical activity classes attended

Aim 2A.b. Assess the percentage of days of use of the self-monitoring device

Aim 2B. Participant-reported program satisfaction

Aim 3. Conduct preliminary analysis of changes in physical activity and depressive symptoms following the physical activity intervention.

Hypothesis 1. Participants in the physical activity program will demonstrate increases in physical activity at three and six months

Hypothesis 2. Participants in the active living program will demonstrate decreases in depressive symptoms at three and six months post-baseline.

Cancer Relevance: This project simultaneously targets two factors (depression and inactivity) related to poor outcomes in breast cancer survivors and provide important information on how to effectively address these risk factors in a real-world setting.

3.0 STUDY DESIGN

3.1 Overview of Study Design

The research project is a pilot study to assess the effects of a multi-component intervention in increasing physical activity among breast cancer survivors with depression. Breast cancer survivors listed in the UT Southwestern Simmons Cancer Center cancer registry will be contacted via mail and invited to complete a brief online questionnaire. Those indicating insufficient levels of physical activity and increased depressive symptoms will be invited to participate. The 12-week physical activity intervention will consist of three evidence-based strategies: print-based materials, active living classes, and activity self-monitoring.

3.2 Duration of Study and Study Timeline

Recruitment of participants will begin in February 2016. We aim to recruit a cohort of 10 subjects in per month through June 2016 for a total of 50 subjects.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

1) positive depression screen (PHQ-9 score ≥ 8) or current antidepressant treatment
2) report <150 minutes of weekly moderate-to-vigorous physical activity (MVPA) on the GPAQ
3) physically able to engage in physical activity
4) written and verbal fluency in English.

4.2 Exclusion Criteria

1) medical condition contraindicating physical activity participation
2) cognitively unable to give informed consent
3) non-English speaking.

4.3 Participant Recruitment and Retention

Based on previously published work utilizing contact of breast cancer survivors from the cancer registry system,[17] we anticipate that approximately one-third (33%) of the contacted survivors (n=150) will return the questionnaire and agree to future contact to learn more about further physical activity interventions. Based on indications of physical activity frequency from the screening questionnaire, we will invite those who meet eligibility criteria (estimated to be at least 33% of respondents [n=50], based on national prevalence of sedentary behavior and depression among breast cancer survivors) to attend an initial in-person screening and baseline assessment session.

5.0 STUDY PROCEDURES

5.1 Informed Consent

Interested persons identified as potential participants will be given an explanation of the study and will undergo a brief pre-screening with trained study personnel. Interested and preliminarily eligible participants will begin the informed consent process. Study personnel will explain the details of the study to the potential participant and then give him or her time to read through the informed consent document. Study personnel will then go through the document with the potential participant and answer any questions he or she may have. Potential participants who choose to provide informed consent and sign the informed consent form will then proceed to the screening assessment.

5.2 Screening

Breast cancer survivors listed in the UT Southwestern Simmons Cancer Center cancer registry will be contacted through an informational letter via mail inviting them to participate in the current study. The letter will include information about the current study and directions to complete an online eligibility screening questionnaire. Potential participants will be screened for eligibility based on all inclusion and exclusion criteria, detailed in sections 4.1 and 4.2. All participants who are screened will complete the Demographics Form.

5.3 Baseline

Potential subjects will meet with a trained project interventionist to be assessed for safety of engaging in physical activity, following recommendations identified in the ACSM guidelines.[18] The Physical Activity Readiness Questionnaire (PAR-Q)[19] is a self-report questionnaire designed to assess safety of engaging in physical activity. In addition, lymphedema and pain will be assessed at baseline and throughout the program to ensure participant safety. Subjects will also be instructed to contact their physician to ensure their safety engaging in physical activity.

Study assessments (described in section 6.0) will be conducted at the baseline assessment visit. Participants will complete the PAR-Q to identify potential medical contraindications. Participants indicating potential contraindications to exercise will be instructed to discuss participation with their physician before engaging in physical activity.

Blood samples will be collected at the baseline assessment visit.

5.4 Treatment and Study Intervention

Participants will be enrolled in the physical activity intervention described in sections 7.0 Assessments will be conducted based on the schedule outlined in section 6.0. Qualified, trained, and certified personnel will conduct clinician-rated assessments (all assessments which are not self-report). During the trial, the outcome assessments will be obtained at Weeks 1, 13, and 25. Participants will be asked to wear an accelerometer during Weeks 1, 13 and 25. If the participant is not able to come to the site and (s)he agrees, some assessments and/or visits may be conducted by phone, by mail, or at appropriate off-site locations, and/or on participants' or other off-site computers via the secure study website(s) if access to a computer with internet service is available. Detailed descriptions of the assessments are provided in section 6.0.

5.5 Participant Discontinuation

In order to ensure safety, female participants who become pregnant during the study will be required to discontinue participation in the intervention. Participants may be asked to stop study intervention if any situation arises that, in the investigator's judgment, poses a safety risk.

Participants who must stop the study intervention will still be asked to complete assessment visits as scheduled.

5.6 Participant Remuneration

Participants will receive monetary remuneration for their participation in the trial to compensate for their time, travel arrangements, and the burden of participation. Essential to the study is appropriate support for participants' time and effort contributing to the study. Reimbursement for attending data collection visits will be made based on the following schedule:

- Reimbursements will be made for participants who complete the initial survey.
- Reimbursements will also be made for the assessment visits (Baseline and Weeks 13 and 25).

25 participants who complete the eligibility screening assessments (described in section 6.2.1) will be chosen randomly to receive a $100 gift card.

Participants will be paid for each eligible visit using a UT Southwestern Greenphire ClinCard, which can be used as a credit or debit card. Participants will also receive instructions on how use the card. In order receive study payments, the participant's name, address, date of birth and Social Security Number (SSN) will be collected by the research staff. All information will be stored in a secure fashion and will be deleted from the UT Southwestern Greenphire ClinCard system once the study has been completed.

6.0 STUDY ASSESSMENTS

6.1 Time and Event Table (Summary of Assessments)

	Screening	Baseline	Week 13	Week 25
Demographics	x			
Locator Form	x			
Prior and Concomitant Medications	x			
PAR-Q	x			
PHQ-9	x			
GPAQ	x			
QIDS-SR		x	x	x
SF-36		x	x	x
PSQI		x	x	x
BFI		x	x	x
FACT-B		x	x	x
Brief COPE		x	x	x
SHAPS		x	x	x
STAI		x	x	x
Relationship status		x		
Couples Satisfaction Index (CSI)		x		
MGH-ATRQ		x		
PASC-Q		x	x	x
PASE-Q		x	x	x
Blood draw		x	x	x
Accelerometer (activity and sleep)		x	x	x

6.2 Types of Assessments

6.2.1 Eligibility Screening Measures

Demographics Form. The demographics form will be administered to all participants at the baseline visit. The form consists of basic demographic information (e.g., gender, race/ethnicity, etc.).

Patient Health Questionnaire-9 (PHQ-9). The PHQ-9[20] is a 9-item scale designed to measure depressive symptoms. We will use the PHQ-9 to identify patients with elevations in depressive symptoms. Patients scoring 8 or higher on the PHQ-9 will be eligible for participation in the study. Large meta-analyses support the utility of the PHQ-9 in identifying MDD and assessing depressive symptom severity.[21,22]

General Physical Activity Questionnaire (GPAQ). The GPAQ[23] is a 16-item scale designed to assess physical activity across three domains (work, transportation, and recreation). We will use the GPAQ to identify patients that do not currently meet physical activity recommendations of 150 minutes of weekly moderate-intensity physical activity.

6.2.2 Diagnostic and Screening Measures

Locator Form. The Locator Form will be used to obtain contact information for each participant. The Locator Form will be filled out at the screening visit and then routinely updated on a monthly

basis thereafter (excluding the final visit). In addition, a Locator Form may be completed/updated any time the participant reports a change in contact information.

Prior and Concomitant Medications. The Prior and Concomitant Medications form assesses prescribed medications taken by the participant. The Prior and Concomitant Medications form will be administered at the screening visit and then monthly thereafter, if the participant endorses a change in medication status.

Physical Activity Readiness Questionnaire-Revised (PAR-Q). The PAR-Q[19] asks 7 health-related questions to determine whether a person needs to consult with their physician prior to engaging in an exercise program. The PAR-Q will be administered at the screening visit.

6.2.3 Study Assessments

Measurements of Physical Activity:

Actigraph GT3X+ accelerometer. – The Actigraph will provide a valid and reliable objective assessment of physical activity.[24] Subjects will be asked to wear the device for a 7-day period at each assessment time point (baseline and weeks 13 and 25). Subjects will be instructed to wear the device on their non-dominant arm and to remove the device only when it may become submerged in water (bathing, swimming, etc.). Following, the 7-day period, subjects will return the accelerometers using a postage-paid envelope.

Measurement of Psychosocial and Physical Outcomes:

Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR_{16}). The QIDS-SR_{16} [25-27] is a 16-item questionnaire to assess severity of depression-specific symptoms. The QIDS-SR_{16} has high reliability (Cronbach's alpha of 0.83), good concurrent validity (correlations between the QIDS-SR_{16} and the 17-item Hamilton Rating Scale for Depression is 0.81)[25].

Short Form 36 Health Survey (SF-36). The SF-36[28] is a 36-item survey of patient-reported general health and quality of life across eight domains of well-being (physical functioning, social functioning, vitality, pain, general health, physical role functioning, emotional role functioning, and mental health).

Pittsburgh Sleep Quality Index (PSQI). The PSQI[29] is a 19-item scale designed to assess sleep quality and disturbances. Scores range from 0 to 21 with higher scores representing worse sleep quality. The PSQI has demonstrated reliability (Cronbach's alpha of 0.80) in the assessment of self-reported sleep quality and validity when compared to sleep diaries and polysomnography.[30]

Brief Fatigue Inventory (BFI). The BFI[31] is a 9-item scale designed to assess fatigue. The BFI demonstrates good reliability (Cronbach's alpha of 0.96) and validity (correlation of 0.86 with the POMS fatigue subscale).

Functional Assessment of Cancer Therapy – Breast (FACT-B) – The FACT-B[32] is a 44-item scale designed to measure multidimensional quality of life in breast cancer patients. The FACT-B has demonstrated reliability (Cronbach's alpha of 0.90) and concurrent validity (0.87 correlation with the Functional Living Index-Cancer and 0.86 correlation with the Functional Assessment of Cancer Therapy-General).

Brief COPE. The Brief Cope[33] is a 28-item scale designed to assess a wide range of coping responses. The Brief COPE has been used in studies of cancer patients and demonstrates good reliability and validity.

Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS[34] is a 14-item scale that measures anhedonia, the inability to experience pleasure. The SHAPS has adequate construct validity, satisfactory test-retest reliability (ICC=0.70) and high internal consistency has also been reported (Cronbach's alpha of 0.94).

State Trait Anxiety Inventory (STAI). The STAI[35] is a 40-item scale that measures state and trait anxiety.

Anthropomorphic assessments. Height will be assessed at baseline. Weight and waist circumference will be measured at each assessment time point. Height and weight measurements will be used to calculate Body Mass Index (BMI).

Metabolic indices. Blood samples will be collected by a trained phlebotomist to allow for evaluation of markers of metabolic health, including blood glucose, triglycerides, and lipids.

Antidepressant Medication Use. The Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ) will be assess the current use antidepressant medication.

Relationship Status. A single-item question will ask participants to indicate their current relationship status from one of 7 categories (single, never married; cohabiting with partner; married, living together; married, not living together; separated; divorced; widowed). The Couples Satisfaction Index (CSI)[36] is a 16-item form that captures relationship quality among participants who endorsed currently being in a romantic relationship. The CSI is a well-validated and reliable measure that draws from other previously established relationship satisfaction measures.

At the end of the program we will conduct a self-report questionnaire aimed at evaluation participants' satisfaction with the program. This questionnaire will include Likert-scale questions about: 1) satisfaction with the program; 2) program engagement/adherence; 3) program enjoyment; 4) perception of program effectiveness; 5) willingness to recommend program to others; 6) barriers to program participation; 7) intent to maintain physical activity; and 8) attitudes toward physical activity. This assessment will allow for further refinement of the intervention to ensure its sustainability and broad dissemination.

Psychological Mediators/Moderators of Physical Activity Behavior Change:

Physical Activity Stages of Change Questionnaire. The 4-item scale assesses the current stage within the Transtheoretical Model framework (Pre-contemplation, Contemplation, Preparation, Action, Maintenance). These stages are highly correlated with change in physical activity over time.[37]

Physical Activity Self-Efficacy Questionnaire. The 3-item scale assesses self-efficacy for physical activity. Activity-specific self-efficacy is highly correlated with activity change and psychosocial outcomes.[37]

6.2.4 Physiological Measures

Physiological Measures. Physiological measures include height, weight, body mass index (BMI) and waist circumference. Height will be obtained once at baseline and the other measures will be obtained at each assessment visit.

6.2.5 Safety Assessments

Assessments involved in determining participants' ability to safely participate in the protocol (maximal exercise testing, laboratory tests, and physical exam) are described under Diagnostic

and Screening Measures. Additionally, reportable AEs and all SAEs will require completion of an AE Form (and SAE form as applicable) to document and track reportable AEs.

7.0 STUDY TREATMENTS

7.1 Physical Activity Intervention

Print-based education

All participants will receive print-based education focused on physical activity. Provision of print-based materials can result in significantly increases physical activity as demonstrated in a study by Vallance et al.[38] in which breast cancer survivors who received the book, *Exercise for Health: An Exercise for Breast Cancer Survivors*, increased their physical activity levels by 70 minutes per week.[38] All subjects in the current project will be given a copy of *Exercise for Health: An Exercise Guide for Breast Cancer Survivors*,[38,39] a 56-page book based on the theory of planned behavior. The book was developed and evaluated by experts in the field [39] and has been proven efficacious in increasing physical activity in breast cancer survivors.[38] Topics covered within the book include benefits of exercise in breast cancer survivors; recommendations on type, duration, frequency and intensity of exercise; goal-setting; and advice on overcoming common barriers.

Self-monitoring

Subjects will be provided with a commercially available activity monitor (i.e., Fitbit). The project interventionist will instruct subjects on proper use of the device and options for viewing the data collected by the device. Subjects will be instructed to wear the device daily. Those with access to smartphones or computers will be instructed to upload data on a regular basis for continuous self-monitoring. These devices are compatible with both Android and Apple phones or can be synced with any computer with internet access. Individuals without access to a compatible device will be given paper logs and instructed to record their activity counts provided by the activity monitor on a daily basis.

Active Living counseling

The Active Living counseling program will consists of 12 weekly group educational sessions, facilitated by project interventionists. Interventionists will be trained in delivery of the ALED program. These sessions will involve discussion of topics related to increasing physical activity, including: identifying and overcoming barriers, setting goals, social support, and time management.

Facility Access

Subjects will have access to the exercise lab in the UT Southwestern Depression Center consisting of equipment for aerobic exercise (treadmills, stationary bikes, etc.). Subjects can schedule times to access the facility. The facility will be staffed by the Exercise Interventionist or PI at all times.

7.2 Staff Training

The study staff will be trained and certified as specified in the Manual of Procedures and Study Tools Manual. Training will cover protocol-specific training as needed (e.g., assessments, study interventions, fidelity to the protocol and safety procedures, data management and collection, research procedures including understanding reliability and validity, and problem solving), as well as any IRB-required trainings

8.0 STATISTICAL ANALYSES

8.1 Primary Analyses

Based on recommendations of Leon et al.,[40] the Aims 1 and 2 will examine the feasibility of implementing a physical activity intervention for breast cancer survivors. The feasibility of the study will be assessed by the following criteria:

1) Screening - the number of subjects screened through the web-based questionnaire and the percentage of those screened who meet program eligibility requirements
2) Recruitment - the percentage of screened subjects that are ultimately enrolled
3) Intervention Compliance – defined as percentage of weekly exercise does completed by participants randomized to the exercise condition
4) Retention – defined as percentage of assessments completed

Consistent with Aim 3, we will conduct a data analysis examining the effects of the intervention on physical activity and depressive symptoms. A mixed-effects repeated measures model will be used to analyze the primary outcome measures (minutes of MVPA and QIDS-C scores). The independent variables in the model will be time (weeks 1, 13, and 25)(within-subjects factor). The model will allow for random slopes and intercepts while all other factors will be fixed effects. The baseline value of the dependent variable will be included as a covariate as will the other potential covariates if needed [age, race, gender, history of depression]. The need for higher order times terms or the transformation log (time+1) to obtain a better fitting model will be considered. The goodness of fit of the final model will be investigated. The analysis will use all available data from all randomized patients with at least one post-baseline visit (i.e., modified "intent to treat" sample) and all tests will be two-sided with alpha of .05 used for significance. The hypothesis will be tested by the significance of the time effect main effect. The analysis will be done using SAS Proc Mixed. Statistical analysis will be completed by Thomas Carmody, PhD within the Center for Depression Research and Clinical Care.

9.0 REPORTING AND MONITORING

9.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, appropriate ICH guidelines (including current Good Clinical Practice [GCP]), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. The study team must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the UT Southwestern institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

9.2 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be reviewed at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at the study closure.

9.3 Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. The informed consent will be approved by their IRB(s). Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The original signed informed consent for every participant will be stored in a locked, secure location that is in compliance with their IRB and institutional. Every study participant must be offered a copy of the signed consent form. Participants may contact site personnel with any questions after signing Informed Consent.

Prior to signing the informed consent form, research staff who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read. If the participant is interested in participating in the study, a researcher who is authorized to obtain informed consent will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. The participant will consent by signing and dating the consent document. The person obtaining consent will also sign and date the consent document. The consent must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. All persons obtaining consent must have completed appropriate training.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

Study participation is voluntary and there are no benefits lost if an individual declines participation. Individuals who refuse to participate or who withdraw from the study will be treated

without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

Participants will be offered copies of the signed informed consent form, and the originals will be stored in a secure location at each study site. Contract and local monitors will inspect the informed consent forms periodically to ensure that correct signatures and dates were obtained on valid informed consent forms prior to any study interventions.

9.4 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

9.5 Release of Information

Study participants will be asked to sign a release of information form that will give study staff permission to seek and acquire their treatment records. This release of information is voluntary. There will be no benefits lost if study participants refuse to release information. They may continue to participate in the study.

9.6 Study Documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

9.7 Records Retention and Requirements

All research records for all subjects will be stored by the investigator in a secure location to be accessed only by authorized research personnel. Study records will be stored in accordance with local IRB, State, and Federal Regulations but, in any case, will be kept for a minimum of 7 following study completion.

9.8 Safety Monitoring

9.8.1 Data and Safety Monitoring

Drs. Rethorst and Trivedi will meet weekly to examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. These meetings will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

9.8.2 Protocol Violations Reporting and Management

A protocol departure is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself

is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure the integrity of the trial. The PI or designee will make the decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation. All protocol violations and deviations will be reported to the IRB as required.

9.8.3 Subject Confidentiality/Privacy

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure and separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

All research information obtained on participants is confidential, and disclosure to any third parties without specific authorization is strictly prohibited. To maintain subject privacy, all study forms and reports will be identified by a coded study identification number only. No subject identifying information will be included in any presentations or publications resulting from the study.

Study records may be inspected by the sponsor and its authorized representatives, other government agencies such as the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), authorized Node Staff, or the local IRB for quality assurance purposes.

9.8.4 Adverse Events (AEs) and Serious Adverse Events (SAEs)

The Primary Investigator (PI) may appoint a Study Clinician (MD, PhD, or PI) for this study, who will review or provide consultation for each Serious Adverse Event (SAE) as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events.

9.8.5 Definitions of Adverse Event and Serious Adverse Event

Standard definitions for Adverse Events and Serious Adverse Events, their identification, characterization regarding severity and relationship to the study intervention and processing are described in Appendix 1.

9.8.6 Non-Reportable Adverse Event and Serious Adverse Events

Adverse Events

For the purpose of this study, the following AEs will not require reporting in the data system and will not be captured:

- Grade 1 (mild) unrelated event.
- Grade 2 (moderate) unrelated event.

This would typically include physical events such as headache, cold, etc that was considered unrelated to study participation by the PI.

Serious Adverse Events

For the purpose of this study, the following SAEs will not be recorded in the data system but will be documented:

- Admission to a hospital/surgery center for preplanned/elective surgeries (captured in the Visit Summary/Progress Note).
- Admission to a hospital for scheduled labor and delivery (captured in the Visit Checklist/Progress Note).

Local documentation and reporting guidelines should also be followed based on IRB requirements.

10.0 DATA MANAGEMENT AND PROCEDURES

10.1 Data Collection Forms

The data collection process consists of data entry into the CRFs according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the CRFs for each research participant. Selected CRFs may also require the investigator's written signature. CRFs will be monitored for completeness, accuracy, and attention to detail throughout the study.

10.2 Data Acquisition and Entry

Data entry into an electronic database shall be performed by authorized individuals. Data will be double entered to ensure accuracy.

11.0 HUMAN SUBJECTS PROTECTION

All requirements relating to obtaining institutional review board (IRB) review and approval and informed consent will be met. Written informed consent will be obtained from each study participant utilizing the local IRB-approved informed consent form. Appropriate research personnel will explain all aspects of the study to each participant, answering all questions and ensuring that all basic elements of the informed consent process are covered.

All study personnel will be required to complete Human Subject Protection, Good Clinical Practice and HIPAA training (as required) and will be instructed to act under those guidelines at all times when working with participants, participants data or protected participant health information.

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APPENDIX 1

Adverse Event Reporting Definitions and Procedures

1.0 Definitions of Adverse Events and Serious Adverse Events

1.1 Adverse Event (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event including any new illness, symptom, sign or worsening of a pre-existing condition or abnormality that occurs during the course of an individual's participation in a clinical trial, *whether or not* the event is considered related to the clinical trial intervention.

Stable chronic conditions, such as arthritis, which are present prior to an individual's enrollment in a clinical trial and that do not worsen during the course of their participation are not considered AEs. In order to avoid the reporting of pre-existing conditions as new AEs, and to assist with the assessment of a condition that may have worsened in intensity or severity, a thorough medical history should be performed during the eligibility assessment phase to record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs.

An AE case report form (CRF) is used to capture reported AEs (as defined by the protocol) and may also be used to record follow-up information for unresolved or ongoing events that were reported previously.

A site study investigator is responsible for reviewing and characterizing each AE that is reported, and is expected to follow appropriate reporting procedures.

Adverse events and their resolution outcome should be elicited from study participants at each study related contact. The site must actively seek information about the AE until it is resolved or medically stable or until the participant is lost to follow-up and terminated from the study.

1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event that is deemed serious by a study investigator because it meets one or more of the following criteria (although the event may meet more than one of the criteria below, investigator's should choose only the most serious when reporting the event):

An adverse event is serious if it results in:

- Death: A death that occurs either during the course of the clinical trial or that comes to the attention of the investigator during the protocol-defined follow-up period and after the completion of therapy, whether or not it is considered treatment-related must be reported.
- Life threatening: Any adverse event that when it occurs places the participant at immediate risk of death (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
- Admission to the hospital or is responsible for the prolongation of an existing hospitalization.
- A persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.

- Requiring a medical intervention to prevent one of the above outcomes.

A SAE case report form is used to capture reported SAEs and may also be used to record follow-up information for unresolved or ongoing events that were reported previously.

A site study investigator at the site is responsible for reviewing and characterizing each SAE that is reported, and is expected to follow appropriate reporting procedures, including the reporting of the event to their IRB as per local IRB guidelines.

Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA appointed Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or medically stable or until the participant is lost to follow-up and terminated from the study.

In the event that a FDA MedWatch form is generated and distributed by the NIDA appointed Safety Monitor as a result of a related and unexpected event, the site staff will be responsible for reporting this to their IRB as per local IRB guidelines and for maintaining this information in their regulatory binders.

1.3 Pregnancy

All pregnancies that are reported during the course of the clinical trial will be captured on a Visit Checklist/Progress Note and not separately reported as an AE or SAE. Pregnancies will be followed through resolution, regardless of the outcome.

2.0 Eliciting and Monitoring Adverse Events

The assessment of Adverse Events will begin once a participant has signed consent and will continue through last study visit or the participant's study termination date, whichever comes first. Follow up of an event will continue for up to 30 days past the Adverse Event assessment date. Qualified research staff is responsible for consistently and thoroughly eliciting medical and/or psychiatric AEs/SAEs from participants during every study assessment visit in order to complete the AE/SAE CRFs in a timely manner. This may require consent in the form of a release of information (ROI) from the participant in order to request medical records, hospital discharge summaries, etc.

Qualified research staff is responsible for reviewing all clinician progress notes and checklists following each participant contact in order to ensure that all AEs/SAEs have been appropriately reported. Reported AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and related AEs/SAEs will be followed until resolution or stabilization, even beyond the end of the study. The study principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

3.0 Assessment of Severity and Relatedness

A study investigator is responsible for reviewing all reported AEs on a weekly basis in order to characterize their seriousness, severity, and relatedness to the study intervention.

3.1 Severity

The seriousness of an event is determined by whether or not it meets one or more of the criteria for a serious adverse event. The severity of an event refers to the intensity of the event.

Severity grades are assigned by the study site to indicate the severity of adverse experiences. Adverse events severity grade definitions are provided below:

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy and/or required hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.
Grade 5	Death	

3.2 Relatedness

The relatedness of the event refers to causality of the event to the study intervention. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors and plausibility.

Relationship to intervention is defined as:

- Definitely related: An adverse event that follows a temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test intervention and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
- Probably related: An adverse event that follows a reasonable temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.
- Possibly related: An adverse event that follows a reasonable temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure, but could have been produced by the participant's clinical state or by other therapies.
- Unrelated: An adverse event that does not follow a reasonable temporal sequence after administration of the test intervention and/or procedure and is most likely explained by the participant's clinical disease state or by other therapies.

4.0 Reporting Procedures of AE/SAEs

Standard reporting, or the process of reporting an event within 7 days of the site becoming aware of the event, is required for all reportable AEs, whether or not they are considered related to the clinical trial participation.

Expedited reporting, or the process of reporting an event within 24 hours of the occurrence of the event and/or the site's knowledge of the event, is required for all SAEs, including deaths. The SAE case report form and a progress note summary as well as any other relevant documentation related to the event should also be submitted with the initial report. If complete information about the event is not available at the time of the initial report, the event should still be reported with as much information as possible within the 24 hour window. The research staff is then responsible for gathering as much additional information as possible, and submitting this information within 14 days to the electronic database. If the SAE is not resolved or medically stable at this time or if new information becomes available after the SAE form is submitted, follow-up SAE information must be submitted as soon as possible, but at most within 14 days after the site learns of the information.

Additional information may need to be gathered in order for the research staff and investigator to evaluate the SAE and to complete the AE and SAE case report forms. This information is necessary to provide a complete and clear picture of the SAE and of the events preceding and following the event and may include obtaining hospital discharge reports, physician records, autopsy records or other types of records or information.

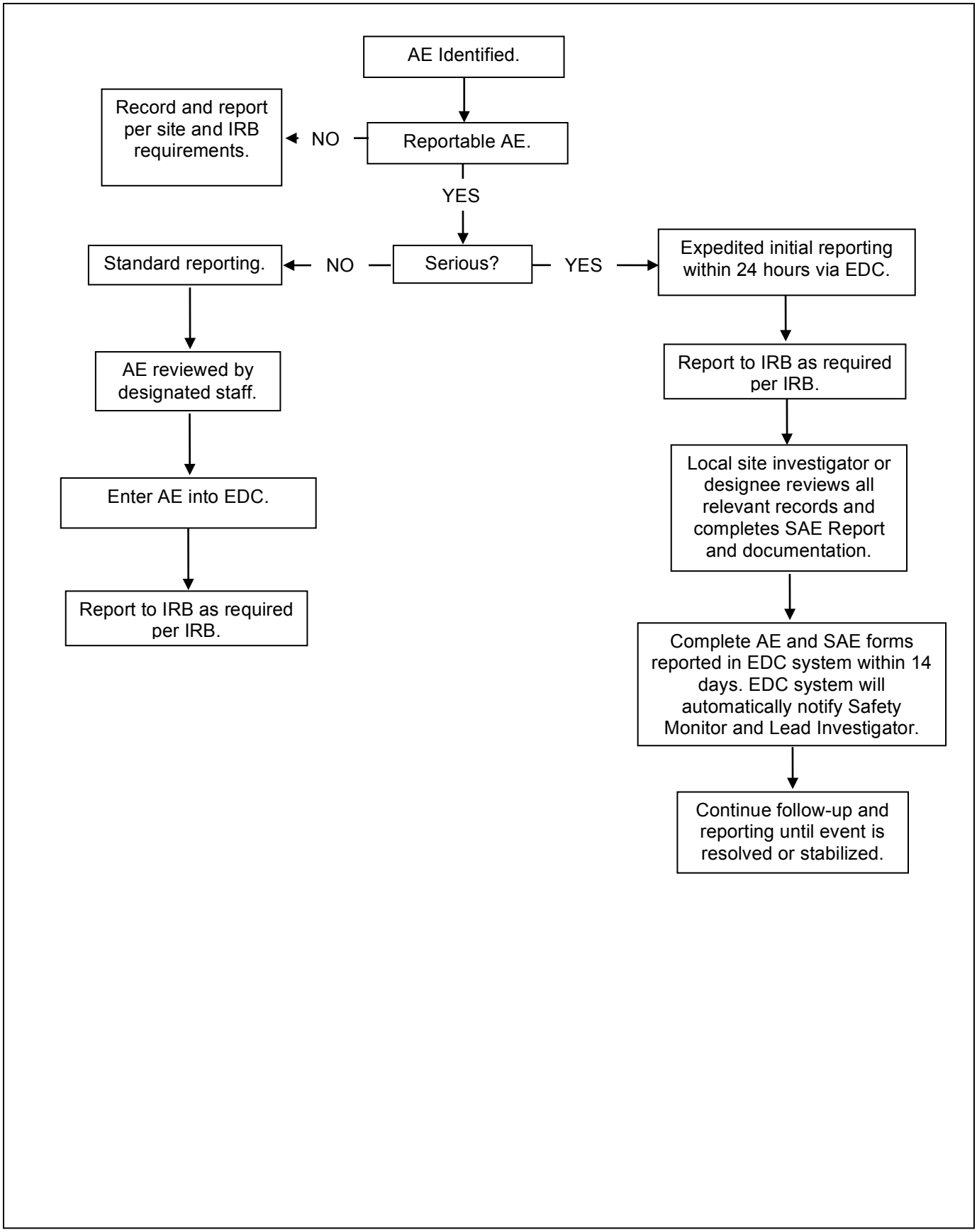
Drs. Rethorst and Trivedi will receive and review summary reports of all reportable adverse events associated with a clinical trial at least annually. Details regarding adverse events, if requested by the, local IRB or regulatory authorities, should be summarized in writing by the Principal Investigator and should include the treatment and resolution.

5.0 Discontinuation of Participant From a Clinical Trial Related to a Reported AE/SAE

The principal investigator must apply his/her clinical judgment in order to determine whether or not an AE/SAE is of sufficient severity to require that a participant be removed from the study intervention. If necessary, the Investigator may suspend any trial treatments and institute the necessary medical therapy or refer a participant to appropriate medical care in order to protect a participant from any immediate danger.

Subsequent review of the event(s) by the IRB or the sponsor may also suspend further trial treatment at a site. The study sponsor retains the authority to suspend additional enrollment and treatments for an individual study site or the entire study as applicable.

A participant also has the right to voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to continue (at least limited) scheduled evaluations, complete an end-of-study evaluation and be referred to appropriate care for medical supervision until the symptoms of any adverse event resolve or until their condition becomes stable.


AE Identified.
Reportable AE.
NO
Record and report per site and IRB requirements.
YES
Serious?
NO
Standard reporting.
YES
Expedited initial reporting within 24 hours via EDC.
AE reviewed by designated staff.
Enter AE into EDC.
Report to IRB as required per IRB.
Report to IRB as required per IRB.
Local site investigator or designee reviews all relevant records and completes SAE Report and documentation.
Complete AE and SAE forms reported in EDC system within 14 days. EDC system will automatically notify Safety Monitor and Lead Investigator.
Continue follow-up and reporting until event is resolved or stabilized.