Developing Interoperable Tools for Anxiety and Depression Screening in Epilepsy

National Clinical Trial (NCT) Identified Number: NCT05864612

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CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Council 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).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials 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 IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) 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: Developing Interoperable Tools for Anxiety and Depression Screening in Epilepsy

Grant Number: R03 TR004251

Study Description: This study will develop evaluate four (4) different screening methods to screen for anxiety and depression in patients with epilepsy.

Adult patients scheduled an epilepsy clinical visit at either site will be randomized to one of the four groups - to complete standard care screening questionnaires on anxiety and depression, delivered by one of four methods:

1. Twilio text message
2. REDCap email survey link
3. EHR portal (with reminder)
4. EHR portal (no reminder)

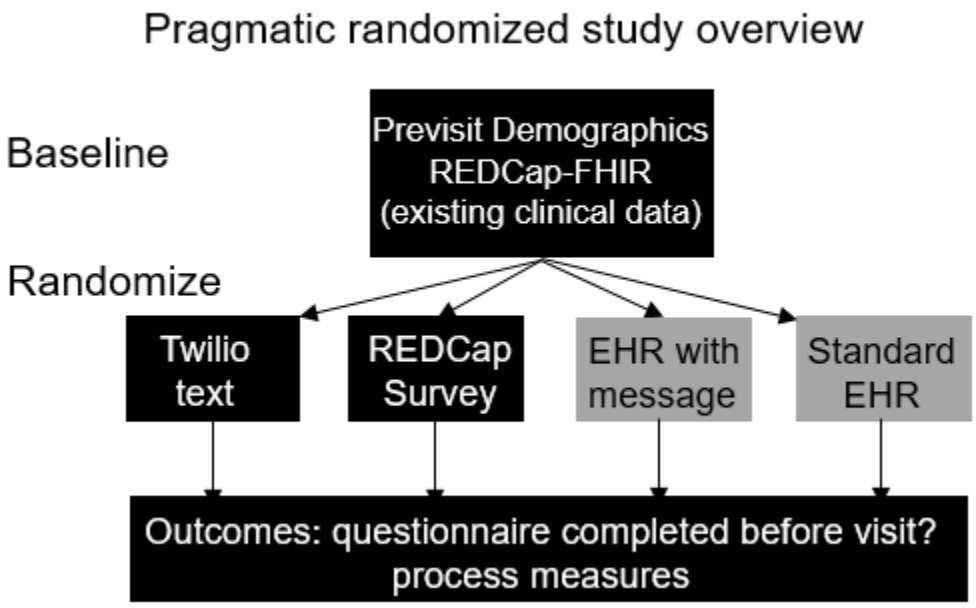
Hypothesis: the screening completion proportion will vary across the 4 modalities tested.

Research team will evaluate which of the screening methods were completed. In addition, the study will implement and evaluate a reproducible approach to EHR and research system integration via Epic's Kit API integration with REDCap for Epic EHR flowsheet data, using flowsheet-stored anxiety and depression instruments from epilepsy clinics as a demonstration case.

Objectives*:	**Aim 1**: To evaluate screening completion (primary outcome) and process measures comparing interoperable, REDCap-based methods to EHR patient portal-based methods for delivering standard care validated anxiety and depression instruments to epilepsy clinic patients. In a randomized pragmatic study of four modalities with N=220 individuals per arm and primary outcome proportion fully screened prior to clinic visit, we will compare Twilio text message delivery via REDCap vs. REDCap email survey links vs. EHR portal questionnaires with reminder message vs. standard EHR portal questionnaires without reminder. **Aim 2a:** To implement and evaluate a reproducible approach to EHR and research system integration via Epic's Kit database views and integration with a REDCap plug-in for Epic EHR flowsheet data, using flowsheet-stored anxiety and depression instruments from epilepsy clinics as a demonstration case. We will evaluate this approach by measuring accuracy and staff time for data collection via Kit REDCap plug-in versus manual data collection. **Exploratory Sub-aim 2b** [NOT HUMAN SUBJECTS RESEARCH]**:** To develop and disseminate a governance process for integration of REDCap-originated data into EHR flowsheet discrete data fields via Epic's AddFlowsheetValue API.
Endpoints*:	**Primary Endpoint**: screening completion prior to scheduled clinic visit
Study Population:	**Sample**: 880 adult patients scheduled for an epilepsy clinic appointment at Atrium Health Wake Forest Baptist or High Point locations
Facilities Enrolling Participants:	(1) Atrium Health Wake Forest Baptist (2) Atrium Health High Point 880 adults scheduled for epilepsy clinic visits
Description of Study Intervention/Experimental Manipulation:	Participants are not exposed to any interventions or procedures that are not a part of their usual standard of care, but the delivery of standard care screening instruments will vary as below. Adult patients scheduled for a clinical visit at either site will be randomized to one of four methods for standard care screening instrument delivery: 1. Twilio text message 2. REDCap email survey link 3. EHR portal (with reminder) 4. EHR portal (no reminder; current delivery practice)
Study Duration*:	Total study duration anticipated 2 years, up to 3 years if needed

Participant Duration:	Participants will be asked to complete a self-reported standard care screening for their clinic visit. Participants will not be contacted for additional follow-up.

1.2 SCHEMA


Pragmatic randomized study overview
Baseline
Previsit Demographics
REDCap-FHIR
(existing clinical data)
Randomize
Twilio
text
REDCap
Survey
EHR with
message
Standard
EHR
Outcomes: questionnaire completed before visit?
process measures

1.3 SCHEDULE OF ACTIVITIES

	Baseline Day 0 to 7	Scheduled clinic visit Day 7	Post-visit Chart Review*	Secondary Data Collection (Aim 2a) **
Baseline Data Collection from the EHR	X			
Randomization	X			
Send instruments, information sheet consent via randomized method	X			
Patient instrument completion/consent	X			
Research staff enter REDCap-completed screening results into EHR	X			
Research staff notify epilepsy clinician if high risk response received on depression instrument	X			
Instrument completed?		X		
Clinic visit completed?			X	
Process Measures	X	X		X
Kit Flowsheet collection				X
Manual instrument result collection				X

*Review of information from day 7
**These procedures only occur among individuals from EHR-delivery method arms who completed the anxiety and depression instruments

2 INTRODUCTION

2.1 STUDY RATIONALE

Anxiety and depression are prevalent yet under-recognized and undertreated among people with chronic conditions requiring specialty care including neurological disorders.[1-4] In some conditions, anxiety and depression impact quality of life and other outcomes more than the primary condition targeted by neurology or other subspecialty care.[5-8] Epilepsy is a key example, with a third or more of screened patients in clinical epilepsy settings having anxiety or depression symptoms.[9-13] However, clinician screening uptake is low despite a quality measure to screen with validated anxiety and depression instruments at every visit,[14-16] and most epilepsy patients with anxiety or depression do not receive treatment,[17-19] despite treatment being a patient priority.[20] Further, our prior work indicates epilepsy patients prefer neurologist prescribing for anxiety and depression over psychiatry referral or primary care prescribing.[20] Specialty providers including epileptologists report time to conduct screening as a major barrier,[15,16,21] yet repeated symptom monitoring using anxiety and depression instruments is a key component of successful anxiety and depression management by non-psychiatrists,[22-24] including

collaborative care, an evidence-based intervention[25] meriting investigation in neurology clinics to close treatment and outcome gaps.

Thus, **tools and strategies are needed reduce the burden of screening for anxiety and depression in subspecialty clinics, to close care gaps and to conduct multicenter** implementation and effectiveness **studies of evidence-based interventions such as collaborative care** in neurology settings. Our group successfully implemented electronic health record (EHR)-based screening in a tertiary epilepsy center using a theory-informed implementation strategy and EHR-based tools enabling patient self-completion of screeners following brief nursing staff activation. This more than quadrupled screening, but a substantial gap remained due to the nursing activation step in this model, and barriers to scaling included lack of EHR/research database integration and need for custom EHR build at each potential site for future multicenter studies. Interoperable tools facilitating independent patient self-completion are needed to scale and refine our initial implementation strategy and support recruitment and symptom monitoring in multisite intervention trials. Thus, **to overcome roadblocks to scaling our research program and to disseminate for broader use** in implementation and pragmatic research, **we aim to develop and evaluate interoperable tools for anxiety and depression screening** in neurology clinics serving epilepsy patients using REDCap (Research Electronic Data Capture)[26] and Epic EHR Application Programming Interfaces (APIs).

Our Specific Aims are:

Aim 1: To evaluate screening completion (primary outcome) and process measures comparing interoperable, REDCap-based methods to EHR patient portal-based methods for delivering validated anxiety and depression instruments to epilepsy clinic patients. In a randomized pragmatic trial of four modalities with N=220 individuals per arm and primary outcome proportion fully screened prior to clinic visit, we will compare Twilio text message delivery via REDCap vs. REDCap email survey links vs. EHR portal questionnaires with reminder message vs. standard EHR portal questionnaires without reminder.

Hypothesis: the screening completion proportion will vary across the 4 modalities tested.

Aim 2a: To implement and evaluate a reproducible approach to EHR and research system integration via Epic's Kit integration with REDCap for Epic EHR flowsheet data, using flowsheet-stored anxiety and depression instruments from epilepsy clinics as a demonstration case. We will evaluate this approach by measuring accuracy and staff time for data collection via a Kit Flowsheet REDCap plug-in versus manual data collection.

Exploratory Sub-aim 2b: [NOT HUMAN SUBJECTS RESEARCH] To develop and disseminate a governance process for integration of REDCap-originated data into EHR flowsheet discrete data fields via Epic's AddFlowsheetValue API.

2.2 BACKGROUND

Depression and anxiety are prevalent and impactful across various neurological and medical conditions, and multiple practice guidelines recommend screening. Numerous chronic conditions treated by subspecialists are associated with high prevalence of anxiety and/or depression, and these comorbidities are associated with poor outcomes including worsened primary chronic condition outcome, reduced treatment adherence, and worse quality of life.[1-3,27-29] Guidelines and quality measures

targeting primary care, specialty care, or neurology care settings recommend screening and management of depression and/or anxiety.[14,30-34]

Depression and anxiety are especially impactful in epilepsy, a high-risk condition with well-documented gaps in screening and management. 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 worsened seizures.[5,9-12,35-39] Multiple consensus statements for epilepsy recommend routine screening using standardized instruments to detect depression and/or anxiety, and anxiety is under-recognized without structured assessment.[9,14,40,41] Yet significant gaps in both screening and treatment exist, with US and international surveys of epilepsy clinicians indicating only 10-30% use validated screening instruments, and multiple studies and our own preliminary data demonstrate <50% of symptomatic patients receive treatment.[17-19,42] The top barrier to screening was clinician time required to screen.[15,16] Improving the anxiety and depression screening rate from 15%[15] to 60%, with *action* to initiate management in 50% of untreated symptomatic individuals would result in an additional 100,000 people with epilepsy receiving treatment for anxiety and/or depression in the United States.[18,19]

Depression and anxiety instruments have important roles in both detection and treatment monitoring in evidence-based interventions to manage anxiety and depression across various conditions. Collaborative care models for managing anxiety and depression are highly effective in primary care and some medical subspecialty settings to improve anxiety and depression symptoms, quality of life and other outcomes including some chronic disease specific outcomes.[24,25,43-47] These models typically involve initial symptom detection via validated screeners and care coordination involving measurement-based care with repeated symptom monitoring using anxiety and depression instruments.[24,25,48] Other care models involving repeated use of screening instruments for symptom monitoring during treatment by non-psychiatrists have demonstrated effectiveness, with clinical outcomes similar to treatment in a psychiatry specialty practice.[22,23] While these models have strong evidence supporting their use in primary care and some subspecialty settings, they have not been investigated in neurology or epilepsy clinic settings, nor epilepsy patient samples other than a home-visit oriented program.[49,50] Thus, to close gaps in anxiety and depression screening in subspecialty care settings and implement and evaluate evidence-based interventions such as collaborative care in neurology and other subspecialty settings, streamlined tools for anxiety and depression instrument delivery to promote patient self-completion are needed.

Electronic solutions promoting patient self-completion of depression and anxiety instruments may overcome barriers to screening and symptom monitoring and facilitate research recruitment for anxiety and depression effectiveness trials in routine care settings. Not only does prior research suggest patients are more likely to report psychiatric symptoms via electronic instruments than interview,[13,51] but electronic patient reported outcome instruments are acceptable, feasible, and they facilitate patient reported outcome completion[52] especially when accompanied by reminders.[53] Further, electronic patient completion of anxiety and depression instruments reduces clinical staff burden to conduct screening and facilitates screening completion.[54] Use of EHR-based or external survey application-based instruments have different advantages, such as better integration in clinical workflow (EHR instruments) and better usability (external applications that are more easily tailored for usability). Text-message delivery was also recently demonstrated to facilitate access, care engagement, and outcomes.[55,56] However, these various modalities have not been investigated in a rigorous head-to head comparison despite the potential advantage for implementation scaling to offer more than one modality to adopting sites. Further, research among patients with neurological conditions is needed to evaluate any potential impact of cognitive limitations or other disease features on instrument completion. Implementation and use is also limited by roadblocks to scalability and integration of external systems with the EHR, and overcoming these barriers would facilitate screening implementation research, efforts for research recruitment embedded in routine care, and symptom monitoring components of interventional studies.

Scalability of electronic tools is hampered by lack of EHR-research database integration and limited interoperability, including across institutional versions of the same EHR platform. While the use of EHR data for research is still impaired by a disconnect between the data standards used in patient care and those used in clinical research, efforts to bridge this gap are underway. Substitutable Medical Applications and Reusable Technologies (SMART) on Fast Health Interoperability Resources (FHIR) is a web based standard platform that enables solutions to enhance interoperability with EHRs and other systems including clinical research data capture (e.g., REDCap). REDCap has implemented SMART on FHIR to bridge the gap between clinical care and data capture systems to improve clinical research execution by reducing redundant workflows. SMART on FHIR implementations can support FDAs guidance on Electronic Source (eSource) Data and align with Electronic Source Data Interchange (eSDI),[57] which aims to encourage community to use electronic source data and available data standards.[58,59] However, various types of EHR-stored discrete data reside in flowsheets, including anxiety and depression instruments used by the study team and other patient reported outcomes, yet these are not supported by FHIR and thus require new solutions to support scalability. Further, published EHR-REDCap integration projects to date have significant limitations to scalability or functionality, including designs with multiple intermediary platforms or other complexity that would be difficult to scale across systems,[60,61] or internally built, clinically dedicated REDCap systems.[62] Some integrations are limited to presenting a link to REDCap from the EHR, rather than data flow between systems.[63]

Our research team developed local EHR-based methods for anxiety and depression screening and EHR and REDCap-based preliminary recruitment in randomized trials of anxiety and depression in epilepsy.[64,65] However, for next step multi-site recruitment for individually randomized collaborative care trials for anxiety and depression in epilepsy and screening implementation trials, REDCap/EHR integration is needed for seamless data transfer and flexibility of use across sites (REDCap vs. EHR-based, depending upon site capabilities and preferences). Further, tools to facilitate better patient self-completion of screening instruments are needed. Thus, in this projectl we aim to evaluate success of patient self-completion of instruments in a pragmatic randomized trial comparing two REDCap-based methods to two EHR-based methods (Aim 1), and to demonstrate REDCap-Epic integration for flowsheet-stored EHR instrument data via a generalizable Epic Kit based approach, and support preliminary steps to bidirectional flowsheet integration (Aims 2a-2b).

Relevant Preliminary Data

The investigators conducted a depression and anxiety screening implementation targeting epilepsy center nursing staff, to mitigate provider time-related barriers to screening. The result was quadrupling of screening, but with substantial provider-level variability, and a key barrier was the nursing activation step (see Summary of Research for details). The PI and investigator team have demonstrated success using EHR- and REDCap based tools including anxiety and depression instruments for preliminary recruitment in pragmatic randomized trials[64,65] and collecting outcomes using Epic EHR-portal methods.[42,65] The next phase is to develop scalable tools and preliminary data for multi-site trials in two areas: 1. effectiveness-implementation trials of collaborative care (tools from this proposal for recruitment & symptom monitoring) and 2. refined implementation proposals to close gaps in anxiety and depression screening and provider action. Specifically, Aim 1 addresses key next steps by investigating instrument delivery methods for patient self-completion to overcome nursing activation barriers, and generating key preliminary data (completion rates by modality & patient characteristics) for future multisite study planning.

Novel strategies for capturing, monitoring, and displaying metrics data. Our team developed several external modules for REDCap currently in use (Table 1). Streamlining clinical research execution and data capture with implementation of available standards could have a large impact on quality issues within studies.

While this work demonstrates our team's expertise in integration and successful tool development, none of the current tools transfer discrete, flowsheet-based data including EHR-based epilepsy anxiety and

depression instruments from EHR to REDCap (or REDCap to EHR) in a generalizable way easily scaled across centers.

Table 1: Wake Forest School of Medicine developed REDCap tools for data coordination	
REDCap Modules	**Function**
Stratification & randomization hooks	Hooks written to stratify & randomize participants based on various randomization models
Caps	Hooks written to cap number of participants
Cancer Trials Support Unit (CTSU) Open RandoNode	Implemented to randomize and register subjects to REDCap via CTSU Open for 800+ NCI Community Oncology Research Program (NCORP) Sites utilizing APIs
COMPASS Care Planning	Bidirectional API with COMPASS (Comprehensive Post-Acute Stroke Services) Care Planning middleware between Epic and REDCap.
Schema Resolver	Python application to compare schema differences between REDCap projects utilizing APIs

Drs. Munger Clary, Topaloglu, and consultant computer scientist Cody Hudson conducted a successful proof- of-concept data transfer from Epic Test platform to REDCap for flowsheet-based anxiety & depression instruments via the GetFlowsheetRows Epic webservice during Dr. Munger Clary's KL-2 project. This was not fully implemented due to a 72-hour lockout parameter that Epic imposes; this roadblock prevented collection of flowsheet data after 72 hours. Aim 2 directly addresses this translational roadblock via Kit flowsheet integration with REDCap. Due to performance degradations, Epic has started to encourage data access to be done through its Caboodle data warehousing solution. Caboodle has capability to import external data generated outside of Epic to provide a fully functional data warehouse. The Kit API is the recommended interface for accessing data in Caboodle, which has granular access control (i.e. each API has to be added to the app) in Epic's App Orchard, similar to FHIR apps.[66] *Integrating Kit Flowsheets with REDCap is the next phase in this aspect of the research program.*

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This is not a treatment/intervention study and risks to the study participants are low. The only risk would be in loss or mismanagement of sensitive data.

Participants are not exposed to any interventions or procedures that are not a part of their usual standard of care. Patients will be prospectively randomized to one of the four methods of delivery for standard care anxiety and depression screening instruments - (responses to the screening questionnaire will be used in the standard of care clinic) by either:

1. Twilio text message via REDCap
2. REDCap email survey link
3. EHR portal (with reminder)
4. EHR portal (no reminder; current standard clinical delivery method)

Standard care anxiety and depression screening instrument results received via the REDCap methods will be entered into the EHR by study staff prior to the scheduled clinic visit, and clinicians will be notified if high-risk results to depression screening occur, to further minimize risk. (This notification represents an additional risk-reduction measure beyond what is currently in place for these screeners in routine care in

this setting). Robust methods to maintain privacy of clinical and research data will be used, as described in section 10.3.1.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no direct benefits to the patient, but this research will benefit the larger community and population if it is able to successfully contribute to improving screening and treatment of depression and anxiety in this patient population, and potentially other populations for whom depression and/or anxiety screening is recommended.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While there is not direct benefit to the patient, this is considered a minimal-risk study that may provide benefit to the larger community and population.

Minimizing risks

Maximal efforts to maintain privacy including use of HIPAA-compliant secure tools will be in place. Measures to minimize risk by ensuring data privacy and security and ensuring timely communication of sensitive results to clinicians when identified prior to the clinical visit will be taken as described in more detail in section 8.2. If a response to the depression instrument indicates potential passive suicidality, research staff will notify the treating clinician. This notification represents an additional risk-reduction measure beyond what is currently in place for these screeners in routine care in this setting, where pop-up alerts do not occur until an alert-activating action in the EHR occurs during the scheduled clinic visit. Standard clinical care privacy regulations will be followed for each delivery method of the standard care screeners.

- The study is classified as minimal risk because the anxiety and depression screening instruments are a best practice clinical and quality tool currently in use at the center without consent. The screener questions in the proposed research are identical to those in current clinical use, with the research involving only minor changes in the delivery method (while adhering to clinical communication policies and privacy regulations). Randomizing delivery method does not increase the study risk level. Otherwise, the research involves collecting a small amount of pre-existing clinical EHR-based information and data on screener and clinic visit completion. Strict efforts to maintain confidentiality/privacy will be followed, and all study team members will have rigorous training in maintaining confidentiality.

3 OBJECTIVES AND ENDPOINTS

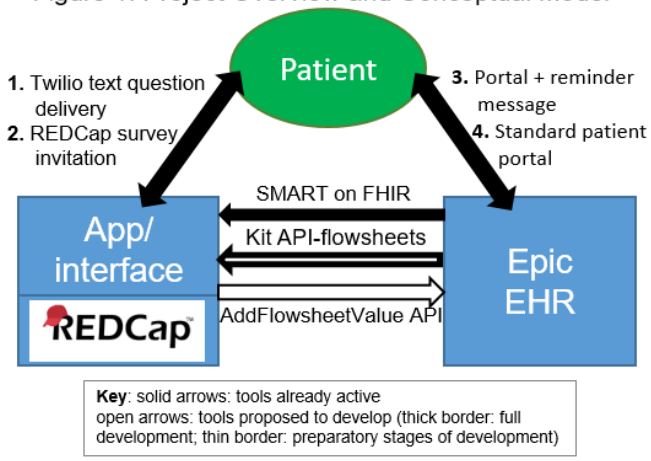
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate screening completion (primary outcome) comparing interoperable, REDCap-based methods to EHR patient portal-based methods for delivering validated standard care anxiety and depression instruments to epilepsy clinic patients (Aim 1).	Screening completion – Yes or No	Proportion of screening instruments completed by each of the 4 methods prior to clinic visit will be used to compare the effect of the different methods on patient self-completion, and to estimate completion rates by different methods for use in future screening implementation trials.
Secondary		
To evaluate process measures comparing interoperable, REDCap-based methods to EHR patient portal-based methods for delivering validated anxiety and depression instruments to epilepsy clinic patients (Aim 1).	Research team time: -sending instruments -instrument data entry Participant time from instrument delivery to completion	This data will provide information to calculate staff resources needed to prepare for screener delivery and data entry in future studies. This data will provide additional potential information about whether the different screener delivery methods vary in promptness of patient response to screeners.
To evaluate accuracy of a reproducible approach to EHR and research system integration via Epic's Kitintegration with REDCap for Epic EHR flowsheet data, using flowsheet-stored anxiety and depression instruments from epilepsy clinics as a demonstration case (Aim2a).	Accuracy of Kit flowsheet REDCap plug-in data entry vs. manual data entry	This will provide key information about whether a Kit flowsheet REDCap plug-in enabled data collection may improve accuracy of EHR-based data collection compared to manual collection.
Tertiary/Exploratory		
To explore visit attendance among individuals who completed or did not complete anxiety and depression screeners (Aim 1). To explore research team time required to collect anxiety and	Clinic visit attendance: Visit completed vs. canceled vs. no-show	To explore for association between visit completion and screener completion for the different delivery methods.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
depression screener results from the EHR via Epic's Kit integration with REDCap for Epic EHR flowsheet data (Aim 2a).	Time for data collection (Kit vs. manual entry)	To explore potential research staff time savings resulting from data collection via Kit flowsheet integration with REDCap.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Figure 1: Project Overview and Conceptual Model



Aim 1: In a randomized trial, to compare patient-completion success of REDCap- and EHR-based anxiety & depression instrument delivery methods (1-4, Figure 1).

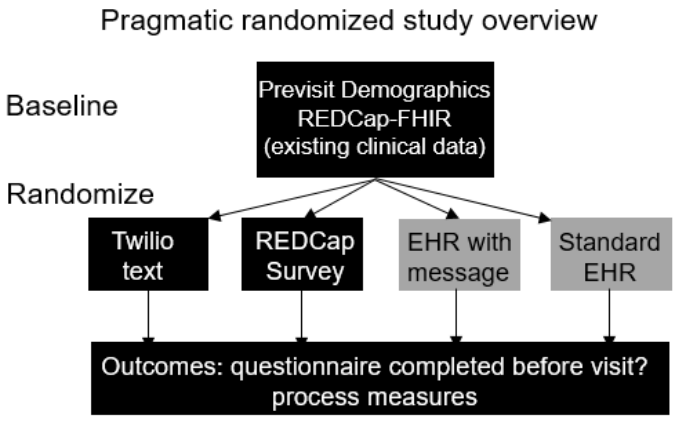
In this randomized study of four modalities with N=220 individuals per arm and primary outcome proportion fully screened prior to clinic visit, we will compare Twilio text message delivery via REDCap vs. REDCap email survey links vs. EHR portal questionnaires with reminder message vs. current standard delivery EHR portal questionnaires without reminder (Figure 2). Screening instruments will be delivered by randomized method 7 days prior to scheduled clinic visit and outcomes occur by the time of the scheduled clinic visit. The study setting is the Wake Forest Comprehensive Epilepsy Center, with 2 clinic sites where adult patients are served (Atrium Health Wake Forest Baptist main campus, Atrium Health High Point Medical Center). EHR portal questionnaires without reminder is the current standard care screener delivery method.

Hypothesis: the screening completion proportion will vary across the 4 modalities tested.

Process measures will also be compared among the modalities.

Trial Phase: Non-FDA regulated pragmatic trial.

Aim 2a: To demonstrate Epic's Kit integration with REDCap for Epic EHR flowsheet data (anxiety & depression instrument test case in epilepsy). We will evaluate this approach by measuring accuracy and staff time for data collection via Kit flowsheet REDCap plug-inversus manual data collection.



Following build and testing, Kit Flowsheet REDCap plug-in will be launched in a production REDCap project and activated for double data entry of the flowsheet data generated via participant screener completion in the two EHR allocated arms of the randomized screening instrument delivery study (EHR with message and standard EHR). Entry #1 will be

manual and data entry #2 will be the REDCap Kit plug-in collected by a study team member without access to the manually collected data. A user who did not collect either the manual or Kit plug-in data (the reviewer) will review discrepancies between entries using a REDCap tool. **Accuracy** will be assessed by comparing Kit REDCap plug-in collected values to manually-collected values for the EHR-allocated visits. **Reproducibility/generalizability** of the Kit REDCap plug-in data collection method will be evaluated in a 2nd instance of Epic (Encompass) via use of the Kit flowsheet plug-in to pull the same anxiety and depression screening data from Encompass instance flowsheets (generated during clinical data conversion of the original WakeOne Epic instance based flowsheets to the new health system-wide Encompass Epic instance).

Exploratory sub-aim 2b: (this portion is NOT HUMAN SUBJECTS RESEARCH) To develop a governance process for integration of REDCap data into EHR discrete data fields via Epic AddFlowsheetValue API.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This project is designed to overcome key roadblocks to future research to close screening, action, and outcome gaps for anxiety and depression in epilepsy, specifically: 1. multi-site implementation-effectiveness trials to evaluate collaborative care in epilepsy, and 2. Implementation-focused trials to close the screening and treatment gap for anxiety and depression in epilepsy.
This will be accomplished by developing tools that can be used flexibly to facilitate multi-site research while generating key preliminary data to estimate recruitment potential for collaborative care studies and evaluate potential impact of an instrument-delivery focused component of a refined, theory-informed implementation strategy for anxiety and depression screening.

Each of the 4 arms of the randomized trial represents a screener delivery method that could be used at sites in future trials and in routine clinical care, with the standard EHR arm representing the current standard practice at Wake Forest Comprehensive Epilepsy Center. This project will generate the preliminary data on screener completion for each modality to support options for screening and symptom measurement in future research that could be used flexibly at different sites in future implementation research. This project will also generate valuable quality improvement-related clinical data that could result in immediate change in practice for screener delivery in routine care to enhance care and improve performance on epilepsy quality measures.[14]

4.3 JUSTIFICATION FOR INTERVENTION

Patient completion of instruments. The patient-focused screening delivery methods are informed by a Capability, Opportunity, Motivation-Behavior (COM-B)-Behavior Change Wheel framework-informed implementation strategy model.[67] Patient-level barriers were identified and mapped to COM-B constructs (physical opportunity and automatic motivation), then intervention functions (enablement, environment restructuring), then a corresponding behavior change technique (prompts & cues).[67]
The four instrument delivery methods to be used in this pragmatic trial represent distinct prompts & cues for screening instrument completion [1.text message, 2.customized email prompt, 3.generic EHR portal email prompt with customized EHR portal message after login to EHR portal, or 4.no message but presence of previsit questionnaires associated with a visit in the EHR portal]. Examining these multiple instrument delivery methods will generate outputs that will support flexibility in instrument delivery modalities across multiple sites in future multicenter studies in this area, as mentioned above.
These 4 distinct delivery methods are used to deliver identical standard care validated anxiety and depression screening instruments.

The specific wording and appearance of the instrument delivery methods will be further informed during study planning by input from five patient stakeholders (with whom the research team has a prior relationship) who will participate in a semi-structured interview on barriers and facilitators to pre-visit screening completion, informed by the COM-B-Behavior Change Wheel framework and will provide usability feedback on the screener delivery methods and reminder message wording. (Additional stakeholders may potentially be engaged, to provide five individuals the opportunity to participate in both feedback sessions).

4.4 END-OF-STUDY DEFINITION

The only participant interaction in this study is completion of the standard care anxiety/depression screeners prior to the epilepsy clinic visit after viewing the brief consent information. Delivery of screeners occurs 7 days prior to scheduled clinic visit and outcomes occur by the time of the clinic visit (instrument completion, visit completion). All data for Aim 1 is generated by completion of the epilepsy clinic encounter. Aim2a involves secondary data collection among some participants who completed EHR based screening instruments and thus will have consented for research use of the screener data.

The end of the study is defined as completion of all data collection for all participants as shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

AIM 1*:* All visits scheduled at least 7 days in advance at two adult epilepsy-focused clinics of the Wake Forest Comprehensive Epilepsy Center will be included.

AIM 2a: All visits with completed anxiety and depression screening questionnaires from the EHR-allocated arms of the randomized study.

5.2 EXCLUSION CRITERIA

AIM 1: Age<18 years at baseline (7 days prior to the scheduled epilepsy clinic visit)

AIM 2a: no exclusions.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Individuals not included in the study due to age<18 years at one point in the study period who later meet inclusion criteria for a later visit (by attaining the age of 18 years prior to a later epilepsy clinic visit) may then be included.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment. Eligible patient visits will be identified via EHR clinic schedules. Baseline collection of the EHR-based existing clinical and demographic data will occur under a HIPPAA waiver.
Due to the minimal risk classification for this study involving modified delivery methods for otherwise identical standard care screening instruments, a modified informed consent process is acceptable as outlined below.
Eligible participants will be randomized to method for delivery of pre-visit standard care screeners, and all screeners will be delivered with adherence to clinical communication and privacy policies, with an identical brief consent/information sheet prior to the screening questionnaires. The same wording will be used for all study arms to reduce the chance of group allocation bias that would undermine the research results:

- *Your epilepsy doctor has included questionnaires about your mood and anxiety as part of your clinic visit. Taking part in this survey may involve providing information that you consider confidential or private. Depending upon how you answer these questions, the responses may be shared with your neurology provider. Some information you provide may be used for research. Careful efforts will be made to keep your information confidential. You will not lose any services, benefits, or rights if you choose not to participate in this voluntary survey.*

This brief consent format is acceptable because the study is minimal risk (see section 2.3.3 for more information about the minimal risk classification).
Thereby, those who complete anxiety/depression screening instruments will provide consent for use of research data and potential epilepsy provider notification of passive suicidality screen if needed to minimize risk/enhance safety (see section 8.2 for details of safety plan).

For those who do not complete the anxiety/depression screeners, epilepsy provider notification is not applicable, and it is impractical to obtain informed consent:

- 1. It is impractical to approach individuals who canceled or missed the clinic visit.
- 2. For individuals who do not complete the anxiety/depression screeners but do attend the epilepsy clinic visit, it is impractical for appropriately trained staff to approach them for consent at the clinic visit, since these visits may occur at any time on any day, including simultaneously at disparate clinic sites.
- Thus, among those who do not complete the screening instruments, waiver of informed consent and HIPAA waiver are acceptable because the study is classified as minimal risk (see section 2.3.3 for more explanation of this) and because obtaining consent is impractical.

Our N=880 sample size compares favorably with the typical >1500 visits at Wake Forest Comprehensive Epilepsy Center adult clinics over 6 months, and with our experience during COVID-19-related volume disruptions, when 1097 visits were scheduled and 866 were completed over a 5-month period. Finally, based on our clinic data we expect only a modest decrease in numbers from visits to individuals, and we estimate 923 unique individuals will complete visits over 6 months and thus the sample size goal will be achieved within the 6-8 months of recruitment planned for this study.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

While this is not a treatment study, below we describe the different methods of delivering standard care screening instruments that are examined in the study.

AIM 1: Methods to deliver screening instruments.

The anxiety and depression screening instruments are a best practice clinical and quality tool currently in use at the center without consent. The screener questions in the proposed research are identical to those in current clinical use, with the research involving only minor changes in the delivery method (while adhering to clinical communication policies).

The delivery methods are described below.

- Standard EHR: visit-attached instruments in patient portal available ≤7 days before visit (current practice)
- EHR with message: portal message encouraging completion sent and visit-attached instruments available ≤7 days prior (system sends generic email; specific portal message visible after patient login to EHR portal)
- REDCap survey: custom email with instrument link sent ≤7 days before visit encouraging completion
- Twilio® text via REDCap: secure text message delivery of questionnaires ≤7 days prior to visit

AIM 2a: THIS ONLY INVOLVES COLLECTION OF DATA FROM THE EHR for EHR-arm participants who completed the anxiety & depression instruments in the EHR, and thus consented for research use of this data.
There are no participant interactions.
The study methods for this secondary data collection and analysis are described below, but these methods do not constitute an intervention.

Implementation and evaluation of EHR/research database integration via Kit Flowsheet REDCap plug-in

Diverse patient data are stored in the Epic EHR as flowsheet rows built for clinical care or research as discrete data collection fields. In addition to custom data collection forms, flowsheets are how standard instruments are programmed into Epic including Promis® measures, GAD-7, NDDI-E and other validated patient-reported outcome measures. However, integrating flowsheet discrete data with other research systems such as REDCap is a roadblock to translational research, and Epic's flowsheet webservices enforce a 72-hour lockout timeframe due to potential performance risk. Therefore, the GetFlowsheetRows webservice is not feasible for research data collection occurring >72 hours after entry. Epic's Kit is a set of database views available in all Epic systems with Caboodle data warehouse implementation.[66] It is designed to perform large data extracts and analytical reporting in an accessible manner. Furthermore, it requires less training for developers and enables quicker runtimes and quicker report writing compared to the Clarity relational database.[66] Similar to Clarity, the data accessible by Kit could be 24 hours old, but there is no lockout time, which makes Kit ideal for research applications involving retrospective data extraction for analysis. Thus, Kit integration is more generalizable for REDCap research database integration than native Epic webservice approaches, and it overcomes the prior roadblocks our research team encountered with the GetFlowsheetRows webservice. In this aim, an experienced consultant computer scientist will collaborate with Drs. Munger Clary and Topaloglu to integrate REDCap API functionality with Epic's Kit Flowsheet API by developing a REDCap plug-in. As mentioned in preliminary data, the team has prior experience developing REDCap APIs and the necessary tools. Epic provides a sandbox development environment for all Kit APIs,[66] including the Flowsheets API to be integrated with REDCap. Akin to other Epic webservices including FHIR, Epic's App Orchard platform controls the allowed APIs and other respective authentication details. Atrium Health Wake Forest Baptist is equipped and licensed with the Kit functionality and is populating flowsheets now.

Kit Flowsheet API REDCap Integration & Data Collection. Following build and testing, the REDCap plug-in for Kit Flowsheet integration will be launched in a production REDCap project and activated for data entry of the flowsheet data generated in the EHR allocated arms of the randomized instrument delivery study. Entry #1 will be manual and data entry #2 will be the via the REDCap Kit flowsheet plug-in by a user without concomitant access to the manual data entry fields. A user (the reviewer with rights to review discrepancies between entries and the source data will use a REDCap instrument to review for discrepancies and reconcile discrepancies.

6.1.2 ADMINISTRATION AND/OR DOSING

REDCap anxiety and depression instruments (Generalized Anxiety Disorder-7, GAD-7 and Neurological Disorders Depression Inventory-Epilepsy, NDDI-E) currently in use by the PI will be adapted and enabled for Twilio text functionality and custom survey link email messages via REDCap developer services. EHR patient portal messages to encourage instrument completion will be prepared with support as needed by Epic analyst team, similar to the study team's prior work.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

N/A.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization and blinding. Visits will be randomized 1:1:1:1 to the 4 conditions using blocked randomization to reduce the chance of imbalances, and to help protect against temporal trends. Randomization will be stratified by presence of an existing antidepressant prescription. The randomization table will be prepared with consideration of our previously observed rates of antidepressant prescribing in our epilepsy clinic setting (152 of 536 consecutive screened individuals with epilepsy prescribed an antidepressant). Prior to the start of enrollment, the randomization table will be prepared by the study statistician and submitted to the REDCap developer to put into production. For each visit, the participant's baseline data collection will be completed; activation of the random assignment may then occur. Until that time, the assignment will be concealed to the PI and all other study team members to enhance ***rigor and reproducibility***. The nature of outcome collection prevents study team blinding to allocation for primary outcome ascertainment. Study team will enter instrument results obtained via REDCap into the EHR flowsheets prior to clinic visit (identical EHR location as with EHR allocation). Timely entry is feasible using REDCap email alerts to the study team (method used by PI in prior projects).

The brief consent will have identical wording for all delivery arms to minimize potential bias that could be introduced by the informed consent process related to the different study arm allocations (see sections 5.5 and 10.1.1.1 and 10.1.1.2).

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

N/A

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A as there are no ongoing study interactions/this is not a treatment study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

N/A as the only participant interaction is a one-time completion of standard care screeners delivered by one of the allocated methods.

7.3 LOST TO FOLLOW-UP

N/A

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Baseline demographics and clinical information (including whether there is evidence of an existing antidepressant prescription) will be collected from existing EHR based information using SMART on FHIR REDCap integration. These also include: sex, race, ethnicity, age, diagnoses, zip code, and prescriptions.

Anxiety and depression instruments.
Generalized anxiety disorder-7 (GAD-7)[68,69] & Neurological Disorders Depression Inventory-Epilepsy (NDDI-E)[70,71] are well-validated, freely available anxiety and depression instruments that satisfy the American Academy of Neurology Epilepsy Quality Measure for anxiety and depression screening at every visit[14] and are National Institute of Neurological Disorders and Stroke(NINDS) Common Data Elements. Automated EHR-based procedures are already in place for these instruments to be attached as EHR-portal previsit questionnaires and available prior to a scheduled visit for all active adult epilepsy specialty providers at the Wake Forest Comprehensive Epilepsy Center.

AIM 1 ***Outcomes.*** Outcomes are determined by the scheduled clinic visit (Table 2), with primary outcome defined as instrument completion prior to visit date/start time. Technical reasons for lack of instrument completion (eg. no patient portal account, no email address available in EHR system, text messages cannot be sent via clinical protocols) will be recorded, but the primary analysis will follow intention to treat principles and include all randomized individuals.

Table 2: Aim 1 Outcomes		
Outcome	**Source**	**How obtained?**

Instrument completion (primary)	EHR or REDCap (allocated method)	Review REDCap (REDCap arms) Manual EHR review (EHR arms)
Research team time: sending instruments	REDCap	Start stop timing fields REDCap (seconds)
Research team time: instrument entry (into EHR or REDCap, based on allocation)	REDCap	Start stop timing fields REDCap (seconds)
Patient time from instrument delivery to completion among screening completers	REDCap (and EHR if randomized to EHR)	Send time: study team-activated REDCap timing field at instrument delivery Completion time: review of instrument completion timestamp in EHR or REDCap
Clinic visit completion: visit completed, canceled or patient no-show?	EHR	Manual chart review

Baseline instrument completion proportion over a few month timeframe prior to pragmatic trial initiation may be collected via a CLARITY data pull to estimate pre-trial completion rate using the standard EHR method.

AIM 2a: Accuracy of Kit Flowsheet REDCap plug-in data entry will be assessed by comparing Kit REDCap plug-in-collected values to manually-collected values for the EHR-allocated visits, with review of original-source EHR entries to determine true values for all discrepancies identified
Staff time for data collection will be measured to the nearest second using REDCap timestamps as in Aim 1.

8.2 SAFETY ASSESSMENTS & SAFETY PLAN

The NDDI-E standard care depression screening instrument contains a passive suicidality item that has been validated as a suicidality screener.[72] Tools to notify providers of a positive passive suicidality screen have been implemented in the EHR as part of the study team's prior work and are active at present in the EHR in routine care; these include a pop-up alert to clinicians that typically appears during the clinic visit.[73] Tools to evaluate and manage passive suicidality were also developed as part of the study team's prior work and are currently available as well.[73] These tools will continue to be available to epilepsy clinicians for all participants since NDDI-E instruments will be completed in the EHR for the EHR arms, and they will be entered into the EHR by study team for REDCap completers prior to the scheduled clinic visit.

To ensure additional safety measures, since study staff will review REDCap-based screening results prior to clinicians and study staff may view EHR based screening results prior to the clinicians, an additional clinician notification process for possible passive suicidality will be in place and will be tracked by the study team.

For screeners completed via the two REDCap-based methods, high urgency email alerts indicating a positive passive suicidality screen will be triggered to the PI and coordinator team members from REDCap (in addition to alerts indicating completion to facilitate entry of results into the EHR). In response to the alerts, the epilepsy clinician will be notified by the study team and these notifications will be tracked. REDCap email alerts based on NDDI-E passive suicidality positive screen are feasible and currently already used by the PI in another collaborative study (*IRB00051120*).
For EHR-arms, automated alerts with NDDI-E results and critical value flag will be sent to the PI and study team as inbasket messages, and study team will notify the epilepsy clinician in a similar manner to the

REDCap-based methods. These additional measures enhance safety by alerting clinicians to high-risk results earlier than occurs at present in standard care practice.

Safety Action Plan Summary:

- **Automated alerts to the PI and study coordinator** from the screener delivery system (REDCap or the EHR) for any positive NDDI-E passive suicidality screens.
- In response to the automated alerts, **PI/study coordinator will notify the treating epilepsy clinician** of the NDDI-E results.
- Next step in management/response to results will be allocated to the treating clinician.
- The study team will track these actions to ensure adherence to this notification plan.

This plan is in addition to actions already implemented during our prior work:

- Pop-up clinician notification in EHR during clinic visits if NDDI-E with potential suicidality [active for all screeners during project, including the REDCap screens when entered in EHR by study team].
- Resources for clinician action to evaluate and manage suicidality: EHR-built smart phrase tool, handouts on suicidality protocol and resources to clinicians posted in clinic and provided prior to study start.

As mentioned above, we have prior experience using automated alerts for screening results in both REDCap and the EHR. Thus, the additional action plan is highly feasible.

Based on our prior work screening >500 consecutive individual patients, we anticipate <5% will require action, and very few if any of these will have active suicidal ideation.

All study procedures will be conducted by appropriately qualified personnel.

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

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

N/A as this is not a treatment study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). 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 PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). 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: life-threatening, require hospitalization, cause persistent or significant incapacity or substantial disruption of ability to conduct normal life functions for >48 hours) will be reported to the IRB and to the study sponsor/funding agency within 24 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the funding agency within 7 days of the investigator becoming aware of the problem
- 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

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint: AIM 1

Hypothesis: the screening completion proportion will vary across the four modalities tested.

9.2 SAMPLE SIZE DETERMINATION

Sample size and Power. We based our sample size calculation on our primary outcome and hypothesis of a difference in proportions for instrument completion among the 4 groups. With N=220 in each group, we will have statistical power equal to at least 80% to detect an overall difference (two-sided chi-square testing, alpha = 0.05), given a true range among the proportions equal to 0.16 (16%). We believe this range represents a clinically meaningful change in screening rate and would be relevant to sample size calculations for future larger studies.

Our N=880 sample size compares favorably with the typical >1500 visits at Wake Forest Comprehensive Epilepsy Center adult clinics over 6 months, and with our experience during COVID-19-related volume disruptions, when 1097 visits were scheduled and 866 were completed over a 5-month period. Finally, based on our clinic data we expect only a modest decrease in numbers from visits to individuals, and we estimate 923 unique individuals will complete visits over 6 months.

9.3 POPULATIONS FOR ANALYSES

The analysis will follow intention-to treat principles.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A pre-specified analysis plan (SAP) will be developed for the primary outcome with additional details on computational specifications, potential covariates, diagnostics, alternative approaches if assumptions are not met, and supportive analyses. A p value of 0.05 will be considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We will test our primary outcome and hypothesis of a difference among the 4 proportions for instrument completion using chi-square testing (two-sided, alpha = 0.05). Point estimates for the proportions and corresponding 95% confidence intervals will be used for descriptive purposes. These analyses will follow intention-to-treat principles, and will include all first visits in our target N=880 individuals.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

AIM 1:
Secondary process measure outcomes will be analyzed similarly to the description above for the primary outcome.

AIM 2a:
Point estimates and 95% confidence intervals (e.g. Wilson or score intervals) will be calculated for each modality and differences between modalities. (Kit REDCap plug-in-collected values vs. manually-collected).

9.4.4 SAFETY ANALYSES

The proportion of NDDI-E screening completers who have a positive passive suicidality screen will be calculated, as will the proportion of those who demonstrated any evidence of active suicidality on clinical follow-up.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic and clinical characteristics will be reported for each group using descriptive statistics.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Summaries of demographic, geographic, technical, and clinical characteristics (e.g., technical barriers to instrument delivery, missed or canceled visits) by instrument completion status will be used for hypothesis generation and future study planning. Pre-specified subgroup analysis are not planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

There are no plans for tabulation of individual participant data.

9.4.9 EXPLORATORY ANALYSES

AIM 1: Summaries of demographic, geographic, technical, and clinical characteristics (e.g., technical barriers to instrument delivery, missed or canceled visits) by instrument completion status will be used for hypothesis generation and future study planning.

Analyses based on visits, i.e., including all randomized visits through randomization of the 880th individual, are planned as potentially supporting the individual-based analyses, though we acknowledge the possibility of real differences between visit- versus individual-based population characteristics due to differences in behaviors associated with visit frequency, for example.

AIM 2: Staff time for data collection: mean time per visit will be compared between modalities.(Kit REDCap plug-in-collected values vs. manually-collected)

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

As this is a minimal risk non-treatment study, consent will involve a brief consent process, with screening instrument completion being the indicator of consent. The wording of the brief consent that will appear before screening instruments delivered by all 4 methods is below and has been submitted with this protocol.

-brief consent/study information

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The study is **classified as minimal risk** because the anxiety and depression screening instruments are a best practice clinical and quality tool currently in use at the center without consent. The screener questions in the proposed research are identical to those in current clinical use, with the research involving only minor changes in the delivery method (while adhering to clinical communication and privacy policies). Randomizing delivery method does not increase the study risk level. Otherwise, the research involves collecting a small amount of pre-existing clinical EHR-based information and data on screener and clinic visit completion. Strict efforts to maintain confidentiality/privacy will be followed, and all study team members will have rigorous training in maintaining confidentiality.

Because of the minimal risk classification of this study, the informed consent process has been modified in the following ways:

- The following **informed consent** will appear at the start of the anxiety/depression screening questions for all delivery methods:
    - *Your epilepsy doctor has included questionnaires about your mood and anxiety as part of your clinic visit. Taking part in this survey may involve providing information that you consider confidential or private. Depending upon how you answer these questions, the responses may be shared with your neurology provider. Some information you provide may be used for research. Careful efforts will be made to keep your information confidential. You will not lose any services, benefits, or rights if you choose not to participate in this voluntary survey.*
    - This **brief consent format is acceptable because the study is minimal risk**.
    - Thereby, **those who complete anxiety/depression screening instruments will provide consent** for use of research data and potential epilepsy provider notification of passive suicidality screen.
- For those who do not complete the anxiety/depression screeners, epilepsy provider notification is not applicable, and it is impractical to obtain informed consent:
    - 1. It is impractical to approach individuals who canceled or missed the clinic visit.
    - 2. For individuals who do not complete the anxiety/depression screeners but do attend the epilepsy clinic visit, it is impractical for appropriately trained staff to approach them for consent at the clinic visit, since these visits may occur at any time on any day, including simultaneously at disparate clinic sites.
    - Thus, **among those who do not complete the screening instruments**, **waiver of informed consent and HIPAA waiver are acceptable because** the study is classified as **minimal risk and because obtaining consent is impractical.**

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 investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP).

10.1.3 CONFIDENTIALITY AND PRIVACY

Data for analysis will be housed in REDCap[26] and data quality will be monitored by our team throughout the study.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

Authorized representatives of the sponsor or funding agency, 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) for the participants in this study. The clinical study site will permit access to such records.

The only contact information accessed for participants will be the minimal information necessary for screener delivery by the allocated method, and this will not be recorded in study records other than as required for screener delivery.

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/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at Wake Forest University Health Sciences. This will not include the participant's 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 research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Wake Forest University Health Sciences.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Wake Forest University Health Sciences. After the study is completed and results published by primary study team, de-identified, archived data will be stored for potential use if requested by other qualified researchers including those outside of the study.

When the study is completed and results published by primary research team, access to study data may be provided by the PI if requested by qualified investigators.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator:
Heidi M. Munger Clary, MD, MPH
Wake Forest University School of Medicine
1 Medical Center Blvd.
336-716-7110
hmungerc@wakehealth.edu

Study team workgroups:
-bioinformatics
-data management/statistical analysis
-operations

10.1.6 SAFETY OVERSIGHT

Safety oversight for this minimal risk, non-treatment study will be conducted via study team self-assessments guided by the Quality Management Plan, supervised by the Principal Investigator. Actions to notify clinicians of potential suicidality will be tracked and monitored for timely adherence to this procedure (see section 10.1.8). Any safety concerns will be promptly reported to the IRB.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study team will perform internal quality management of study conduct, data collection, documentation and completion, according to the quality management plan.

Quality control (QC) procedures will be implemented as follows:

Source documents and the electronic data --- Some data will be initially captured in the electronic health record or source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data (where applicable) against the database, targeting key data points in that review.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Safety/clinical alerts – the study team will track and review timeliness and completion of clinician notification in response to screening instruments for all results requiring alerts and corrective action will be carried out immediately if any notification delays are identified. The study team will track and review timeliness of EHR entry of REDCap-origin screening results on a weekly basis initially during study conduct

and take corrective action for any delayed entries. Frequency of this tracking may be reduced to monthly for a subset of participants if initial review demonstrates consistent timely entry.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, 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 will be the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets as applicable will be provided for use as source document worksheets for recording data for some data elements in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including medications and other data) will be entered into REDCap,[26] 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, including the EHR as the source document for some data. Some data will be entered directly by participants in the REDCap system as outlined earlier in the protocol.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years from the date of the Federal Financial Report (FFR) submission. 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/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council 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 will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It will be the responsibility of the investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to NCATS Program Official if required. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigator will be 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 by contacting Dr. Heidi M. Munger Clary. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence. 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 NCATS 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 AND SPECIAL TERMS

AE	Adverse Event
API	Application Programming Interface
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EHR	Electronic Health Record
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
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures

NCT	National Clinical Trial
NDDI-E	Neurological Disorder Depression Inventory-Epilepsy
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMART on FHIR	Substitutable Medical Applications, Reusable Technologies (SMART) on Fast Healthcare Interoperability Resources (FHIR)
SOA	Schedule of Activities
SOP	Standard Operating Procedure
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.

Version	Date	Description of Change	Brief Rationale
2.0	April 28, 2023	Clarify pragmatic trial, standard care previsit questionnaires & clinical privacy policies to be followed, stratify by antidepressant status, consent information wording modified following stakeholder input	Follow-up changes after funding received, stakeholder engagement and further communication with study team and privacy officer
3.0	Dec 5, 2023	Corrected wording of brief consent to align with IRB recommended changes made after prior protocol submission.	Ensure alignment between consent document and protocol wording.
4.0	March 15, 2024	-Update description of Aim 2 procedures to align with necessary updates in technical approach identified in technical build of kit tools. -Add additional reproducibility/generalizability assessment enabled by Encompass harmonization.	Ensure protocol captures accurate description of technical approach to aim 2a kit technology build and data collection approach. -Evaluate generalizability of Kit flowsheet REDCap plug-in data collection on the same dataset in an additional instance of the Epic EHR, enabled by health system Epic instance transition and data transfer from prior instance.

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