Anxiety and depression in epilepsy: assessing outcomes using the electronic medical record (EMR)

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STATEMENT OF COMPLIANCE

The study 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 staff who are responsible for the conduct, management, or oversight of this study 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: assessing outcomes using the electronic medical record (EMR)

Study Description:

This is an observational, randomized study among N=30 individuals with epilepsy and high or borderline anxiety or depression symptoms receiving usual care at the Wake Forest Comprehensive Epilepsy Center. Participants are randomized to one of two outcome assessment methods [EMR-based-interventional method vs. telephone-based-standard method] for collecting quality of life, anxiety and depression outcomes at 3 and 6 months, under usual care management.

The primary aim of the study is to assess feasibility of EMR-based outcome assessment by measuring 6-month retention. We hypothesize that the primary endpoint, retention within the EMR-outcome assessment arm (defined completion of the 6 –month outcome assessment instruments via the EMR), will be greater than 60%.

This hypothesis will be tested by randomizing 30 patients with borderline or clinically significant anxiety or depression symptoms [Generalized Anxiety Disorder-7 (GAD-7) >7or Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) >13] to both outcome assessment methods during usual care and assessing 3- and 6-month quality of life, anxiety, and depression outcomes using the allocated outcome assessment method (N=15 in each arm).

We will also estimate 6-month change in epilepsy-specific quality of life in the entire study group (N=30) during usual care.

Objectives:

Primary Objective: To assess whether retention in the EMR-based outcome method arm at 6 months is sufficient in pilot testing to support use of this outcome assessment method in future pragmatic trials of management interventions for anxiety and depression in epilepsy.

Secondary Objectives:
- To quantify retention at 3-and 6- months in the study population using a standard pragmatic trial outcome measure (telephone outcome assessment), and at 3 months using the EMR based outcome assessment method
- To estimate 6-month change in epilepsy-specific quality of life (QOLIE-10, primary outcome) and depression and anxiety (secondary) at 3 and 6 months during usual care, among the feasibility cohort of individuals with

	epilepsy and borderline to high anxiety or depression scores at baseline (GAD-7>7 or NDDI-E>13 at time of screening).
Outcomes:	Primary Endpoint: --% retention in the EMR outcome arm, defined as the % of participants who complete the 6 month outcome instruments in the EMR Secondary Endpoints: --% retention in the telephone outcome arm, defined as the % of participants who complete the 6 month outcome instruments via telephone Quality of life under usual care: --6 month change in QOLIE-10 (Quality of Life in Epilepsy-10) from baseline --3 month change in QOLIE-10 from baseline Other outcomes of usual care: --change in anxiety (GAD-7) score from baseline to 3 and 6-month outcome assessments --change in depression (NDDI-E) score from baseline to 3- and 6-month outcome assessments
Study Population:	30 adults with epilepsy seen in follow-up at the Wake Forest Comprehensive Epilepsy Center with borderline or clinically significant anxiety and/or depression (GAD-7>7 and/or NDDI-E >13) at baseline
Phase:	N/A: this is not a treatment study
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.
Study Duration:	Up to 3 years
Participant Duration:	6 months

1.2 SCHEMA

Figure 1: Study Overview

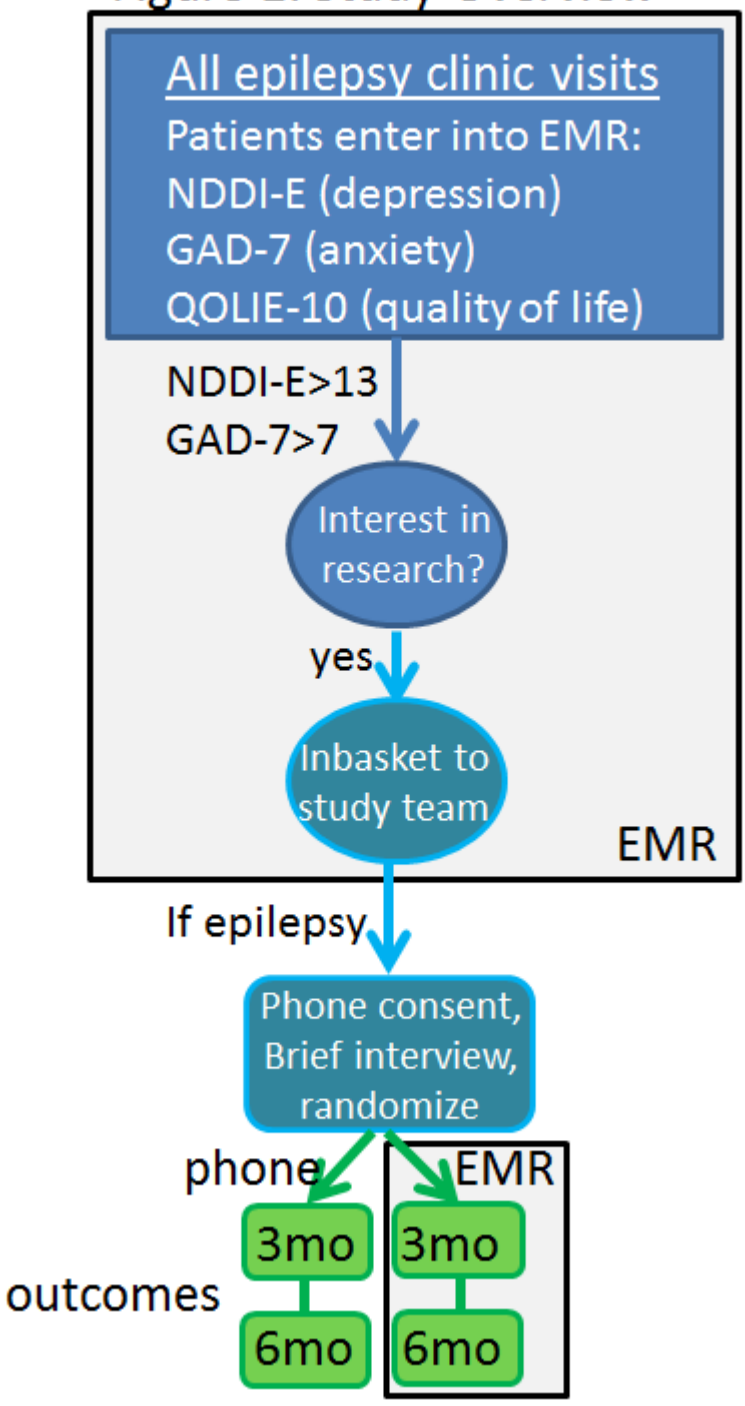
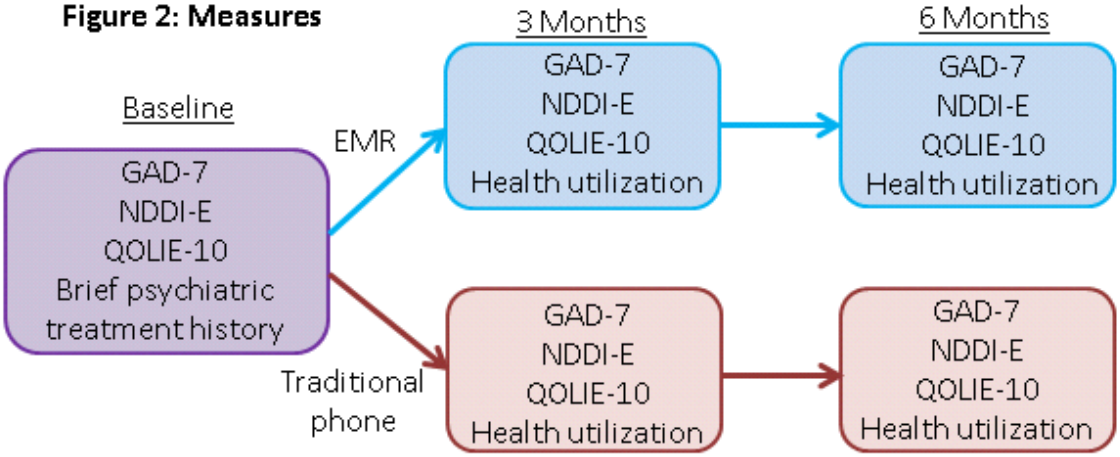


Table 1: Enrollment Criteria
Age≥18 years
Completed electronic questionnaires independently in clinic
Borderline or high anxiety and/or depression symptoms GAD-7>7 NDDI-E>13
Epilepsy diagnosis (clinician impression or EEG-based)
NO passive suicidal ideation (NDDI-E item 4 score NOT 3 or 4)

Figure 2: Measures



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures*	Screening Clinic Visit	Post-visit screening	Consent/ Enrollment/ Randomization	3 month outcome assessment	6 month outcome assessment
NDDI-E	X			X	X
GAD-7	X			X	X
QOLIE-10	X			X	X
EMR question to patient: interest in research?	X				
Eligibility verification: medical chart		X			
Telephone consent			X		
Collect additional brief psychiatric history			X		
Randomize			X		
EMR baseline: demographics			X		
EMR baseline: medications			X		
Management plan from screening usual care visit			X		
Health utilization outcomes				X	X
Feasibility assessments	X			X	X

Key for Schedule of Activities:

***:** procedures with green X above are administered as part of routine clinical care

2 INTRODUCTION

2.1 STUDY RATIONALE

Anxiety and depression are highly prevalent and major contributors to poor quality of life and other poor outcomes in epilepsy, including increased mortality, health care cost, cognitive dysfunction, medication adverse effects, and poor seizure outcomes[1-7]. Despite this importance, **anxiety and depression are under-recognized and undertreated in epilepsy**, and a recent survey indicated top barriers to addressing anxiety and depression in epilepsy were poor access to psychiatrists and other mental health providers[8-10]. Due to poor access to mental health, solutions such as colocation of psychiatrists and psychologist-driven internet behavioral approaches are not feasible for most epilepsy or neurology clinics[8-12]. In response, neurologist-driven solutions are proposed, including a new epilepsy quality measure for conducting validated anxiety and depression screeners at every neurology visit and many expert publications encouraging direct medication treatment by neurologists[10; 13-17]. However, significant barriers to screening exist, as >50% of surveyed epileptologists indicated inadequate time to administer screeners[10]. In implementing validated anxiety and depression screening during our ongoing learning health system trial, we demonstrated *substantial staffing effort is needed to administer screeners and document in the medical record*. There is also a paucity of data on outcomes of screening and/or treatment of anxiety and depression in epilepsy populations, especially real-world epilepsy clinic populations. Despite conceptions that most epilepsy patients are not receiving treatment for anxiety or depression[10; 14] our preliminary data indicates ***nearly half of those with active anxiety or depression symptoms are on medication treatment, and thus have inadequate symptom relief despite treatment***.

Considering these challenges, streamlined methods of screening and longitudinal outcome assessment are fundamental to assessing outcomes of standard treatment and developing effective pragmatic interventions for anxiety and depression in epilepsy. We propose to **implement and assess a learning health system, electronic medical record (EMR)-based screening and outcome assessment for anxiety and depression in the epilepsy clinic**.

2.2 BACKGROUND

Anxiety and depression 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[18-20], and without structured assessment, anxiety is under-recognized[1]. Although depression and anxiety are more important predictors of poor quality of life than seizure frequency[2; 21; 22], *these symptoms are underdiagnosed and undertreated in epilepsy*[23; 24]. Treatment of depression and anxiety in epilepsy is important to prevent suicide[25] which contributes to excess mortality[3], as a potential way to reduce excessive health care use[4; 26], and to improve quality of life[2; 22]. However, **a substantial unmet mental health care need exists in epilepsy**[8; 9].

The 2014 American Academy of Neurology Epilepsy Quality Measurement Set introduced a measure to screen for "psychiatric or behavioral health disorders" at each visit, and well-validated, free and brief anxiety and depression screeners exist for epilepsy (the GAD-7 and NDDI-E)[27-33]. Despite this, my 2016 survey of leading epileptologists indicated few used validated anxiety and depression screening instruments (<9% and <19%, respectively), due to

poor availability of mental health providers and lack of time to administer validated screeners[10]. Since then, a newly published Epilepsy Quality Measure (2017 Measure) ***requires using validated screeners for anxiety and depression at every visit***[13]. Our experience with an ongoing learning health system pilot trial of neurologist treatment for anxiety and depression has demonstrated extraordinary manpower efforts are required to accomplish screening in an entire epilepsy practice (up to 80-90% effort split among different staff). This validates concern about time-related barriers to administering screeners raised in the 2016 epileptologist survey[10] and **indicates need to develop efficient methods to conduct screening in ways that minimize clinical or research staff time**. Patient entry of questionnaires directly into the medical record via patient portal interfaces, with responses stored as discrete data fields that can then be exported for data analyses are a potential timesaving technique to conduct outcomes research and achieve clinical quality metrics simultaneously. Through the existing multicenter AHRQ-funded collaboration, the Neurology Practice Based Research Network (NBPRN), we currently utilize EMR-based entry of validated anxiety, depression, and epilepsy-specific quality of life measures as discrete data fields[34; 35]. We also now have access to patient-entered versions of these instruments (Generalized Anxiety Disorder-7, GAD-7, Neurological Disorders Depression Inventory for Epilepsy, NDDI-E, and Quality of Life in Epilepsy-10, QOLIE-10). **Thus, we are uniquely poised to test feasibility of these novel tools for conducting EMR-based outcomes research.**

Identifying effective interventions for mental health comorbidities and testing treatment outcomes are ***epilepsy research priorities recognized by the Institute of Medicine, and the National Institute of Neurological Disorders and Stroke (NINDS) epilepsy benchmarks include limiting adverse effects on quality of life for people with epilepsy, including mental health***[36; 37]. 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 and lack of funding for mental health providers[10-12]. Based upon an assumption that medications effective for anxiety and depression in the general population are also effective among people with epilepsy (selective serotonin reuptake inhibitors, SSRI and serotonin and norepinephrine reuptake inhibitors, SNRI), expert publications frequently suggest neurologist treatment of anxiety and depression, and many epileptologists report willingness to prescribe a medication for depression or anxiety[10; 15; 16]. *However, there is a paucity of data on longitudinal outcomes of anxiety or depression treatment in epilepsy* (whether under experimental treatment conditions or usual care) *and a total lack of longitudinal data on those with potentially clinically significant borderline symptom scores* (GAD-7: 7-9, NDDI-E: 14-15)[29; 31]. Our preliminary data raise questions regarding whether SSRI/SNRI medications are effective to relieve symptoms of anxiety and depression in epilepsy, as 47% of 106 epilepsy clinic patients with high anxiety or depression scores (GAD-7≥10, NDDI-E>15) were already treated with an SSRI or SNRI (compared to 24% of all consecutive patients examined in a prior analysis). Our data also raise concern that many patients may be too sick from a psychiatric perspective to be managed by a neurologist, as 28% of 106 with high anxiety or depression scores had a prior psychiatric hospitalization. **Thus, further research to assess longitudinal outcomes of anxiety and depression under usual care circumstances is essential for designing appropriate pragmatic interventions to test in future trials.**

In this study, we aim to introduce a standard care screening and outcome assessment paradigm for anxiety and depression in epilepsy using EMR-based direct patient reported measures to overcome high staffing burden of screening, to assess the feasibility of obtaining

EMR-based research outcome measures, and to generate preliminary longitudinal quality of life outcome data in the setting of usual care.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This is not a treatment study and the risks associated with study participation are minimal. The anxiety and depression instruments used for eligibility screening are already administered as standard care in our epilepsy center. The current epilepsy quality measurement set includes using standardized instruments to screen for anxiety and depression at each visit, and assessing quality of life at each visit[13].

Outcome assessments administered during the trial pose minimal if any risk to participants (use of time to complete assessments is the main impact on participants). Completing questionnaires about anxiety or depression may result in awareness of emotional symptoms that participants may not have otherwise recognized.

There is a slight chance that suicidality may be identified during outcome assessment due to the underlying anxiety or depression condition we aim to study. We have outlined robust safety measures used in prior studies by the investigator team, which go beyond institutional clinical protocols for response to these symptoms and thus provide additional safety measures beyond what is typical in standard care. We also anticipate that this would be a rare occurrence, especially because our design excludes individuals with possible passive suicidal ideation at the time of initial screening.

Potential breach of confidentiality is an additional risk; we have outlined methods to minimize this risk in section 10.

2.3.2 KNOWN POTENTIAL BENEFITS

As this is not a treatment study, there is no expected benefit for the participants. The study is expected to yield generalizable knowledge to support future research to improve quality of life in epilepsy.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

As described above, there is minimal risk and no expected benefit to individual participants.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess whether retention in the EMR-based outcome method arm at 6 months is sufficient in pilot testing to support use of this outcome assessment method in future pragmatic trials of management interventions for anxiety and depression in epilepsy.	-% retention in the EMR outcome arm, defined as the % of participants who complete the 6 month outcome instruments in the EMR	*-obtain realistic estimate of feasibility of long-term EMR-based outcome assessment in this population*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
To quantify retention at 3-and 6-months in the study population using a standard pragmatic trial outcome measure (telephone outcome assessment), and at 3 months using the EMR based outcome assessment method.	-% retention at 6 months in the telephone outcome arm, defined as the % of participants who complete the 6 month outcome instruments via telephone -% retention at 3 months in the EMR outcome arm, defined as the % of participants who complete the 6 month outcome instruments via telephone -% retention at 3 months in the telephone outcome arm, defined as the % of participants who complete the 6 month outcome instruments via telephone	*-to estimate future retention & develop retention strategy* *-to assist in determining whether future studies should include telephone-or EMR-based outcome assessment for shorter and longer outcome assessment durations*
To estimate 6-month change in epilepsy-specific quality of life (QOLIE-10, primary outcome) and depression and anxiety (secondary) at 3 and 6 months during usual care, among the feasibility cohort of individuals with epilepsy and borderline to high anxiety or depression scores at baseline.	--6 month change in QOLIE-10 from baseline --3 month change in QOLIE-10 from baseline --change in anxiety (GAD-7) score from baseline to 3 and 6-month outcome assessments --change in depression (NDDI-E) score from baseline to 3- and 6-month outcome assessments	*-to generate preliminary estimates of effect for change in quality of life (and anxiety and depression) at 3- and 6-months from baseline during usual care, inputs that will be important for future trial planning with likely usual care control group*
Tertiary/Exploratory		
To explore health utilization outcomes among individuals with epilepsy and high or borderline anxiety and/or depression symptoms at baseline.	*-hospitalizations from baseline to 6 month follow-up* *-Emergency visits from baseline to 6 months follow up*	*-explore associations between longitudinal anxiety and depression symptom outcomes and health utilization*
To assess implementation of point-of care electronic medical record based screening in the epilepsy clinic.	*-RE-AIM framework measures*	*-to explore implementation metrics for the clinical screening protocol*

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a pilot pragmatic observational study of usual care quality-of life outcomes at 3- and 6-months among adults seen in a tertiary care epilepsy clinic. It is a feasibility pilot designed to specifically assess feasibility (retention) of a novel, EMR-based outcome assessment method among 30 adults with epilepsy and high or borderline anxiety and/or depression symptoms. Participants will be randomized 1:1 to either a traditional pragmatic outcome collection method (telephone interview) versus the EMR-based outcome assessment method. We will consider the EMR-based outcome assessment feasible if 60% of subjects in this arm are retained at 6 months. We will also assess retention in the telephone based outcome arm.

The 3- and 6-month outcome assessment instruments are brief and freely available measures amenable to future pragmatic trial use in outcome assessments (QOLIE-10, GAD-7, NDDI-E). Secondary objectives of the study include generating preliminary estimates of effect of usual care on quality of life outcomes (primary) as well as anxiety and depression outcomes (secondary).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

EMR-based tools to assess patient-reported outcomes are increasingly being proposed and used as a streamlined method for obtaining these patient reported measures and using them in care. In our previous pilot interventional study of neurologist treatment for anxiety and depression in epilepsy, we used IPad screening for anxiety and depression via REDCap to deliver standard care symptom screening and simultaneously screen individuals for potential research participation. This method required substantial coordinator effort to convey the screening results to clinicians for care purposes and to enter the results in the electronic medical record. Entry of patient reported measures directly into the electronic medical record has the potential to streamline clinical care while simultaneous pragmatic research is accomplished, because the instruments are entered as discrete data fields. Long-term outcome assessment via the patient portal interface of the electronic medical record may be feasible and potentially efficient for research staff.

In this study, we will screen patients for eligibility for the observational outcome study via implementation of standard care anxiety and depression screening and quality of life assessment directly into the patient entered section of the EMR, administered on arrival in the clinic. We will assess feasibility of EMR-based outcome assessment based on the primary endpoint of retention in the EMR-outcome arm as described above. We have decided to do a randomized feasibility trial comparing EMR outcome assessment to telephone outcome assessment, because the information from the telephone arm will also be valuable for future trial planning. This is because although telephone outcome assessment is often used in pragmatic trials, typical retention rates in epilepsy populations are unclear. Our study design aims to also assess retention using the telephone method in addition to the EMR method, to aid in determining future outcome assessment methods for interventional trials down the road. We will also use the quality of life and anxiety and depression outcome data at 3- and 6-months across the entire study population to generate estimates of long term effect of usual care among individuals with high or borderline anxiety and/or depression symptoms in epilepsy.

4.3 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. Male or female, age 18 or older
2. Adequate cognition (able to complete NDDI-E and GAD-7 independently in clinic)
3. Diagnosis of epilepsy: EEG with documented seizure or epileptiform discharges OR non-epileptiform EEG and seizure remission with antiseizure drug OR treating epilepsy specialist's leading clinical impression is epilepsy
4. NDDI-E score >13 AND/OR GAD-7 score >7 at regular clinic visit at the Wake Forest Comprehensive Epilepsy Center

5.2 EXCLUSION CRITERIA

1. High risk passive suicidal ideation score on NDDI-E: score on item 4 (I'd be better off dead) of 3 or 4 (sometimes OR always or often, respectively)

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to be screened for the study but are not subsequently randomly assigned 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 study (screen failure) because of a lack of current clinically significant anxiety or depression symptoms or other reasons may be rescreened.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample size: 30 to be randomized; up to 40 consented. Anticipated number of participants to be screened: up to 1000
- Anticipated accrual rate: 5 per month

- Number of sites: 1
- Recruitment venue: clinic of Wake Forest Comprehensive Epilepsy Center, adult-focused epilepsy practices
- Participants will be identified using a learning health system care model which includes ALL patients completing the GAD-7, NDDI-E and QOLIE-10 instruments as a part of standard care upon check-in for a regular clinic visit. This will occur via a link from the clinic visit workspace to questionnaires in the patient portal interface (mywakehealth). Those who have borderline or high anxiety or depression (GAD-7 > 7 or NDDI-E >13) will be prompted to answer a question about interest in research.
- An inbasket message to study team will be triggered if an adult's GAD-7 and/or NDDI-E scores meet eligibility criteria and the individual indicates potential interest in research by answering yes to the following prompt.
    - We are doing a research study to see how patients in the epilepsy clinic with possible symptoms of anxiety or depression are doing 6 months after a clinic visit. The study includes one phone call over the next few days. Then in 3 and 6 months, you would answer some questions similar to those you just finished. Each time might take 5-10minutes.
      May we contact you to tell you more about this study if you are eligible?
- When study staff receive the inbasket message, the medical chart will then be reviewed to assess whether a diagnosis of epilepsy is present. If epilepsy is present, the potential participant will be contacted by telephone and consent process will be initiated over the phone.
- For those eligible individuals who complete telephone consent for study participation, a brief baseline telephone interview focused on past psychiatric treatment history will be completed and the participant randomized. If necessary, mywakehealth activation will be done at the time of enrollment. Instructions for the allocated outcome assessment process will be provided.
- Multiple reminders and communications will be utilized to enhance participation in the outcome assessments. Telephone calls will be scheduled at the time of enrollment if possible. The outcome instruments will be mailed to telephone arm participants 10 days before scheduled outcome calls, and they will be sent electronically 10 days prior to target completion date for EMR-arm participants. Two telephone reminders for telephone arm participants, and two electronic reminders for EMR-arm participants will be provided prior to scheduled outcome assessment. Up to 5 attempts to call participants in the telephone outcome assessment arm will be made on separate days, starting at the originally scheduled outcome assessment time. Up to 5 electronic reminders with survey instructions will be sent via the EMR to the EMR arm participants, starting with target date for EMR outcome completion.
- After criteria for retention outcome at 6 months is met (5 reminders after due date for outcome assessment as described above), to reduce potential missing data for the secondary outcomes of 6-month change in quality of life, anxiety and depression, the following will be done. For any EMR-arm participants without successful 6-month outcome collection, 3 attempts will be made to collect outcomes via telephone. For any telephone arm participants without successful 6-month outcome collection, 3 attempts will be made to collect outcomes via EMR.
- Subjects will receive incentive of $15 gift card for completing the brief baseline telephone interview and $15 for completing each of the two outcome assessments (3 and 6 months).
- Efforts will be made to recruit any eligible participant seen in the practice, including women and under-represented populations

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION

This is not a treatment study, so there is no treatment intervention. The study aims to assess feasibility of EMR-based outcome collection method, versus standard telephone collection method. The below descriptions refer to the experimental component of the study, in which the participants are randomized to one of two outcome assessment groups.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized to one of two outcome collection arms: EMR-based or telephone-based 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 mywakehealth enrollment status at the time of study consent. Outcome group assignment will not be blinded to the primary investigator or primary study coordinator, as it will be necessary for these individuals to know outcome assessment allocation in order for outcome collection to occur. When possible, outcome group assignment will not be shared with the epilepsy provider managing the participant, in an effort to reduce any potential bias in retention that could be introduced by the provider in clinical interactions with the participant.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

Although it is unlikely that a participant would need to be withdrawn from this study given its observational nature, the investigator may discontinue or withdraw a participant from the study for the following reasons:

- 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 consent but are not randomized may be replaced. Subjects who consent, are randomized and receive instructions regarding the allocated outcome assessment arm, 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.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete the 6 -month outcome assessment and is unable to be contacted by the study staff.

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

- Study staff 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, 5 telephone calls or electronic communications in the EMR as outlined above followed by up to 3 attempts by the alternative modality (following primary retention outcome assignment as described in recruitment and retention section) and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's 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, GAD-7, QOLIE-10[38]

Implementation Monitoring:
RE-AIM framework measures

Feasibility assessments:
Enrollment/Baseline Assessments:
-accrual assessment

Retention: defined as outcomes collected via randomized modality within 1 week of the final of 5 scheduled reminders following outcome assessment due date (see recruitment and retention section for details of reminder process for each arm).
-6 month retention in EMR outcome arm
-6 month retention in the telephone outcome arm
-3 month retention in EMR and telephone outcome arms, respectively

Other feasibility assessments:
-# attempts to contact participants in each arm
-staff time for telephone outcome assessment/telephone contact attempts/preparing mailed survey packets vs staff time to send EMR surveys and electronic reminders
-time for participant completion of EMR surveys
-delay from survey delivery to completion by participant

Usual care outcome assessments (3 and 6 months):
-QOLIE-10
-NDDI-E
-GAD-7
-healthcare utilization (ED visits, hospitalizations)

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: in EMR/routine clinic visit
-NDDI-E validated passive suicidality question for safety[39]: if score indicates potential risk of suicidality, the electronic record system will be triggered to alert the treating epilepsy provider to assess for possible suicidality. These individuals will be excluded from study participation.

Other Enrollment Assessments:
-demographics, medications, medical history (largely based on EMR review)
-brief past psychiatric treatment history interview

Outcome Assessments
3-month assessment
-NDDI-E (validated passive suicidality question for safety)

6-month assessment
-NDDI-E (validated passive suicidality question for safety)

Safety plan at outcome assessments:
-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). This will be done immediately during telephone outcome assessments.
If an EMR outcome assessment results in a high-risk score on the NDDI-E, high priority alerts (red flag inbasket message or page to study pager) will be sent to study staff, and study staff will then call the participant at the first opportunity available, to assess need for any further action. All efforts will be made to send the EMR outcome assessment questionnaires at the start of a business day to allow maximal opportunity for rapid responses to occur during hours when study staff are available. Participant emergency contacts may be called if the study staff is unable to reach the participant on the day that a high-risk score was identified. The proposed response time is faster than what may typically occur in standard care practice. For example, new patients to the epilepsy center receive a mailed version of the NDDI-E prior to initial visit, for completion, and these results which may be completed weeks before the visit are only reviewed by clinical staff at the time of the clinic visit.
Further details of safety protocol are outlined in section 8.5 and appendix A.

8.3 EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF EVENTS

As this is not a treatment study, the typical definition of adverse events does not apply, as there is no treatment intervention with which adverse events could be associated.

However, untoward medical occurrences (events) may be identified during the course of the study.

Events that are not related to study procedures and that do not meet criteria for serious adverse events as described below will not be recorded. Events related to study procedures will be recorded.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or event 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 EVENT OR SERIOUS ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For events related to the study procedures, the following guidelines may 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 PARTICIPATION

All serious adverse events (SAEs) must have their relationship to study participation 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.

- **Possibly related** – A "possibly related" serious adverse event reflects a realistic chance of a causal relationship between a study procedure and the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedure as suggested by an event that follows within a reasonable time after the study procedure (i.e., 24 hours), follows a pattern consistent with the study procedure.

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

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether a serious adverse event (SAE) or a study related event is expected or unexpected.

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

- Unexpected: Any event that is not listed in the 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 event or serious adverse event (SAE) may come to the attention of study personnel during outcome assessments or at other contacts between study staff and participants. Serious adverse events (SAE) may come to the attention of study personnel during medical record review for health utilization outcome assessment.

All study-procedure related events not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Given the minimal risk of the study procedures, these events are expected to be rare.
Any SAEs will also be captured on the appropriate case report form.

Information to be collected includes:

- event description,
- time of onset and duration
- clinician's assessment of severity,
- time of resolution/stabilization of the event.

All study related events 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 event. However, if the study participant's condition deteriorates at any time during the study and then meets the definition of an SAE, it will be recorded as an SAE.

Changes in the severity of an event or SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

The Study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious study related events) 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 EVENT REPORTING

All study related events will be reviewed by the PI and will be reported to the IRB if the events meet criteria for IRB reporting via IRB policy, 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 study procedures 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.

Serious adverse events not related to study procedures will be reported to the IRB at the time of continuing review.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A as this is not a treatment study.

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 assessments and other interactions with the subjects. The clinic component of the crisis procedures document is provided to clinical study team members as an additional resource for potential management of symptoms identified in clinic as part of the clinical care depression screening procedure.

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 enrollment to identify 2 persons whom we can contact in case of an emergency and provide 2 telephone numbers for each of these 2 individuals; if possible. 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 this is not a treatment study, because we are excluding individuals with passive suicidal ideation at screening, and given the low rate of active suicidality we identified at baseline during our recent learning health system trial (included screening more than 760 individuals using the NDDI-E instrument), we anticipate that active suicidality will be exceedingly rare. 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 for EMR outcome assessments
If in the EMR outcome assessment arm, a high score on the passive suicidality question of the NDDI-E will trigger an alert with high priority to study staff inbasket and/or study team pager indicating that a high score was received.
The study team will call the participant as soon as feasible upon receiving the notification to assess for active suicidality and respond with further action as appropriate.

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.

Symptom Worsening
If there is significant symptom worsening at 3 month follow-up compared to baseline or at 6 month follow up compared to the prior assessment, a treatment resource handout will be mailed to the participant (see Appendix B). We will define treatment worsening as worsening in GAD-7 or NDDI-E score by 1 standard deviation[12;32].

Specifically, symptom worsening would be defined as the following:
-GAD-7 score increase of 5 points or more
-NDDI-E score increase of 4 points or more

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary feasibility hypothesis: We hypothesize that the primary endpoint, retention at 6 months in the EMR-based outcome assessment arm, will be greater than 60%.

9.2 SAMPLE SIZE DETERMINATION

We are aiming to recruit 30 participants for the randomized outcome assessment feasibility study, with 15 in the EMR-outcome arm and equal allocation between EMR arm and the telephone 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 retained, we are at least 83% confident that the true probability of retention is greater than 0.6. Thus, if at least 11 EMR arm participants meet the primary retention outcome, we will declare acceptable retention for using EMR based outcome assessment in future trials.

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 EMR-arm participants who meet retention criteria will be calculated, and as described above in the sample size determination section, if at least 11 EMR-arm participants meet the primary retention outcome, we will declare acceptable retention for using EMR based outcome assessment in future trials.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

To estimate change in quality of life (QOL) at 6 months during usual care, we will calculate individual level change in QOLIE-10 score from baseline to 6-months among all participants, with positive values (increased scores at 6 months) indicating improvement in quality of life. The mean change in QOL at 6 months (primary) will be compared to zero (no change) using the one-sample T-test with alpha=0.05, and 95% and 90% confidence intervals will be calculated. This will provide preliminary estimates of effect under usual care, to aid in sample size calculation for future intervention trials with usual care control group. Similar exploratory analyses will be carried out for change in QOL at 3 months and change in anxiety and depression scores from baseline to 3 and 6-months follow-up

9.4.4 SAFETY ANALYSES

The proportion of individuals reporting suicidality will be calculated.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographics and scaled scores for anxiety, depression, and quality of life will be compared between the two groups. Two sample t-test and chi square analyses will be used as appropriate to compare the two outcome assessment groups/assess quality of randomization.

9.4.6 SUB-GROUP ANALYSES

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

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and timepoint.

9.4.8 EXPLORATORY ANALYSES

Exploratory analyses will include assessment of the frequency of major health care utilization events (such as ED visits) in the study cohort.

SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.5 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.5.1 INFORMED CONSENT PROCESS

9.5.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Telephone consent process describing in detail the study procedures and risks is required prior to starting the baseline brief telephone interview and completing randomization. An information sheet will be mailed to participants who enroll in the study.
The following consent materials are submitted with this protocol:
-telephone consent script
-study information sheet

9.5.1.2 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 procedures will be Institutional Review Board (IRB)-approved. The study staff 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. The participants will have the opportunity to discuss the study with their family or surrogates, if desired, prior to agreeing to participate. The participant will provide verbal telephone consent 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 study information sheet will be mailed to the participants for their records. The informed consent process will be conducted and documented 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.

9.5.2 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 (very unlikely as this is not a treatment study)
- 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.

9.5.3 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 an area where private phone conversations and other measures to ensure privacy and confidentiality are 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 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.

9.5.4 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.

9.5.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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9.5.6 SAFETY OVERSIGHT

Safety oversight will be carried out by the Principal Investigator. The 3 and 6-month outcome assessments include administration of the NDDI-E instrument, which has a single passive suicidal ideation question that has been validated as a suicide screen[39]. Safety monitoring will include review of the proportion of participants reporting high suicidality scores (3 or 4 on the NDDI-E passive suicidality question).

9.5.7 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.

9.5.8 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. A quality management plan will be developed.

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 study 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.

9.5.9 DATA HANDLING AND RECORD KEEPING

9.5.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study staff 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 study related events, concomitant medications) and self-report instruments will be directly entered into RedCap, or exported from the EMR and then transferred to 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.

9.5.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 6 years after study closure. 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.

9.5.10 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 requiring notification 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 if required, 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.

9.5.11 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.

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.

9.5.12 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.

9.6 ABBREVIATIONS

AE	Adverse Event
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
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
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
QA	Quality Assurance
QC	Quality Control
QOLIE-10	Quality of Life in Epilepsy-10
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

9.7 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	June 3 2019	-As the clinical screener instruments can be completed in clinic regardless of mywakehealth enrollment, enrollment step has moved to enrollment stage for any individuals who enroll and do not already have mywakehealth access. -update screening consent text -Add exploratory implementation monitoring to list of study objectives.	-Based upon updated information regarding the screening instruments, we have modified the planned workflow. -better clarity of study info -To support generating preliminary data for potential future studies/dissemination.
3	July 31 2019	-remove W-9 language and modify randomization plan to reflect stratification by patient portal enrollment at baseline rather than epilepsy provider, add safety plan for significant symptom worsening at follow up	-W-9 is not needed based on further information gathered by research team -it will be more important to stratify by patient portal enrollment than provider, as this factor is more likely to introduce potential bias if unbalanced for the primary outcome assessment -to provide additional safety measures similar to long-term outcome assessment phase of other mental health studies conducted by study team
4	January 29 2020	-added "if possible" to the collection of two emergency contacts with two emergency numbers. (section 8.5)	Either two emergency contacts or two emergency numbers for each contact was not feasible for all subjects contacted
5	March 3, 2020	-removed "BPA" from trigger alert Page 21	System unable to actually trigger a BPA alert
6	June 1 2020	EMR-arm participants without successful 6-month outcome collection, 3 attempts will be made to collect outcomes via telephone. For any telephone arm participants without successful 6-month outcome collection, 3 attempts will be made to collect outcomes via EMR	Reduce potential missing data for the secondary outcomes of 6-month change in quality of life, anxiety and depression assessments.

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