Anxiety and Depression in Epilepsy: A Pilot Epileptologist-Driven Treatment Study

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

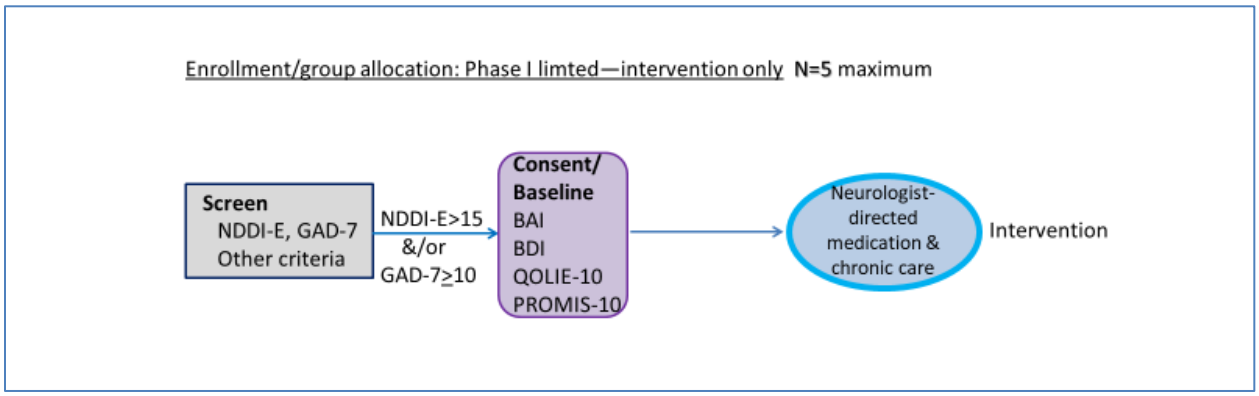
1.1 SYNOPSIS

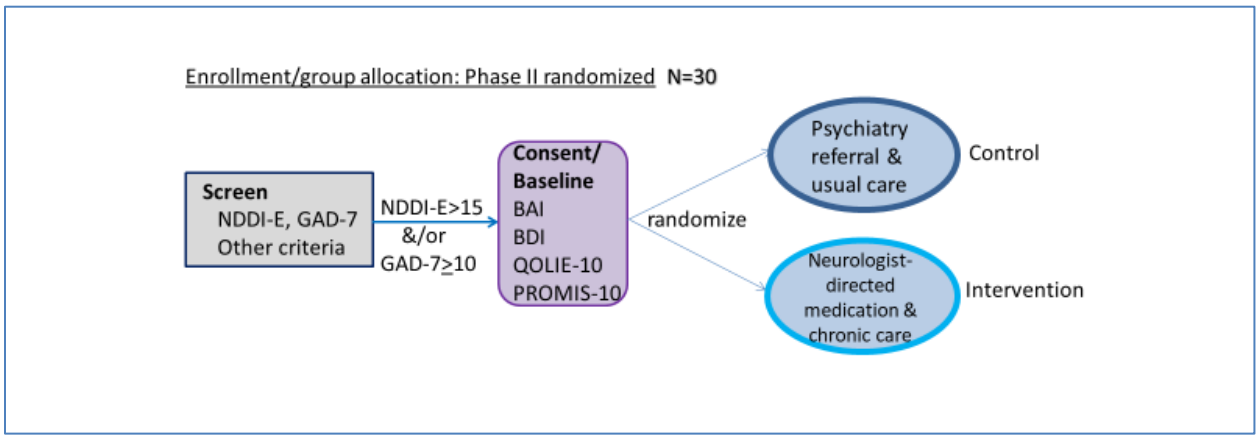
Title:	Anxiety and Depression in Epilepsy: A Pilot Epileptologist-Driven Treatment Study
Study Description:	This is a pilot feasibility trial of an epileptologist-driven medication treatment intervention for anxiety and depression, carried out directly in the epilepsy clinic during a regularly scheduled visit and supported by advanced practice provider (APP), compared to psychiatry referral. In study phase I, we will enroll up to 5 patients in the intervention arm to streamline the recruitment, intervention and outcome assessment process. In our study phase II randomized pilot, we hypothesize that the primary endpoint, adherence within the intervention arm (defined as participant report of taking the prescribed medication at 12 weeks and participation in at least 2 chronic care management encounters), will be greater than 60%. This hypothesis will be tested in study phase II by randomizing a total of 30 patients with clinically significant anxiety or depression [Generalized Anxiety Disorder-7 (GAD-7) ≥10 or Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) >15] to both treatment arms and following them for 12 weeks on allocated therapy (N=15 in each arm).
Objectives:	Primary Objective: To assess whether adherence to intervention study regimen developed for a randomized trial of management of anxiety and

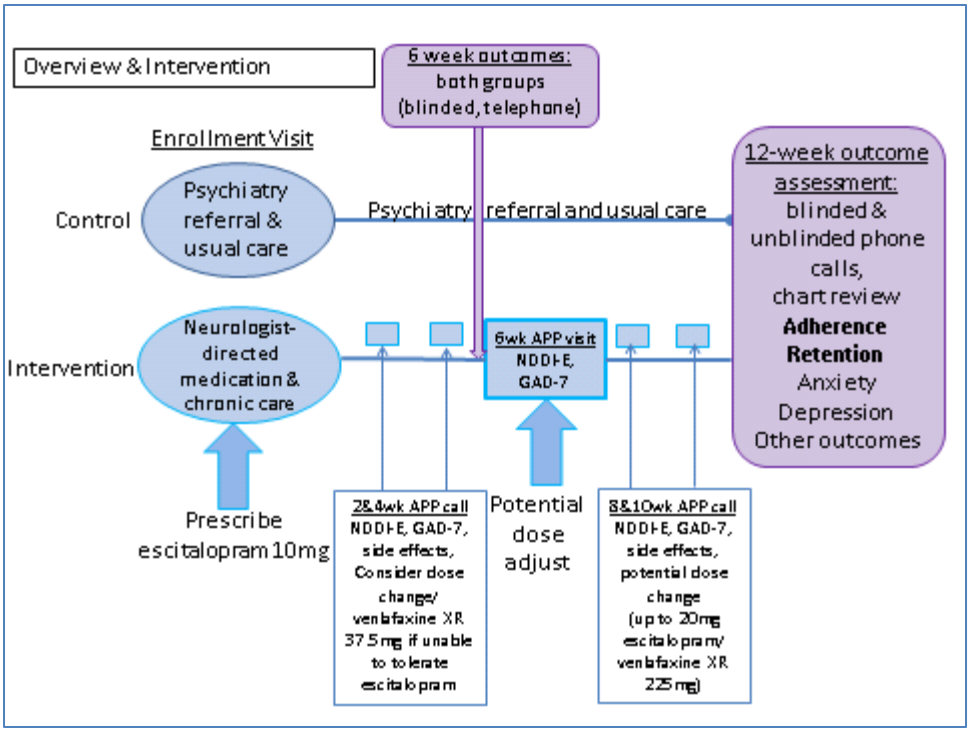
	depression in epilepsy, comparing neurologist/APP-administered medication/chronic care management *versus* usual care with psychiatry referral, is sufficient in pilot testing to support advancing to a larger definitive trial. Secondary Objectives: - To quantify rates of accrual and retention in a randomized trial of neurologist/APP-administered medication/chronic care management of anxiety and depression in epilepsy versus usual care with psychiatry referral, inputs that will inform the design and sample size calculations for a large, definitive trial. - To assess 12-week changes in anxiety and depression symptoms in the medication intervention group versus usual care/psychiatry referral control group, to provide preliminary estimates of effect magnitude to inform sample size calculations for a larger randomized trial. Anxiety and depression will be measured by the Beck Anxiety Index (BAI) and Beck Depression Inventory-II (BDI) respectively. There will be equal allocation of subjects across the 2 groups. As of May 13, 2019, the active major goal of the study has shifted to the original secondary objective related to retention.
Outcomes:	Primary Outcome: -% adherence in the intervention arm, defined as the % of participants who report taking the prescribed medication at 12 weeks AND who have completed at least 2 of the chronic care management scheduled visits (telephone or clinic visit) Secondary Outcomes: -accrual: % of patients screened for the trial who are eligible % of patients eligible who are randomized -retention: % of participants from each arm who complete 12-week outcome assessment Proposed efficacy outcomes: a. 12 week change in Beck Depression Inventory-II (among those with high depression at baseline) b. 12 week change in Beck Anxiety Index (among those with high anxiety at baseline)
Study Population:	Phase I: intervention only pre-piloting: up to 5 adults, characteristics described below Phase II: 30 adults with epilepsy seen in follow-up at the Wake Forest Comprehensive Epilepsy Center who screen positive for clinically significant anxiety and/or depression (GAD-7≥10 and/or NDDI-E >15) at baseline
Phase:	N/A: Non -FDA regulated

Description of Sites/Facilities Enrolling Participants:	Wake Forest Comprehensive Epilepsy Center, a level IV comprehensive epilepsy center in Winston-Salem, NC with a busy outpatient clinic serving patients primarily from Western North Carolina and adjacent states.
Description of Study Intervention:	A best practice chronic care management plan for anxiety and depression carried out in the epilepsy clinic, characterized by: 1. epileptologist-initiated selective serotonin reuptake inhibitor(SSRI)/serotonin norepinephrine reuptake inhibitor(SNRI) therapy 2. repeated phone calls by an APP (at 2, 4, 8, and 10 weeks post-enrollment) to assess for side effects and reassess anxiety and depression symptoms for potential dose adjustment, and 3. one 6-week follow-up clinic visit with the APP for potential dose adjustment.
Study Duration:	Up to 2 years
Participant Duration:	12 weeks

1.2 SCHEMA


Enrollment/group allocation: Phase I limted—intervention only N=5 maximum
Screen
NDDI-E, GAD-7
Other criteria
NDDI-E>15
&/or
GAD-7≥10
Consent/
Baseline
BAI
BDI
QOLIE-10
PROMIS-10
Neurologist-directed medication & chronic care
Intervention


Enrollment/group allocation: Phase II randomized N=30
Screen
NDDI-E, GAD-7
Other criteria
NDDI-E>15
&/or
GAD-7≥10
Consent/
Baseline
BAI
BDI
QOLIE-10
PROMIS-10
randomize
Psychiatry referral & usual care
Control
Neurologist-directed medication & chronic care
Intervention


Overview & Intervention
6 week outcomes: both groups (blinded, telephone)
Enrollment Visit
Control
Psychiatry referral & usual care
Psychiatry referral and usual care
12-week outcome assessment: blinded & unblinded phone calls, chart review
Adherence
Retention
Anxiety
Depression
Other outcomes
Intervention
Neurologist-directed medication & chronic care
6wk APP visit NDDI-E, GAD-7
Prescribe escitalopram 10mg
2&4wk APP call NDDI-E, GAD-7, side effects, Consider dose change/ venlafaxine XR 37.5mg if unable to tolerate escitalopram
Potential dose adjust
8&10wk APP call NDDI-E, GAD-7, side effects, potential dose change (up to 20mg escitalopram/ venlafaxine XR 225mg)

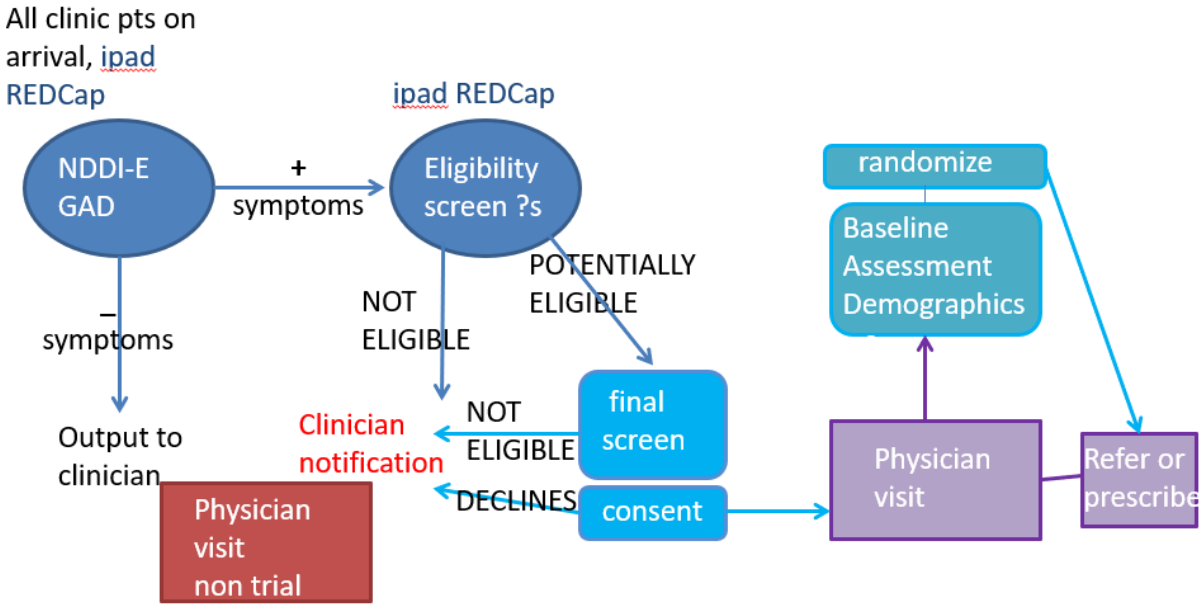
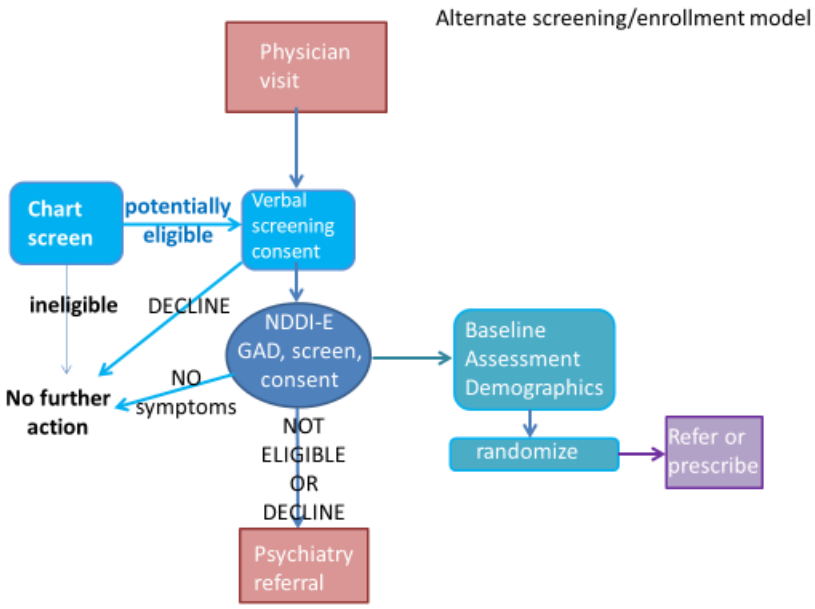

All clinic pts on arrival, ipad REDCap
ipad REDCap
NDDI-E GAD
+ symptoms
Eligibility screen ?s
– symptoms
Output to clinician
NOT ELIGIBLE
POTENTIALLY ELIGIBLE
Clinician notification
NOT ELIGIBLE
DECLINES
final screen
consent
Physician visit non trial
randomize
Baseline Assessment Demographics
Physician visit
Refer or prescribe

Table 1: Enrollment Criteria

Inclusion Criteria	Exclusion Criteria
Age >18years	Psychogenic nonepileptic seizures
Minimum 1 prior clinic visit	Prior psychiatric hospitalization
NDDI-E>15 and/or GAD-7≥10	Pregnancy or lactation
Adequate cognition (able to complete surveys)	History of manic symptoms (MINI DSM-IV past manic episode module)
Diagnosis of epilepsy: • EEG with documented seizure or epileptiform discharges OR • normal EEG & seizure remission with antiseizure drug OR • Neurologist's clinical impression is epilepsy & no significant consideration of alternative	Current treatment by psychiatrist or therapist
	Active suicidality at the time of screening
	Current scheduled anxiety/depression drug (SSRI, SNRI or atypical antidepressant, buspirone)
	Known allergy to escitalopram or venlafaxine

Table2: Exploratory Efficacy Outcome Assessment

Outcome	Measure	Timing	Method
Depression	**BDI-II (primary)**	6 weeks, 12 weeks	blinded phone
	NDDI-E	6 weeks, 12 weeks	blinded phone
Anxiety	**BAI (primary)**	6 weeks, 12 weeks	blinded phone
	GAD-7	6 weeks, 12 weeks	blinded phone
Epilepsy-related quality of life	QOLIE-10	6 weeks, 12 weeks	blinded phone
Patient-reported outcome	PROMIS-10	6 weeks, 12 weeks	blinded phone
Patient satisfaction	CAHPS	12 weeks	blinded phone
Clinical Outcomes	LAEP: Side effects, Seizure frequency	12 weeks 12 weeks	blinded phone blinded phone
Medication Adherence	Morisky-4	12 weeks	blinded phone
Healthcare utilization	ED visits, clinic phone calls, hospitalizations		telephone, medical record


Alternate screening/enrollment model
Physician visit
Chart screen
potentially eligible
Verbal screening consent
ineligible
DECLINE
NDDI-E GAD, screen, consent
Baseline Assessment Demographics
No further action
NO symptoms
NOT ELIGIBLE OR DECLINE
randomize
Refer or prescribe
Psychiatry referral

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures*	Screening Clinic Visit , Day 1	Baseline/*Randomize#* Day 1	APP Telephone Care 1 week 2	APP Telephone Care 2 week 4	Intermediate Outcome week 6	APP Clinic Visit week 6	APP Telephone Care 3 week 8	APP Telephone Care 4 Week10	Final Outcome Week 12
NDDI-E (screening: REDCap on iPad for clinical care)	X		X	X	X	r	X	X	X
GAD-7 (screening: REDCap on iPad for clinical care)	X		X	X	X	r	X	X	X
Eligibility questions: REDCap on iPad	X								
in-person coordinator screening	X								
Eligibility verification: medical chart	X								
Informed consent (enroll/intervention-phase I, enroll/randomize-phase II)		X							
Detail demographics		X							
Collect additional baseline medical history		X							
Record all medications		X							X
MOCA		X							
BDI		X			X				X
BAI		X			X				X
QOLIE-10		X			X				X
PROMIS-10		X			X				X
Randomize (phase II only)		X							
Accrual Outcomes	X	X							
Prescribe escitalopram		X							
Potentially adjust dose/switch drug if not tolerated			X	X		X	X	X	
Brief side effect, adherence assessment			X	X		X	X	X	
Final Adherence Outcomes Taking medication? Modified Morisky-4 Review pharmacy records									 X X X
Retention Outcome									X
Psychiatry referral order		X							
Patient Satisfaction (CAHPS)									X
Medication Adherence (Morisky-4)									X
Side Effects (LAEP)		X							X
Seizure Frequency		X							X
Health Care Utilization/ED visits/hospitalization									X
Assess for other interventions (psychiatry referral in intervention group/SSRI prescription by epileptologist in control group)									X
Assess time to psychiatry visit, intervention by psychiatry									X

Key for Schedule of Activities:

***:** visits listed in **bold** occur for both intervention and control group; visits not bolded and green apply to *intervention group* only, procedures in blue occur for control group only (and only in phase II), procedures in green occur only for those receiving the intervention
#: randomization applies only to phase II
r: review scores collected at the intermediate outcome assessment

2 INTRODUCTION

2.1 STUDY RATIONALE

Depression and anxiety are highly prevalent and major contributors to poor outcomes in chronic diseases managed by medical specialists, including cancer, congestive heart failure, ischemic cardiac disease, chronic obstructive pulmonary disease, and multiple chronic neurologic diseases[1-2]. Depression and anxiety are often undertreated, and solutions such as psychiatrist-supported collaborative care models or co-location of psychiatrists are not feasible for many medical specialty clinics, nor generalizable to the broad health care system due to poor access to mental health specialists[3-5].

Epilepsy is a chronic neurologic condition having particularly high prevalence of depression and anxiety, and these symptoms are associated with increased mortality, health care cost, cognitive dysfunction, medication adverse effects, poor quality of life and poor seizure outcome[6-12]. Substantial unmet mental health care need exists in epilepsy, and a survey I conducted indicated top barriers to addressing anxiety and depression in epilepsy were poor access to psychiatrists and other mental health providers[4,13]. In epilepsy, screening for psychiatric symptoms at every visit is a quality measure, and free, valid and brief screeners for anxiety and depression exist (the Generalized Anxiety Disorder-7, GAD-7 and Neurologic Disorders Depression Inventory-Epilepsy, NDDI-E, respectively)[14-16]. Measurement-based depression care is effective in primary care populations, and Advanced Practice Providers (APPs) improve quality of care in mental health settings[17-18]. Thus, we have launched a research program to first pilot, and then definitively test, *a neurologist-directed, measurement-based, APP-supported medication and chronic care management intervention for depression and anxiety in the epilepsy clinic*, utilizing FDA-approved medications for anxiety and depression (specifically escitalopram or venlafaxine if escitalopram is not tolerated). In the currently proposed pilot trial, after an up to 5 patient intervention-only phase I, 30 patients will be enrolled and randomized to assess the feasibility of conducting a definitive trial of this intervention (study phase II). Specifically, the goals of this trial are to quantify recruitment and adherence rates - inputs required for planning the definitive trial; and to provide preliminary estimates of effect magnitude to inform sample size calculations for a larger trial.

2.2 BACKGROUND

Depression and anxiety in epilepsy are highly prevalent and major independent predictors of poor quality of life. Depression and anxiety occur in up to 40-55% of tertiary care epilepsy patients[21-25], and without structured assessment anxiety is under-recognized[6]. Although depression and anxiety are more important predictors of poor quality of life than seizure frequency[7,22,26], *these symptoms are underdiagnosed and undertreated in epilepsy*[27-28]. Treatment of depression and anxiety in epilepsy is important to prevent suicide[29], a contributor to excess mortality[8], as a potential way to reduce excessive health care use[10,30], and to improve quality of life[7,26]. However, *a substantial unmet mental health care need exists in epilepsy*[13]. Despite the American Academy of Neurology Epilepsy Quality Measure to screen for psychiatric symptoms at each visit, and existence of well-validated, free and brief screeners for anxiety and depression in epilepsy (the GAD-7 and NDDI-E), my recent survey of leading

epileptologists indicated that few use validated anxiety and depression screening instruments, largely due to poor availability of mental health providers[4,14-16,31-33].

Approaches to treating anxiety and depression in epilepsy (e.g. colocation of a psychiatrist in an epilepsy clinic or internet based cognitive behavioral therapy) may have some impact, but their generalizability is limited due to scarcity of mental health providers[4,5,34]. A **potential solution to address poor mental health care access is neurologist-driven medication treatment of depression and anxiety**[35]. Small studies suggest these symptoms improve with standard, FDA-approved therapies effective for depression and anxiety in the general population[36-37]. The majority of epileptologists surveyed were willing to prescribe antidepressants (55.9%)[4]. Repeated use of validated screening tools for anxiety and depression facilitate treatment of these symptoms by non-psychiatrists, as has been shown in primary care, geriatrics, and large-scale general population studies[17,38-39]. Given the high prevalence and unmet need, it is *important to use a learning healthcare system approach to assess feasibility and potential impact of measurement-based, neurologist-driven and APP-supported medication chronic care management of depression and anxiety*, to address these symptoms directly in the epilepsy clinic and potentially circumvent substantial barriers to mental health care.

We propose an innovative learning healthcare system approach to translate the concept of measurement-based depression care into a specialty clinic setting and extend the concept to treat depression *and/or anxiety*. Our neurologist/APP-administered medication intervention utilizes FDA-approved drugs with advantageous features for use in epilepsy (escitalopram and venlafaxine)[36-37] and a telephone-based chronic care management plan for repeated symptom measurement and side effect surveillance. The proposed **intervention may overcome barriers to implementing mental health treatment interventions in generalized clinical settings** by using healthcare providers commonly present in specialty clinics (physicians and APPs) along with a billable, best practices chronic care management intervention package.

To test this idea, we seek to pilot a *randomized trial of neurologist/APP medication management of depression and anxiety versus usual care with psychiatry referral* in our epilepsy clinic, **using epilepsy as a paradigm for chronic medical illness with high prevalence of psychiatric comorbidity**[14-15,31-32]. The goal is to assess feasibility of this pragmatic, *learning healthcare system* intervention (primary outcome adherence, secondary outcomes accrual, retention) and estimate anxiety and depression outcomes to explore whether a larger trial would be appropriate.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks of participating in this trial are similar to risks encountered in standard clinical practice, where FDA-approved SSRI/SNRI medications (escitalopram and venlafaxine XR) are commonly prescribed in primary care, psychiatry practices, and by some neurologists/epileptologists. Potential side effects of these drugs are well-known and listed in the package insert for each of the drug, with the most common side effects being minor symptoms including headache, nausea, diarrhea, insomnia, drowsiness, and sexual dysfunction[40-41]. Suicide is a known risk among patients with anxiety and/or depression, and there is a black box warning for potential increased suicidal thoughts among children, adolescents and potentially young adults treated with antidepressants. Monitoring is recommended[40-41]. Other serious risks are rare, and overall risks are no higher than in standard clinical practice using these drugs.

Psychiatry referrals are commonly employed in standard/usual care of patients who would be eligible for the trial.

Outcome assessments and repeated symptoms screening administered during the trial pose minimal if any risk to participants (use of time to complete assessments is the main impact on participants).

2.3.2 KNOWN POTENTIAL BENEFITS

The main benefit of prescribing SSRI/SNRI therapy and adjusting dose based on repeated assessment of depression and anxiety symptoms is improvement in these symptoms. Trials of primary care prescribing of antidepressant therapy with biweekly repeated symptom screening found that one-third of patients experienced remission of depression and nearly half responded to therapy[17]. Phase III trials have shown both escitalopram and venlafaxine XR to be effective in treating major depressive disorder and generalized anxiety disorder[40-41].

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk of the intervention in this study is minimal and no more than that experienced during standard clinical care (risk actually may be lower, as increased symptom monitoring and patient contact will occur in the best practice intervention via re-screening for anxiety and depression every 2 weeks). The benefit may be substantial. Since subjects are randomized to a treatment option in phase II, although both arms consist of appropriate clinical care for anxiety depression, randomization may pose some risk to participants if one arm proves to be more efficacious than the other.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess whether adherence to intervention study regimen developed for a randomized trial of management of anxiety and depression in epilepsy, comparing neurologist/APP-administered medication/chronic care management versus usual care with psychiatry referral, is sufficient in pilot testing to support advancing to a larger definitive trial.	-% intervention adherence in the intervention arm, defined as the % of participants who report taking the prescribed medication at 12 weeks (escitalopram or venlafaxine) AND who have completed at least 2 of the chronic care management scheduled visits (telephone or clinic visit)	*-obtain realistic estimate of feasibility of intervention implementation, i.e. adherence*
Secondary		
To quantify rates of accrual and retention in a randomized trial of neurologist/APP-administered medication/chronic care management of anxiety and depression in epilepsy versus usual care with psychiatry referral, inputs that will inform the design and sample size calculations for a large, definitive trial.	-accrual: % of patients screened for the trial who are eligible % of patients eligible who are randomized -retention: % of participants from each arm who complete 12 week outcome assessment As of May 13,2019, the main active study goal is focused on the retention endpoint.	*-to provide more accurate estimate of future trial accrual rate for planning of next step trial* *-to develop strategies to improve accrual in future trial* *-to estimate future retention & develop retention strategy*
To assess 12-week changes in anxiety and depression symptoms in the medication intervention group versus usual care/psychiatry referral control group, to provide preliminary estimates of effect magnitude to inform sample size calculations for a larger randomized trial. Anxiety and depression will be measured by the Beck Anxiety Index (BAI) and Beck	Proposed efficacy outcomes: a. 12 week change in Beck Depression Inventory (among those with high depression at baseline) b. 12 week change in Beck Anxiety Index (among those with high anxiety at baseline)	*-these are well validated common data elements for the intervention-targeted conditions; by 12wk, dose titration & clinical effect are expected to be achieved*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Depression Inventory-II (BDI) respectively).		
Tertiary/Exploratory		
To explore the impact of the intervention on potential future secondary efficacy measures, including 12 week epilepsy-specific quality of life, patient reported outcome, and 6 week change in anxiety and depression.	*Potential secondary future efficacy measures:* *-change in epilepsy-specific quality of life at 12 weeks (QOLIE-10)* *-change in generic patient reported outcome at 12 weeks (PROMIS-10)* *-change in depression (BDI) at 6 wk* *-change in anxiety (BAI) at 6 wk*	*-brief QOL instrument, QOL highly associated with anxiety and depression* *-brief generalizable patient outcome* -assess whether intervention has an early impact on symptoms compared to control condition
To explore the impact of the intervention on seizure frequency, adverse effects, health care utilization, patient satisfaction, and overall medication adherence.	*- seizure frequency* *-adverse medication effects* *-health care utilization, particularly ED visits and hospitalizations* *-patient satisfaction (CAHPS)* *-medication adherence (Morisky-4)*	*-worsened seizures, adverse effects and health care utilization are associated with presence of anxiety and depression* -assess impact of intervention on care satisfaction and overall medication adherence

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a pilot pragmatic, randomized trial of a medication treatment/chronic care management intervention for anxiety and depression in epilepsy implemented in the epilepsy clinic vs. psychiatry referral. Treatment is open-label, but secondary and exploratory outcome measures are collected by a research assistant blinded to treatment assignment. The goals of the trial are to assess feasibility of a potential larger trial of the intervention versus psychiatry referral and to generate preliminary estimates of the proposed primary outcomes of a larger trial (change in anxiety and depression from baseline among those with symptoms at baseline). The study is carried out at a single center (Wake Forest University). *Prior to the start of the randomized phase II for the trial,* ***a limited intervention-only pilot*** *will be carried out with up to 5 participants (phase I).* The purpose of this is to streamline enrollment, intervention and outcome assessment procedures to ensure they are optimized by the start of the randomized phase.

The intervention will consist of initiating a chronic care management plan in the epilepsy clinic and an initial prescription for escitalopram 10mg daily. Escitalopram dose adjustment will be made based on biweekly repeated screening of anxiety and depression symptoms using the NDDI-E and GAD-7 brief validated instruments for depression and anxiety, respectively, as well as side effects identified on biweekly telephone calls or the 6-week APP follow up visit. Escitalopram dose may be titrated up to a maximum of 20mg daily in 5-10mg increments every 2 weeks for treatment effect, or titrated down to 5mg if needed for adverse effects. If a participant is unable to tolerate escitalopram, then venlafaxine XR 37.5mg will be substituted, to be titrated in a similar manner biweekly based on side effects and anxiety and depression symptoms (with 37.5-75mg increment dose changes and maximum dose of 225mg daily). At the end of the 10 week chronic care intervention, participants will receive a prescription for the most recent dose of escitalopram or venlafaxine XR, and there may be a plan to transfer this prescription to the participant's primary care provider (PCP), depending upon epileptologist preference.

Participants randomized to control will have a psychiatry referral order placed by the treating epileptologist under typical care circumstances. This will be an internal or external referral order based on patient preference. If external, the order will be printed along with instructions for the patient to follow to find a provider covered by insurance.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Current usual care for anxiety and depression in epilepsy is highly variable, with underdetection of symptoms highly likely, as most epileptologists do not use validated screening instruments for depression or anxiety[4]. When symptoms are detected, management varies from referral to a mental health provider, referral to a PCP for management of symptoms, or epileptologist prescribing of an antidepressant or anxiolytic, with referral to mental health providers and epileptologist prescribing being the most common management approaches[4]. In this study, typical usual care with its current variability is not a feasible control condition, as the likely variability would dilute the intervention condition, since some control patients could be prescribed intervention drug or related medications. Considering the risk of suicide associated with anxiety and depression, it would be unethical to offer no treatment to the control group. Referral to psychiatry is a current acceptable standard of care for management of anxiety and depression in epilepsy despite the various barriers to access mental health

specialists. Thus, a psychiatry referral control group will reflect the reality of treatment approach for many epilepsy patients with anxiety and depression under current care circumstances.

4.3 JUSTIFICATION FOR DOSE

The starting doses for escitalopram and venlafaxine are commonly used, recommended starting doses for these agents and titration schedules are consistent with package insert recommended titration schedules. The maximal doses are within the FDA approved dosing range[40-41].

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, age 18 or older
4. Ability to take oral medication and be willing to adhere to the intervention regimen
5. Minimum 1 prior clinic visit at the Comprehensive Epilepsy Center
6. Adequate cognition (able to complete NDDI-E and GAD-7 independently)
7. Diagnosis of epilepsy: EEG with documented seizure or epileptiform discharges OR non-epileptiform EEG and seizure remission with antiseizure drug OR treating epileptologist's leading clinical impression is epilepsy
8. NDDI-E score >15 AND/OR GAD-7 score $\geq$10

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy or lactation
2. Known allergic reactions to escitalopram or venlafaxine
3. Comorbid psychogenic nonepileptic seizures
4. Prior psychiatric hospitalization
5. Prior suicide attempt
6. History of manic or psychotic symptoms (past manic episode (MINI-DSM-IV), or psychotic symptom screen positive)
7. Current treatment by a psychiatrist or counselor/therapist
8. Active suicidality at the time of screening
9. Current treatment with buspirone or an SSRI/SNRI/atypical antidepressant (specifically bupropion, fluoxetine, levomilnacipran, citalopram, milnacipran, desvenlafaxine, mirtazapine, duloxetine, paroxetine, escitalopram, sertraline, fluvoxamine, venlafaxine, vilazodone, vortioxetine)

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to be screened for the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a lack of current clinically significant anxiety or depression symptoms or other reasons may be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample size: phase I: up to 5, phase 2: 30 (30 to be randomized). Anticipated number of participants to be screened: up to 5000
- Anticipated accrual rate: 5 per month
- Number of sites: 1
- Recruitment venue: clinic of Wake Forest Comprehensive Epilepsy Center, adult-focused epilepsy physician practices
- Participants will be identified using a learning health system care model which includes ALL patients completing the GAD-7 and NDDI-E instruments upon check-in for a regular clinic visit in REDCap on an ipad. Those who have anxiety or depression (GAD-7 ≥ 10 or NDDI-E >15) will be prompted to complete additional eligibility questions in REDCap after brief screening consent, followed by in-person screening by the study coordinator if all of the electronic questions indicate potential eligibility. If eligible, then the full informed consent process will be completed by the study coordinator. If the participant consents, then they will proceed to the epilepsy clinic visit with the physician, followed by baseline research assessment and randomization. At randomization, the epilepsy physician will be informed of assignment and will either prescribe 10mg escitalopram or place a psychiatry referral order. See Figure on page 5 for diagram of screening/enrollment flow.
- Additional screening and enrollment procedures may be completed, including:
    - A post clinic visit screening and enrollment procedure (see figure on page 7) in which individuals who appear potentially eligible based on prior medical chart review are approached for screening immediately on completion of a regular clinic visit. Verbal screening consent is obtained, followed by NDDI-E and GAD-7 instruments, then additional screening if GAD-7 ≥ 10 or NDDI-E >15. Consent and enrollment, followed by randomization is then completed for those who are eligible and consent. All ineligible individuals with high GAD-7 and/or NDDI-E scores in this screening procedure will be offered a psychiatry referral. This model will be primarily utilized in the practices of epilepsy physicians newly added to the study team who had not previously participated in the learning health care system model described above.
    - New patients with high anxiety or depression symptoms identified via the learning health system model, if otherwise eligible and interested in the study will be offered a rapid follow-up visit with the epilepsy center physician to address anxiety and depression and potentially enroll in the study if still eligible at the time of follow-up.
    - We will expand the learning health system model of care by administering paper or electronic versions of the GAD-7 and NDDI-E to patients scheduled to see Kelly Conner, PA-C at the epilepsy center. Kelly will then have the option of scheduling patients for a fast-track follow up visit with their epileptologist for management of anxiety and/or depression/potential study enrollment.
- Multiple mailed/written reminders and telephone communications will be utilized to enhance participation in the outcome assessment telephone calls. These will also be scheduled at the time of enrollment if possible.
- Subjects will receive incentive of $25 gift card for completing 6 week outcome assessment call, and another $25 gift card for completing the 12-week outcome assessment calls.

- Efforts will be made to recruit any eligible participant seen in the practice, including women and under-represented populations
- Pregnant women will be excluded due to potential risk to unborn offspring due to introduction of a new medication during pregnancy, considering the potential risks associated with SSRI/SNRI use in pregnancy (pregnancy category C)[40-41].

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is a complex, chronic care management model of care for anxiety and depression in epilepsy characterized by the following components:

- prescription for escitalopram 10mg daily initially by the treating epileptologist

Chronic care management:

- biweekly APP telephone calls (2 weeks, 4 weeks, 8 weeks and 10 weeks)
  - use of standardized instruments to reassess anxiety and depression symptoms (NDDI-E and GAD-7)
  - assess for side effects
  - assess for manic and psychotic symptoms since last contact
  - potential medication dose adjustments/switch to venlafaxine XR based on symptom response and side effects identified
- 6-week follow-up clinic visit with the APP to review NDDI-E and GAD-7 symptom status, side effects and potentially adjust dose
- Maximal potential daily medication doses: escitalopram 20mg, venlafaxine XR 225mg

At the 10-week APP call, a prescription will be sent for the intervention medication with sufficient refills to last to the next regularly scheduled epilepsy clinic visit, or until a scheduled visit with the participant's primary care provider (PCP). The participant's epileptologist/APP team will continue to manage the medication as appropriate, along with ongoing usual epilepsy care, unless the intervention medication prescription was transferred to the participant's PCP due to epileptologist preference.

Control condition: psychiatry referral order placed by epileptologist under typical care circumstances (internal or external referral based on the participant's geographic preferences). Internal referrals will be processed by current clinic/institutional protocols. External referral orders will be printed and provided to the patient along with brief instructions on how to find a provider covered by the patient's insurance.

6.1.2 DOSING AND ADMINISTRATION

*see page 18 for definition of symptoms improved

- Initial treatment: escitalopram 10mg by mouth daily
- 2 week call:
  - if no side effects, continue 10mg escitalopram daily
  - if side effects, reduce to 5mg escitalopram daily
- 4 week call:
  - If symptoms are not improved, increase escitalopram daily dose by 5-10mg
  - If symptoms are improved, continue current dose
  - If side effects, reduce escitalopram daily dose by 5mg
  - If intolerable side effects at 5mg daily, stop escitalopram. Start *venlafaxine XR* 37.5mg daily, then increase to 75mg daily in 1 week.
- 6 week visit:
  - If symptoms are not improved, increase escitalopram daily dose by 5-10mg (up to maximum 20mg daily)

  - If symptoms are improved, or patient is already taking 20mg escitalopram daily and there are no side effects, continue current dose
  - If side effects, reduce escitalopram daily dose by 5mg
  - If intolerable side effects at 5mg daily, stop escitalopram. Start *venlafaxine XR* 37.5mg daily, then increase to 75mg daily in 1 week.
  - If *venlafaxine XR* was started previously:
    - If symptoms are not improved, increase daily dose by 75mg
    - If symptoms are improved, continue current dose
    - If side effects, reduce daily dose by 37.5mg
- 8 week call:
  - If symptoms are not improved, increase escitalopram daily dose by 5-10mg (up to maximum 20mg daily)
  - If symptoms are improved, or patient is already taking 20mg escitalopram daily and there are no side effects, continue current dose
  - If side effects, reduce escitalopram daily dose by 5mg
  - If intolerable side effects at 5mg daily, stop escitalopram. Start *venlafaxine XR* 37.5mg daily, then 75mg daily in 1 week.
  - If *venlafaxine XR* was started previously:
    - If symptoms are not improved, increase daily dose by 75mg (up to maximum 225mg daily)
    - If symptoms are improved, continue current dose
    - If side effects, reduce daily dose by 37.5mg
- 10 week call:
  - If symptoms are not improved, increase escitalopram daily dose by 5-10mg (up to maximum 20mg daily)
  - If symptoms are improved, or patient is already taking 20mg escitalopram daily and there are no side effects, continue current dose
  - If side effects, reduce escitalopram daily dose by 5mg
  - If intolerable side effects at 5mg daily, stop escitalopram. Start *venlafaxine XR* 37.5mg daily, then 75mg daily in 1 week.
  - If *venlafaxine XR* was started previously:
    - If symptoms are not improved, increase daily dose by 75mg (up to maximum 225mg daily)
    - If symptoms improved or already taking 225mg daily and no side effects, continue current dose
    - If side effects, reduce daily dose by 37.5mg

Definition of symptoms improved:

- if the GAD-7 and/or NDDI-E scale score(s) for which the patient screened positive for trial entry are lower than the score(s) from the most recent measurement (2 weeks prior). [ALSO: IF the patient met trial entry criteria based on GAD-7 score alone, then the current NDDI-E score must also be ≤15. OR IF the patient met trial entry criteria based on NDDI-E score alone, then the current GAD-7 score must also be <10.]

OR

- If the GAD-7 and NDDI-E scores are BOTH <10 and ≤15, respectively

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

N/A: this is a pragmatic trial in which the intervention and control will be carried out during normal clinical care, via standard prescribing and referral ordering.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A

6.2.3 PRODUCT STORAGE AND STABILITY

N/A

6.2.4 PREPARATION

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

In the randomized phase II, subjects will be randomized to medication/chronic care management intervention vs. psychiatry referral at the time of enrollment. Participants will be allocated to study group using fixed allocation randomization procedures, with a computer-based random number generating algorithm. Blocked randomization will be considered, with planned block sizes greater than the group number, and randomization will be stratified by epilepsy physician. Treatment group assignment will not be blinded to the treating physician, primary investigator, and primary study coordinator. Outcome assessment phone calls for gathering scaled instrument scores will be carried out by a second study coordinator blinded to treatment assignment (for both phases of the study). In discussions between study coordinators with the PI regarding outcome related items while the trial is running, all efforts will be made if feasible to prevent the PI from knowing the treatment group allocation at that time.

6.4 STUDY INTERVENTION COMPLIANCE

See outcome section for primary adherence outcome.
Adherence will be assessed by a single question at each chronic care management APP phone call and the APP clinic visit. The primary adherence outcome will be assessed in the intervention group at 12 weeks by the unblinded primary study coordinator along with a modified Morisky-4 scale. Also, the primary study coordinator will contact participant pharmacies to ascertain number of refills obtained for the intervention medication to compare to expected number of refills in the setting of complete adherence. Time to psychiatry appointment scheduling, whether an appointment was scheduled, and whether the participant attended the scheduled psychiatry appointment will be collected at 12 weeks by the primary study coordinator (unblinded). Medication adherence in general will be assessed using the Morisky-4 scale at 12 weeks in both groups by the blinded outcome assessment study coordinator.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from escitalopram or venlafaxine XR does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- 6 week (if not yet completed) and 12 week outcome assessment will still be completed unless the participant withdraws consent

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the Discontinuation Case Report Form (CRF). Subjects who sign the informed consent form but are not randomized/do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may be replaced, but will also be included in outcome assessment unless the participant withdrew consent.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete the 12-week outcome assessment and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to complete an outcome assessment appointment:

- The site will attempt to contact the participant and reschedule the missed outcome assessment within <1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Screening Assessment
-NDDI-E and GAD-7

Enrollment/Baseline Assessments:
-BAI
-BDI
-QOLIE-10
-PROMIS-10
-LAEP (Liverpool adverse events profile); also includes a seizure frequency assessment
-accrual assessment

Intervention Efficacy Assessments (blinded coordinator completes, except *data points collected by unblinded coordinator)
6 weeks
-BAI
-BDI
-QOLIE-10
-PROMIS-10
-NDDI-E
-GAD-7

12 weeks
-primary adherence assessment (patient reported medication adherence in intervention group)*
-secondary adherence assessments*
    -review of pharmacy fill records*
    -modified Morisky scale for intervention medication*
-retention assessment (was blinded outcome phone call completed?)
-BAI
-BDI
-QOLIE-10
-PROMIS-10
-NDDI-E
-GAD-7
-LAEP (Liverpool adverse events profile); includes a seizure frequency assessment as well
-CAHPS (patient satisfaction)
-Morisky-4 (medication adherence)
-time to psychiatry visit/appointment outcomes and psychiatry management plan in control group*
-healthcare utilization (ED visits, hospitalizations)

Clinical Care/Chronic Care Management (obtained from the medical chart)
NDDI-E and GAD-7 at 2 weeks, 4 weeks, 8 weeks, and 10 weeks
APP assessment of side effects: 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks
Dosing of intervention SSRI/SNRI prescribed: 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks
Adherence: whether participant completed the visit

Review of Clinical Chart: this will be done for preliminary eligibility assessment and for supplementary information on medications prescribed and health care utilization during the study period.

Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable.

8.2 SAFETY AND OTHER ASSESSMENTS

Screening Assessments for Safety and Eligibility (on Ipad):
-assess psychiatric history exclusions: prior psychiatric hospitalization, current treatment by a psychiatrist or therapist, current anxiety and depression medications, history of psychogenic nonepileptic seizures
-MINI DSM-IV past manic episode module (2-12 questions depending upon response)
-psychotic symptom screen (auditory hallucinations)

In-person screening
-past suicide attempt?
-further assess for active suicidality if score on suicidal ideation question of NDDI-E is 3 or higher (using crisis procedures questions outlined in manual and Appendix A)

Other Enrollment Assessments:
-detailed demographics
-MoCA (cognitive assessment)
-LAEP (Liverpool adverse events profile)

6 week assessment
-NDDI-E (validated suicidality question for safety)
-BDI suicidality question

12 week assessment
-NDDI-E (validated suicidality question for safety)
-LAEP (Liverpool adverse events profile)
-BDI suicidality question

Clinical Care/Chronic Care Management (obtained from the medical chart)
NDDI-E at 2 weeks, 4 weeks, 8 weeks, and 10 weeks (validated suicidality question for safety)
APP assessment of side effects: 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks
Dosing of intervention SSRI/SNRI prescribed: 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

The following events are considered **Serious adverse events (SAE)**

- death
- a life-threatening adverse event (Stroke, MI, fracture, suicide attempt)
- inpatient hospitalization
- prolongation of existing hospitalization
- a persistent or significant incapacity (last more than 48 hours and limits activities of daily living)
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study intervention must always be suspect.

- **Related** – A "related" adverse event reflects a realistic chance of a causal relationship between a study intervention and the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention as suggested by an event that follows within a reasonable time after the intervention (i.e., 24 hours), follows a pattern consistent with the study intervention, and improves when the study intervention has stopped and/or the reaction reappears when the intervention is readministered.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected.

- Expected: Any adverse event that is listed in medication package insert, protocol, consent form, or part of the normal disease condition.

- Unexpected: Any adverse event that is not listed in the current investigator brochure, protocol, consent form, or is not part of the normal disease progression.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes

- event description,
- time of onset and duration
- clinician's assessment of severity,
- relationship to study intervention (assessed only by those with the training and authority to make a diagnosis),
- time of resolution/stabilization of the event.

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be reported on a quarterly basis to the Safety Monitoring Committee (I-DSMB) and upon continuing review to the IRB, or at a timeframe and in a manner specified by the study sponsor.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any serious adverse events related to the intervention will be reported to the IRB within 24 hours of knowledge of the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A as the study intervention involves use of FDA-approved drugs commonly used in standard clinical care; potential side effects will be discussed with participants as part of standard clinical care

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

If a participant becomes pregnant while receiving the medication treatment intervention, risks and benefits of continuing the medication would be discussed with the participant and discontinuation of the medication intervention would be offered to the participant after the discussion of risks and benefits.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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** of the following criteria:

- 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;
- 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
- 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.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) related to the intervention will be reported to the IRB immediately (within 24 hours) upon the investigator becoming aware of the event.
- Any other UP will be reported to the PI within 7 days of the investigator becoming aware of the problem and to the IRB.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 1 week of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Study team will not be reporting unanticipated problems to participants.

8.5 CRISIS PROTOCOL/SAFETY

Crisis procedures: see Appendix A for instructions/crisis procedures document which pertains to the outcome assessment calls and all clinical encounters with the subjects (in the clinic, during telephone based chronic care management, or other clinic telephone encounters).

If there is a need for immediate treatment (e.g., active suicidal ideation, active psychotic symptoms, disorientation, active substance abuse) at any point in time, staff will notify the PI. In both cases, the participant may be referred for psychiatric care. Dr. James Kimball, study psychiatrist, will be available for input/guidance if needed. As an additional safety precaution, we will ask each participant upon study entry to identify 2 persons whom we can contact in case of an emergency and provide 2 telephone numbers for each of these 2 individuals. All participants will receive information about safety precautions and procedures to follow in the event that a participant becomes imminently suicidal. Each participant will be given telephone numbers for the Wake Forest Baptist Health psychiatrist-on-call and crisis hotline. Participants will be able to reach study staff or the psychiatrist-on-call 24-hours a day. If it is determined that a participant is not at risk of imminent harm, we may refer them for additional psychiatric care. If a participant continues to report active suicidal ideation and is at imminent risk, we will ask if there is anyone at home with the participant, speak with that person, and have that person take the participant to the nearest emergency room for an immediate evaluation. If there is no one with the participant, study staff will contact the person's emergency contacts and instruct them to take the

participant to the nearest emergency room for an immediate evaluation. If there is no one available to do this, mobile crisis management teams will be contacted and local law enforcement will be called to transport the participant to an emergency room.

Because active suicidal ideation and history of suicide attempt are exclusion criteria for the study, we anticipate that the risk of participants becoming suicidal during the study will be minimal. All study staff will receive training on the crisis protocol and will have regular meetings with the team to discuss clinical issues.

Additional safety procedures at outcome assessments (6 and 12 week outcome calls)
If any participant indicates a significant worsening in anxiety or depression scores (1 standard deviation increase on the BDI or BAI from baseline, 11.75 and 9.08, respectively)[19-20], the computer software system will facilitate identifying the worsening and an e-mail will be sent to the Wake Forest School of Medicine Project Manager and to study psychiatrist Dr. James Kimball. The patient will be assessed to determine if there is a need for immediate treatment, under the guidance of Dr. Kimball.

Staff will be instructed to follow the crisis protocol outlined in Appendix A and complete the Crisis Protocol Event Form. In both cases, the participant may be referred for psychiatric care by a physician or provider: their primary care physician, neurologist, APP, or emergency department physician.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary (pertains to randomized study phase II): We hypothesize that the primary endpoint, adherence within the intervention arm (defined as participant report of taking the prescribed medication at 12 weeks and participation in at least 2 chronic care management encounters), will be greater than 60%.

- Proposed Outcome Endpoint(s):

Among those with clinically significant depression at baseline (NDDI-E>15), 12-week change in Beck Depression Inventory Score will be better in the medication/chronic care management intervention group than in the psychiatry referral group.

Among those with clinically significant anxiety at baseline (GAD-7≥10), 12-week change in Beck Anxiety Index Score will be better in the medication/chronic care management intervention group than in the psychiatry referral group.

- Proposed Exploratory Endpoint(s):

Improvement in epilepsy-specific quality of life (QOLIE-10) at 12 weeks will be greater in the medication/chronic care management intervention group than in the psychiatry referral group.

Improvement in patient-reported outcome (PROMIS-10) at 12 weeks will be greater in the medication/chronic care management intervention group than in the psychiatry referral group.

Among those with clinically significant depression at baseline (NDDI-E>15), 6-week change in Beck Depression Inventory Score will be better in the medication/chronic care management intervention group than in the psychiatry referral group.

Among those with clinically significant anxiety at baseline (GAD-7≥10), 6-week change in Beck Anxiety Index Score will be better in the medication/chronic care management intervention group than in the psychiatry referral group.

9.2 SAMPLE SIZE DETERMINATION

Phase I: We will recruit up to 5 individuals in an intervention-only pilot intended to streamline study procedures, not for data analysis.

Phase II: We are aiming to recruit 30 participants for the randomized portion of the pilot study, with 15 in the intervention arm and equal allocation between intervention arm and the control arm. Using a Bayesian design and a simulation study we assessed the probability of declaring acceptable adherence (80% credible interval that true adherence is at least 60%, $Pr(X \geq 0.6) \geq 0.8$) over 10,000 simulated trials with sample size 15 in the intervention arm. We then summarized the results across all possible single trial outcomes and found if 11 to 15 subjects are adherent, we are at least 83% confident that the true probability of adherence is greater than 0.6. Thus, if at least 11 intervention arm participants meet the

primary adherence outcome, we will declare acceptable adherence for proceeding to a larger trial of this intervention.

9.3 POPULATIONS FOR ANALYSES

Intention to treat analysis will be carried out.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Categorical data will be presented using percentages and continuous data using means and standard deviations, unless the data is not normally distributed, in which case medians and ranges will be presented.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The number of intervention arm participants who meet the adherence criteria will be calculated, and as described above in the sample size determination section, if at least 11 intervention arm participants meet the primary adherence outcome, we will declare acceptable adherence for proceeding to a larger trial of this intervention.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Accrual (proportion of participants who screen positive for anxiety or depression symptoms, # participants enrolled per month, proportion of total clinic follow-up patients enrolled per month, proportion consented and reasons for screen failure) and **retention** by group (proportion of randomized participants completing 12-week outcome assessment), will be assessed. These results will be utilized to plan realistic screening and recruitment goals for our larger, next-step trial.

We will ***estimate 12-week change in anxiety and depression symptoms*** (BAI and BDI-II, respectively)[19-20] ***in the medication intervention versus psychiatry referral control groups.*** To estimate effect of the intervention versus psychiatry referral on depression (BDI), we will calculate individual-level changes in total scores from baseline to 12 weeks among those with significant depression on initial screen. Mean changes in scores will then be compared between the two groups, (psychiatry referral vs. intervention group), using a two-sample t test with alpha level = 0.05. To estimate the effect of the intervention versus psychiatry referral on anxiety (BAI), we will similarly calculate individual-level 12 week change in BAI from baseline among those with significant anxiety on initial screening and compare mean changes between the two groups in a similar manner. Similar statistical methods will be used to estimate the effect of the intervention on other exploratory outcomes shown in Table 2 on page 6 between groups for all participants. The primary purpose of this analysis is to provide initial estimates of effect sizes and variability to inform sample size calculations for the large, definitive trial.

9.4.4 SAFETY ANALYSES

Similar statistical methods will be used to test for adverse effects measured by the Liverpool Adverse Event Profile (LAEP), as for the secondary outcomes (2 sample t-test comparing mean change in score from baseline to 12-week assessment), among the entire study population. Also the proportion of individuals in each group reporting suicidality will be compared between groups (separately for the NDDI-E suicide screening question and the BDI suicide question).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographics and scaled scores for anxiety, depression, quality of life, seizure frequency, and patient reported outcome measure will be compared between the two groups. Two sample t-test and chi square analyses will be used as appropriate to compare the intervention and control groups.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A: this small pilot study will not have sufficient power for subgroup analyses

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and timepoint.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will include comparison of patient satisfaction at 12 weeks between the 2 groups, comparison of change in seizure frequency by study group, comparison of the frequency of major health care utilization events (such as ED visits) between the 2 groups. Two sample t-test or chi square analysis will be used as appropriate. Kaplan-Meier modeling of time to remission of symptoms measured by NDDI-E and GAD-7 (score ≤15 and <10 respectively) will be done in the intervention group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:
-brief screening consent
-consent for enrollment and intervention in phase I along with outcome assessment
-consent for treatment randomization and outcome assessment in phase II

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the Wake Forest University Department of Neurology. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Wake Forest University Department of Neurology.
When the study is completed, access to study data will be provided through the Wake Forest University Department of Neurology.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Safety Monitoring Committee (SMC) composed of individuals with the appropriate expertise, including an independent investigator and a biostatistician. We will collaborate with the institutional Data and Safety Monitoring Board (I-DSMB) to establish the SMC. Members of the SMC should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The SMC will meet at least semiannually to assess safety and efficacy data on each arm of the study. Specifically, the main potential serious adverse event in this trial is suicidality. The 6 and 12-week outcome assessment calls include administration of the NDDI-E instrument in both the control and intervention groups, which has a single passive suicidal ideation question that has been validated as a suicide screen[42], and a question in the BDI directly assessing suicidality. Data safety monitoring will include review of the proportion of participants reporting high suicidality scores (3 or 4 on the NDDI-E passive suicidality question or 2 or 3 on the BDI suicide question) in each group, presented at each review. The SMC will provide its input to the primary investigator and study sponsor.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- On-site monitoring early, for initial assessment and training and to a more limited extent later in the study will be completed by the primary investigator and the study coordinator. This will consist of initially comprehensive (100% data verification) review of the first 5 subjects enrolled followed by targeted data verification of endpoints and or random review of a few additional subjects and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. A quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the investigator/coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol and International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and self-report instruments will be entered into RedCap, a 21 CFR Part 11-compliant data capture system provided by Wake Forest University Health Sciences. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 6 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigators to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents,

reported to the appropriate funding organization Program Official and the primary investigator. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x 7years after the completion of the primary endpoint by contacting Dr. Heidi Munger Clary.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership, in conjunction with the funding agency, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
APP	Advanced Practice Provider
BAI	Beck Anxiety Index
BDI	Beck Depression Index
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DRE	Disease-Related Event
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GAD-7	Generalized Anxiety Disorder-7
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
I-DSMB	Institutional Data and Safety Monitoring Board
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LAEP	Liverpool Adverse Events Profile
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
NCT	National Clinical Trial
NDDI-E	Neurologic Disorders Depression Inventory-Epilepsy
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PCP	Primary Care Provider
PI	Principal Investigator
PROMIS-10	Patient Reported Outcome-10
QA	Quality Assurance
QC	Quality Control
QOLIE-10	Quality of Life in Epilepsy-10
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2	5/14/2018	Change manic symptom exclusion from SCID-II screen to MINI for DSM-IV	Observation that SCID-II was oversensitive: many individuals were ineligible due to irritability but not true past manic episode
3	6/21/2018	Change MoCA to a baseline variable, modify cognitive inclusion criteria to ability to complete questionnaires independently. Add 3rd physician Dr. Cormac O'Donovan	To boost recruitment based on observations of reasons for screen failure and frequency during enrollment to date.
4	7/21/2018	Remove strict +/- 2 day timeframe for each study activity	We now recognize that strict time windows such as these are not practical or commonly used in these types of behavioral trials.
5	9/10/2018	Add additional recruitment strategies and related changes	We have recognized that additional recruitment strategies are required due to unexpectedly high screen failure rate and decline of consent.
6	5/13/2019	Clarify current goals of the project related to secondary retention endpoint. Add potential for electronic GAD-7 and NDDI-E administration by study team in clinics of Kelly Conner, PA-C.	Major goals have shifted to generating preliminary retention data. Clarification of goals requested by DSMB. An electronic tool for administering the GAD-7 and NDDI-E has become available for clinical use in the electronic medical record.

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