Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Early-phase Schizophrenia: Practice-based Research to Improve Outcomes (ESPRITO) - Disengagement in CSC: Identifying those at risk & addressing their needs- Phase 2
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IRB Number:	22-0662

Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
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- Start by entering study information into the table above, according to these rules:
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1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

Many individuals leave treatment programs for first episode psychosis before they have completed the treatment program. The technical term for this is disengagement from treatment. Disengagement from treatment can cause individuals to experience relapses of symptoms and also to not receive the full benefits of a treatment program. The causes of disengagement vary from individual to individual. We have developed a smartphone application (app) named CoPilot that is designed to support remaining in treatment. CoPilot is not itself a treatment program. Instead, it is designed to provide an engaging way for patients to do the tasks that are part of their regular treatment program and to access information that is provided in their regular treatment program.

The purpose of this study is to determine if patients who receive their regular treatment program plus have access to CoPilot will be less likely to drop out of treatment over a 6-month timeframe than patients who receive their regular treatment program without access to CoPilot. Sites in the study will be randomly assigned to either provide access to CoPilot to their patients or to just do their usual care. Study participants at both types of sites will complete a questionnaire about how burdensome it is to them to get treatment. The questionnaire will be completed at study entry, 3 months later and at 6 months. Participants at the sites randomized to provide CoPilot will be given free access to CoPilot for 6 months. At the completion of the study, we will compare dropout rates by participants who did or did not have access to CoPilot. If CoPilot is successful at decreasing dropout rates, it could become a useful clinical tool.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*

- *Describe the importance of the knowledge expected to result*

Even with state-of-the-art coordinated specialty care (CSC) for first episode psychosis, many patients with first episode psychosis will prematurely drop out of treatment. In phase 1 of this study, we examined dropout rates and characteristics of who dropped out of treatment in our Learning Health System (LHS) that includes 12 clinics across the US. We had a sample of 565 participants in our LHS who had been in treatment for varied lengths of time. Of the 565, 87 (15.4%) prematurely left treatment over a 6-month follow-up. In univariate analyses of factors associated with dropout, the following factors were associated with greater risk of dropping out: being in CSC treatment for less than 6 months versus those who had been in treatment longer; being homeless versus other housing arrangements; not being in court-mandated treatment versus being in court mandated treatment; not being prescribed a long-acting formulation of an antipsychotic versus prescribed a long-acting formulation; having poorer compared with better social functioning and participants reporting on a rating scale that they were less versus more likely to complete the treatment program. In multivariate analyses, none of the above predictor variables were significantly associated with dropout.

In phase 1 a subset (N = 266) of the LHS population participated in a study specific to addressing disengagement predictors. In this study participants completed a 2-item questionnaire every month for 6 months. Of these 266 participants, 17 (6.4%) dropped out of treatment over the 6-month observation period. These participants were included in the overall LHS results described above. Examining the LHS sample (N = 299) who did not participate in the disengagement-specific study, 70 (23.4%) dropped out of treatment over the 6-month observation period.

Phase 2 is designed to test whether a smartphone app (named CoPilot) designed by our research group can support continued engagement in NAVIGATE treatment, the CSC treatment model in 11 of the clinics in our LHS. CoPilot allows users to access information provided during NAVIGATE sessions in an easy-to-use smartphone format and to practice skills learned in NAVIGATE sessions. CoPilot encourages users to be in contact with their NAVIGATE treatment team and provides supports for contacting the NAVIGATE team. CoPilot thus facilitates NAVIGATE treatment but by itself does not provide treatment. Allowing easy access to NAVIGATE information and skill practice as provided by CoPilot is important as prior studies in many branches of medicine have demonstrated that patient perception of greater burden of obtaining treatment is associated with treatment adherence(Vijan et al. 2005).

How the Phase 1 findings influenced the design of Phase 2 of the study: First, the marked difference in disengagement rates between LHS participants who did and did not participate in the disengagement-specific study were not surprising. Participants who are ambivalent about staying in treatment are also unlikely to agree to participate in research assessments. For phase 2, this suggested that we require the least effort by participants that would meet the scientific objectives of the study. Second, although there are predictors from phase 1 in the univariate analyses of disengagement, there were no predictors in multivariate analyses. Our conclusion was to offer engagement supports to all participants.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

Specific Aim: To compare disengagement rates over a 6-month observation period at sites randomly assigned to provide the CoPilot app in addition to their standard CSC treatment program to disengagement rates at sites randomly assigned to provide only their standard CSC treatment program. Participants will be patients at the clinics who are eligible for treatment in their CSC program for 6 or months longer at study entry. Analysis will be at the participant level and be an intent-to-treat analysis. The hypothesis to be tested is that participants at CoPilot sites will have lower disengagement rates than participants who receive only standard care.

Exploratory Aim 1: If the hypothesis that CoPilot participants have lower disengagement rates is confirmed, we will perform an exploratory analysis addressing the question of the effect of selection bias on outcomes. We will examine associations of consent to participation at the study sites. Significant associations will be included as covariates in an analysis comparing CoPilot and standard care outcomes. This exploratory analysis will provide information about whether better outcomes with CoPilot are due to the effects of the CoPilot app itself or due to the type of participants who agree to use the CoPilot app being themselves more likely to remain in treatment.

Exploratory Aim 2: If the hypothesis that CoPilot participants have lower disengagement rates is confirmed, we will explore participant perception of the burden of obtaining treatment as measured by the Multimorbidity Treatment Burden Questionnaire (Duncan et al. 2018) as a mediator of treatment effects.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
    - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

Sites for the study will be the 11 sites within the ESPRITO network that provide NAVIGATE treatment. Since its inception, our ESPRITO network has enrolled 648 participants. Thus, the sites have the patient population to recruit the 300 number of participants needed for the research.
Each site has a research assistant supported by the ESPRITO grant. Site research assistants have all completed IRB-mandated training in the general conduct of research. Site research assistants will be trained by the central ESPRITO team on the study and specifically recruitment methods and obtaining and documenting informed consent for the study.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

All participants will have consented to our IRB-approved ESPRITO LHS. Data collection for the LHS includes data on length of treatment received in the CSC clinic. Combining these data with the clinics' standards for length of treatment eligibility allows identification of clinic patients who have 6 or more months of eligibility for clinic treatment. Site research assistants will then present the study in its entirety to CSC participants who have been identified as potentially study eligible.

Regarding monetary compensation, the CoPilot app will be provided free to eligible participants. No monetary compensation will be provided for use of the CoPilot app. Assessments for the study will consist of the assessments in the LHS protocol (and no compensation will be provided within this protocol for those assessments) and the Multimorbidity Treatment Burden Questionnaire (MTBQ). As a research procedure separate from clinical care, participants will receive $10 in compensation per MTBQ completed for their time completing the questionnaire. To ensure economic equity of study participation, participants who cannot afford/obtain a smartphone will be provided a smartphone and associated cell coverage during the time of their study participation.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*
- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Inclusion criteria are: 1) enrolled in the ESPRITO Learning Health System and between the ages of 15 and 39 years; 2) eligible for continued treatment by the NAVIGATE team for 6 months or longer; 3) able to provide informed consent (informed assent and informed consent by a parent/guardian for participants below the age of consent in the state in which a site is located).
Exclusion criteria: 1) court-mandated to treatment (Our LHS sites are in states across the country and states vary widely on the specifics of court-mandated treatment. We exclude

participants who are court-mandated to treatment because we would not be able to prevent potential imbalances in the site randomization due to state variability if we included court-mandated participants.) and 2) inability to read English (CoPilot is only available in an English language version).
Special populations: The clinics in the ESPRITO LHS specifically provide treatment to individuals with early phase primary psychotic disorders. Thus, individuals with serious mental illness are the target population for the study. As the usual age of onset of primary psychotic disorders is adolescence and early adulthood, the protocol allows enrollment by individuals below 21 years of age as many individuals with primary psychotic disorders begin treatment before age 21.

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

300 participants will be enrolled across all sites. Northwell is not clinical site for our ESPRITO LHS so no participants will be recruited locally from Northwell.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

The observation period for each participant will be 6 months.

Enrollment will take 15 months at a rate of 20 new participants per month.

Study completion is projected to be by 5/1/24.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

The primary outcome will be disengagement from treatment. The study is designed to address clinically meaningful disengagement. NAVIGATE services include medication treatment, individual therapy, psychoeducation and supported education and employment. NAVIGATE uses a shared decision making model for treatment selection. With this model of treatment, patients can choose to participate in all NAVIGATE services or to participate in only some of the NAVIGATE services. Thus, disengagement from NAVIGATE treatment is defined as not

participating in any NAVIGATE treatment services despite the opinion of the NAVIGATE team that continued NAVIGATE treatment is needed. Clinics vary in their policies regarding formal discharge from their clinic. Our disengagement outcome is therefore based upon the NAVIGATE team's determination that a patient is not engaged in any NAVIGATE service and not on administrative discharge status. Participants who are transferred to other treatment services (e.g., inpatient treatment, substance abuse treatment) by the NAVIGATE team will not be considered disengaged as these are the recommendations of the treatment team. In the course of treatment, some participants may move outside the area that the NAVIGATE team services. Participants who move and who agree to referral for services in their new location will not be considered disengaged. Participants who move and who refuse referral for services in their new location will be considered disengaged.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

Sites will be randomly assigned on a 1:1 basis to provide standard NAVIGATE care or NAVIGATE care plus CoPilot. Data from phase 1 allow us to determine typical rates of disengagement at each site. Prior to randomization we will group sites as much as possible (given the limited site number) into groups based upon the disengagement rates found for each site during phase 1 of this study. Randomization will be within the groups to minimize differences in baseline disengagement rates at sites randomized to standard NAVIGATE care or to NAVIGATE care plus CoPilot.

At all sites, the site research assistant will review the site census to identify patients who have 6 or more months of eligibility for continued treatment in the NAVIGATE program. The research assistant will approach potential participants and describe the study in full detail for those interested and provide potential participants the opportunity to ask any questions about the study. Those who express a continued interest in participating will be given a quiz (attached with the consent form in this application) about key aspects of the study. After demonstrating a full correct knowledge of the items on the quiz, participants will provide informed consent (for participants below the age for providing consent in the jurisdiction of the site, a parent/guardian will compete the quiz and provide informed consent with written assent by the minor).

At all sites, data for the study will come from the assessments that are part of the Common Assessment Battery (CAB) that are collected under the IRB-approved ESPRITO LHS project. The only additional assessment beyond the LHS assessments will be the Multimorbidity Treatment Burden Questionnaire (MTBQ)(Duncan et al. 2018). The MTBQ is composed of 10 items rated on a Likert scale ranging from 0 (not difficult), to 5 (Extremely difficult). The MTBQ will be administered at study entry, 3 months and at 6 months (or study termination when available for participants who do not complete the 6 month follow-up period). The MTBQ will be administered to all study participants regardless of the randomization condition of their treatment site.

Data specific to the CoPilot app are listed at the end of this section. These data are only collected for participants at sites randomized to provide CoPilot.

Participants at sites randomized to provide NAVIGATE plus CoPilot will be given access to the CoPilot app. In the consent process, participants will also be given the opportunity to allow family members/supporters to have access to the Family version of CoPilot (participants may later revoke family/supporter access at any time if they wish; participants who initially did not grant permission for family/supporter access may grant access at a later time if they wish).

Overview of the CoPilot app

The CoPilot mobile application (app) is a newly developed digital health solution providing NAVIGATE-based material and activities via a smartphone app. Apple and Android versions are available. Through patient engagement with a mobile application, we aim to encourage patients to remain engaged in the NAVIGATE program and with their treatment team.

CoPilot is not intended to reproduce or replace what is already done in a clinical setting, but to support patient use of NAVIGATE program materials through features that a mobile app can offer, such as nudges and reminders, personal engagement, diary functions and content.

CoPilot supports concepts from the NAVIGATE program such as:

- Coping strategies
- Goal setting
- Application of Strengths
- Wellness Plan
- Good Things
- SEE practices

The system provides a weekly summary report to the sites' Treatment Team covering their patients which they can use as input for their periodic team meetings. Sites have access to data with identifiers for the participants at their site (but not to participants at other sites).

Identification and description of CoPilot

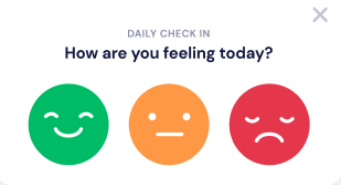
CoPilot comprises (i) a mobile application for study participants (iOS and Android), (ii) a central database and processing unit, and (iii) a Study Portal for the Treatment Team at a site to

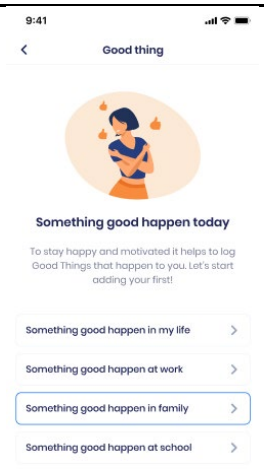
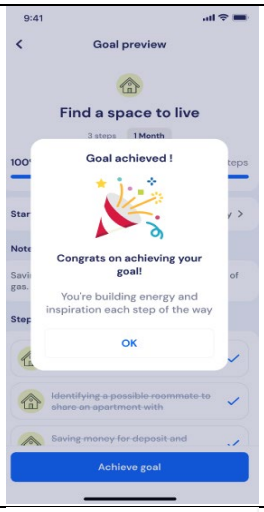
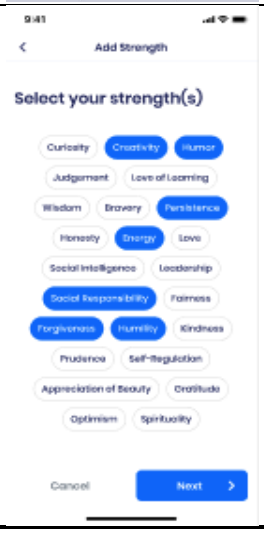
obtain information about their participants at their site, via a web browser, as illustrated in Figure 1.

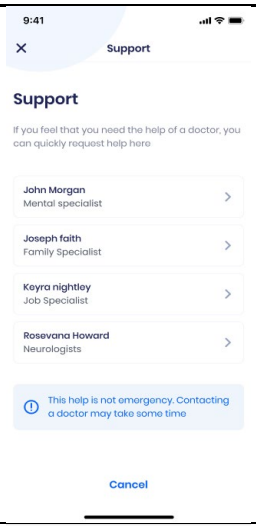
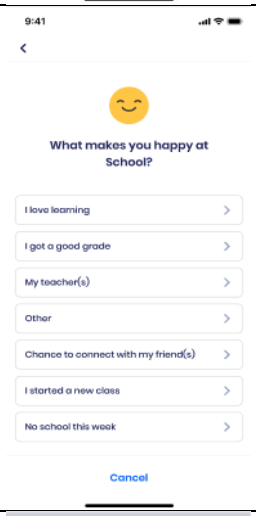
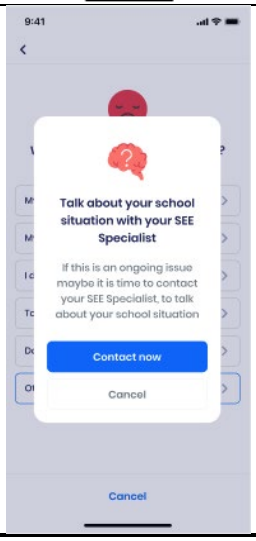


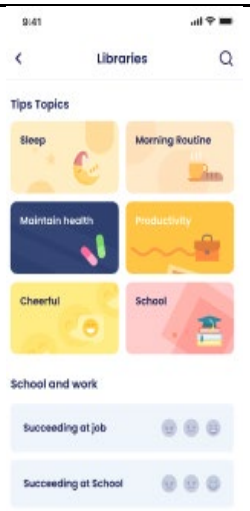
- The **mobile app**:
  - Supplements the manual/handout format of standard NAVIGATE treatment with NAVIGATE material provided via an easy-to-access and use smartphone format.
  - Includes prompts when appropriate for participants to contact their NAVIGATE treatment team
  - Collects activity data through HealthKit and Google Fit, smartphone functions for Apple and Android smartphones respectively. Collection of data from HealthKit and Google Fit is optional, and participants may opt out of HealthKit and Google Fit data collection. Activity data are collected in a de-identified manner from the smartphone. A prime goal of standard NAVIGATE treatment is promotion of healthy lifestyles. Activity data can document the level of success in achieving these goals.
- The **Central database** and processing unit captures, stores, and processes CoPilot data. The central database connects with the IRB-approved ESPRITO ONE data system for our Learning Health System.
- The **Web portal** supports the study team with the administration and monitoring of study participants

The mobile application has the following main features:

Mood tracking ("How do you feel today"): daily invitation for the user to register how they feel on a 3-point likert scale. This function has follow-up questions linking to the following features.	

Good Things: Standard NAVIGATE treatment emphasizes strengths and resiliency. Supporting these concepts, CoPilot allows users to record positive events in their lives "Good Things" using various media.	
Goals: Goal setting is an important component of NAVIGATE treatment. CoPilot has tips and reminders on completing tasks and progressing to new goals and tasks.	
Strengths: In NAVIGATE treatment, patients identify their strengths. CoPilot reminds users of their identified strengths and provides tips on how to apply these strengths in various situations such as feeling good/bad or completing tasks.	

Wellness Plan: In NAVIGATE treatment, patients develop a personal Wellness Plan. CoPilot provides a summary of their Wellness Plan developed during NAVIGATE sessions. Wellness Plans include instructions to contact treatment team staff for specific problems. CoPilot provides users with contact details of the treatment team.	
Tracking participant experience at work/school: NAVIGATE treatment supports patients returning to/continuing in age-appropriate mainstream activities such as attending school or working. For participants who attend school and/or work, CoPilot includes a weekly check-in on how the week at school/work was.	
Remaining or starting work/school: CoPilot includes tips on how to remain at work/school or (re)start work/school with a strong focus on connecting with the NAVIGATE supported education/employment specialist.	

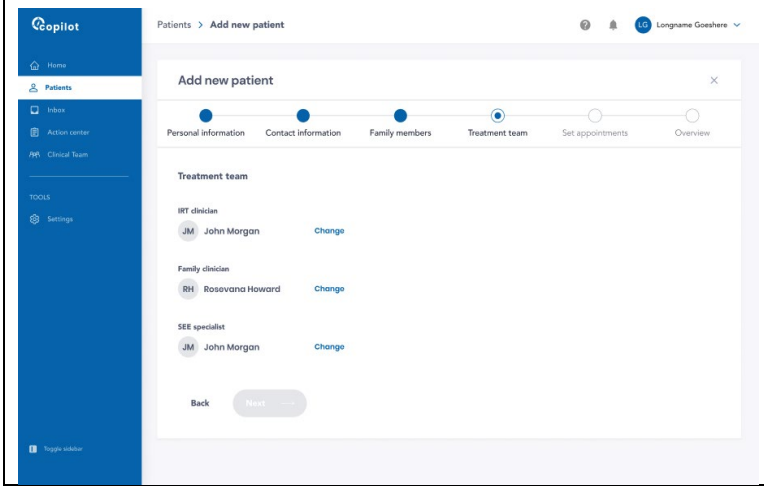
Library: contents with tips and reminders for users	

None of the above features are required for the patient to complete. The notifications and suggestions are intended to activate the users and reward them with positive feedback. There are no consequences for not using these functions.

CoPilot data access after 6-month follow-up completion: After the time of the 6-month study completion, participants will no longer be able to do new activities or add new data to their copy of CoPilot. Participants will continue to have access to view previously entered CoPilot materials for 3 months after study completion. After the 3-month period, participants will no longer be able to view their CoPilot materials. The 3-month period is provided for participants to be able to review their CoPilot materials and make notes about their entries/experiences if they wish.

Web Portal

The Treatment Teams at the study sites will be using regular computers with internet access and common web browsers to access the Web Portal. The central study team and Healios, the app programmer, will provision the initial user accounts for the participating Treatment Teams. The main function of the Web Portal is to register and administer CoPilot.



Installation & instructions

After the participants provides informed consent for the study, the Research Assistant will create the participant's user account through the web portal and help the participant to install the app from the appropriate app store (App Store or Google Play) and gain access to their account.

The Research Assistant will enter basic information from the participant's NAVIGATE file to enable the participant to use the app. Such information includes:

- pseudo-GUIDs
- Connect Treatment Team contacts
- Goals and short-term goals
- Identified Strengths
- Wellness Plan details

These data points do not include private or confidential information.

The mobile app is designed to be self-explanatory and uses technology and approaches generally found in modern mobile apps. Upon registration and start of using the mobile app, the Research Assistant will review the main functionalities of the mobile app with the participant to confirm that they feel comfortable navigating the mobile app.

The Research Assistant will also support the participant in the process of allowing the mobile app to gain access to HealthKit or Google Fit data for participants who have consented to such access. The Research Assistants will also enable access to family members/supporters (if any) who the participant has authorized to have access to the Family version of CoPilot.

If the participant no longer wants to continue to study participation and/or use the mobile app, they can log out and remove the app at any time. App deletion will not affect data already transmitted to the study data server but all further data transmissions to the server will cease.

The system has a reporting function that provides the site Treatment Team with a summary of the main app activities by the participants at the respective site (site treatment teams will not have access to any data from participants at other sites).

The following data specific to CoPilot app usage are collected for participants at sites randomized to provide CoPilot to their patients:

Table 1:

1. Subject Data		
Data Classification	Data Items	Explanation/Comments
1.1. Device Data		
	IP address	IP (Internet protocol) address of the smartphone

	Device model	Device make (manufacturer, e.g., Apple/Samsung/…) and model (e.g., iPhone XS)
	Smartphone cell number	
	Device OS	Device OS version
	App version	ESPRITO app version
	Language	User's language setting
	Access to Google Services	Approval of access to Google Services
1.2. ESPRITO Account		
	Nickname chosen	Nickname set by user (users use nicknames to enhance privacy security)
1.3. ESPRITO analytics		
	Access log	Date and time of using the app
	Time using the App	Duration of app activation and usage
	Screens visited	Screens of ESPRITO app visited
	Crashlytics (bug tracker)	App service to report in case the app crashes and registers and transmits technical data to support the technical team to identify root causes to prevent repetition
1.4. Personal information (This information will be collected at study baseline visit by the study research assistant		
	Gender (optional)	Male/Female
	Participant type (patient/family member)	Patient/family member
	Work/school occupation	Whether participant is going to school and/or working. Information about specific school attended or work location are not collected.
	Mobile platform	iOS/Android
2. Passive activity data from smartphone		
2.1. iOS device (HealthKit) **Note:** Collection of HealthKit data is an **optional** component of the protocol. Participants may opt out of collection of these data during the consent process or at any other time during the study.		
	Basal energy burned	Resting energy is the energy that the user's body burns to maintain its normal, resting state.
	Active energy burned	Active energy is the energy that the user has burned due to physical activity and exercise.
	Heart rate	User's heart rate if user has a heart rate monitor connected to HealthKit
	Heart rate variability SDNN	Standard deviation of heartbeat intervals.
	Resting heart rate	Heart rate when user's body is in normal, resting state.

	Walking heart rate	Heart rate when user's body is active due to physical activity and exercise.
	Distance walking /running	Distance user walks/runs
	Apple exercise time	Amount of time HealthKit registered the user has performed physical activity and exercise.
	Step count	Number of steps counted.
	Flights climbed	Measures the number flights of stairs that the user has climbed as measured by HealthKit and/or connected apps.
	Sleep analysis	Sleep analysis performed by iOS if data is provided by user through manual intervention or connected app or device.
2.2. Android device (Google Fit) **Note:** Collection of Google Fit data are an **optional** component of the protocol. Participants may opt out of collection of these data during the consent process or at any other time during the study.		
	Calories burned	Analysis of calories burned through activity
	Move Minutes	Number of minutes the user has moved as collected through smartphone and/or connected devices and calculated by Google Fit
	Step count cadence	Measures steps per minute. Each data point represents an instantaneous measurement of the cadence in steps per minute.
	Step count delta	Captures the number of steps taken since the last reading.
	Speed	Walking speed calculated based on steps per minute.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

Smartphone apps as a group have the advantage of being low cost to implement widely once development/programming of the app has been completed. In addition, they are usually associated with low risk to users. We carefully considered the best analytic approach that would provide clinicians the information they would need to decide if providing a smartphone such as CoPilot to their patients would be advisable. Comparing a frequentist and Bayesian approach, we decided that the Bayesian approach would be more informative to clinicians. A Bayesian approach provides clinicians the probability (technically known as the posterior probability of being a risk factor (PPRF), also sometimes referred to as the `selected percentage') that providing an app like CoPilot would be better than not providing CoPilot.

Each clinician can determine what probability would be sufficient to provide an app. For example, suppose a Bayesian analysis showed that there was a 70% probability that providing CoPilot decreased disengagement rates compared to not providing CoPilot. With a low cost, low risk app a clinician might decide that providing the app was worth doing even if the probability was only 70%. The probabilities provided by a Bayesian approach are much more informative to clinicians than the p-value provided by a frequentist approach.

The proposed Bayesian analysis will estimate the intervention effect while allowing for the clustered structure of the data by using a hierarchical logistic regression model which allows for the log-odds of disengagement to vary among the sites. From a technical viewpoint, Bayesian approach offers flexibility and several other advantages compared to the traditional frequentist approach for logistic regression modeling. Primarily, with a Bayesian approach, robustness to classical model assumptions may be assessed by using distributions other than normality for the cluster random effects. Secondly, under specification of a flat prior, the Bayesian approach provides a procedure for interval estimation of the Intracluster Correlation Coefficient (ICC) with binary outcome data. Third, interval estimates of combinations of model parameters such as the difference between two variance components can be obtained within a Bayesian framework. Also, from a computational perspective, iterative bias correction procedures especially for the variance components based on traditional analysis of sparse binary data can be substantially more computer intensive than with a Bayesian approach. Yet another valuable advantage of the Bayesian method is the ability to specify informative priors for the ICC.

Overall, we will follow the analytic strategies described in Turner et al (2001). The hierarchical logistic regression model may be expressed as: $\text{logit}(\pi_{ij}) = \alpha + u_i + \beta x_i$ where π_{ij} is the probability of disengagement for j^{th} participant in the i^{th} site; the binary covariate x_i contrasts intervention (app, $x_i = 1$) and control (usual care, $x_i = 0$) sites. The parameter β is the intervention effect; that is, the log-odds of disengagement comparing intervention to usual-care sites. α represents the log-odds of disengagement on the average among the usual-care sites. The random effects u_i will be initially assumed to be distributed $N(0, \sigma_u^2)$; however, alternate distributions such as the t-distribution, the Laplace distribution, the gamma distribution, and the mirrored gamma distribution will also be considered as in Turner et al (2001). Since there is little prior information available for the parameters α and β, we will specify a non-informative prior, specifically, a $N(0, 10^4)$ proper prior. Because of the relatively small number of clusters, an informative prior will be utilized to estimate the clustering parameter σ_u^2. Rather than placing a prior directly on σ_u^2, we will use an approximate relationship between σ_u^2 and the ICC ρ derived in Turner et al (2001), and specify a prior for ρ. We will analyze separately using all the five priors for ρ considered in Turner et al (2001): Uniform (0,1), Fitted half-normal, widened half-normal, fitted beta and Widened beta.

Bayesian analysis will be conducted using Markov Chain Monte Carlo (MCMC) methods, specifically Gibbs sampling via the BUGS software (Spiegelhalter et al 2003). If the mixing of Markov chains for the logistic regression model is slow, then reparametrization strategies will be employed to improve convergence. Reparametrization strategies will include centering the treatment covariate using a coding of +/- ½ and also hierarchical centering, aiming with each strategy to reduce the posterior correlations between parameters in the model. Hierarchical centering will involve replacing the random effects u_i, centered around zero, by random effects

$\alpha_i = u_i + \alpha$, centered around α. Markov chains based estimation will comprise of a burn-in of 5000 followed by a further 50,000 iterations over which the posterior distributions of the parameters will be monitored. Multiple runs with overdispersed starting values will be used in the principal analyses. Cluster randomized trials typically have a limited number of clusters that could cause an imbalance between treatment groups on baseline measures, and this imbalance may confound the relationship between treatments and patient-level outcomes. Analytic strategies that account and adjust for this imbalance have been considered in prior literature (e.g., for RAISE-ETP cluster randomized trial). We will follow the strategy similar to that employed in the RAISE-ETP trial (Kane et al 2016) to detect and adjust for baseline imbalances. Specifically, the two treatment groups will be compared on baseline demographic and clinical variables. If significant baseline group imbalance is detected on a particular variable, and that variable is correlated with outcome at a level of .30 or higher, the variable will be included as a covariate in a secondary analyses of outcome.
In order to conduct these analyses, a sample of 300 participants will be required. The ICC for the LHS is .058. Assuming an average size of 30 participants per site, five sites per treatment condition are required to detect a disengagement rate difference of 25% versus 5%.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

Not applicable

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
  - *What information will be included in that data or associated with the specimens?*
  - *Where and how data and specimens will be stored?*
  - *How long the data will be stored?*
  - *Who will have access to the data?*
  - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

No specimens are collected in this protocol.

Data collection

Data Overview: Data collected for all participants will be 1) data from data collected in the IRB-approved ESPRITO project and 2) patient report of treatment burden with the Multimorbidity Treatment Burden Questionnaire. Clinical sites have data that identifies their participants (but not participants at other sites). The ESPRITO central team will only have access to de-identified files with these data (participants are identified by non-informative pseudo-GUIDS provided by the NIMH NDA). Healios will not receive any of the above described data with the exception of the pseudo-GUIDS that will be used to later combine CoPilot data with the central ESPRITO database data.

The above Data Overview describes all the data that will be collected for participants at the sites that are randomized to not provide CoPilot. Data for these participants are de-identified at the level of the ESPRITO central team. Healios will not receive any data on participants at sites randomized to not provide CoPilot as Healios' study role is confined to proving services to participants at CoPilot sites.

Additional data beyond that described in the above Data Overview paragraph will be collected at sites randomized to provide CoPilot. These are described in Table 1 in the research procedure section of this protocol.

These data contain two identifiers (IP address and smartphone telephone number) that are required for CoPilot to function and will need to be available to Healios in their role of supporting CoPilot functioning.

As required by NIMH, data from this project will be transferred to Westat (NIMH's chosen vendor) which will then forward the data to the NIMH NDA. All identifiers will be removed from data before transmission to Westat.

Data Management System

CoPilot will collect user data from participants' smartphones while they are performing activities. When a study participant completes a task on their smartphone, the mobile app sends the compressed and encrypted raw data to the Healios cloud for storage.

The data captured via the app is directly stored in a table structure that reflects the structure of the app and the activities. Each of the datasets is linked to the user via a coded non-informative patient identifier, along with time and date stamps.

The central database (CoPilot cloud) is a MySQL database management solution that is hosted in an Amazon Web Services (AWS) environment. During the study, the data are managed by Healios database administration. The Healios cloud is internally organized by a multitude of microservices in a "virtual private cloud" (VPC) hosted on a server farm by AWS in North Carolina as the primary zone. California is set-up as the secondary zone with the objective of achieving back-up and high availability. The system architecture is divided into separate, independent microservices, to increase flexibility, scalability, and reusability of codes. The

Healios cloud includes an administrator service as a gateway, a queue service that controls asynchronous jobs in order to reduce the time of response of the system, a user data service to manage the user data, a manager service to manage transactional information related to the activities, e.g., schedule, completion, reporting, and a validator service that validates and parses the raw data and generates a new dataset, called "pre-processed" data. Finally, a processor service runs the different algorithms over the pre-processed data and will generate the processed data ("results", e.g., features/metrics). Each stage of the data (raw, pre-processed and processed/results) will be stored in a database called "Precard DB".

Data security, access, and back-up

The mobile application is downloaded on the personal smartphone of participants by a trained Research Assistant.

CoPilot is hosted on a fully secured and encrypted virtual private network (VPN) Amazon Webservices (AWS) environment. To ensure high security standards, AWS functionalities are used, such as logically isolated virtual private networks, database encryption, user and authentication management, activity logging, DDoS protection as well as daily encrypted backups. Data transmission between Healios and the ESPRITO network center and is encrypted via HTTPS with AWS Certificate Manager. Data from Healios is transmitted to the ESPRITO central team.

Access to data is limited to the designated data manager at Healios, and authorized study personnel who require the data to fulfill their duties within the scope of the research project. The servers are located in North Carolina (primary) and California (secondary). All the databases have an integrated back-up system for regular backups.

Electronic and central data validation

Procedures are in place to monitor that data from the mobile app are captured and stored accurately and completely during the study and data management procedures are in place. The mobile app has completeness and validation checks to support quality of the manually entered data, e.g., when completing validated questions.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

The study compares standard NAVIGATE care plus CoPilot versus standard NAVIGATE care without CoPilot. Adverse events can be associated either with NAVIGATE treatment or with CoPilot. Adverse events for all study participants related to NAVIGATE treatment are already being collected, reviewed and when appropriate reported to the IRB under the IRB-approved ESPRITO project by the same study team as for this protocol. These procedures will cover the NAVIGATE related adverse events for the proposed study. CoPilot is a smartphone app that has minimal risk of causing associated adverse events. However, we will monitor and collect adverse events related to CoPilot using a modified version of the adverse event collection procedures for the ESPRITO project. The modification consists of adding a question of the relationship between the reported adverse event and CoPilot usage.

Reports of adverse events are provided to the central study team located at Northwell for evaluation. Unexpected serious adverse events are reported to the IRB as per IRB requirements. Adverse events are evaluated for unexpected occurrences by the central team and their clinical significance ultimately determined by Dr. Robinson as the Principal Investigator of the study.

The study is funded by NIMH. If NIMH suspends the study, NIMH staff will be aware as they will have initiated the suspension. This, notification of suspension beyond to the IRB is not required.

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

N/A

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*

- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Risks directly associated with CoPilot use are minimal. In the unlikely event that CoPilot use is clinically assessed to be associated with deterioration of participants' clinical status the participant will be removed from the study.

Site investigators may remove a participant from the study at any time if they feel that it is not in the participant's best interest to continue. Participants may also choose to withdraw consent at any time. If a participant requests to withdraw from the study, they will be asked if the site can recontact them during the original 6-month long participation period to determine if they would be interested in continuing in the data collection. If the participant indicates no, the site will not have further contact with the participant regarding this study. When a participant requests to be withdrawn from the study, data collection stops but the already collected data will be kept for use in the overall study analysis. Including these data in the analysis is important for following the principles of intent-to-treat analysis of study outcomes.

The main possibility that participants would be withdrawn from the study is a change during the trial that the participant becomes court-mandated for treatment. Participants who become court-mandated for treatment during the trial will be removed from further study participation.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to results*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

The main risk to participants at the sites randomized to use copilot app is loss of confidentiality.

Confidentiality protections related to data management and the CoPilot app have been described in section 14 of this application.

All study personnel, including those at clinical sites, have received training protection of participant confidentiality.

Participants may inadvertently disclose personal information by allowing others to see CoPilot while in use. Participants will be made aware of this risk to confidentiality.

Participants have the option to allow family members/supporters to have access to a part of CoPilot that is specific to family members/supporters. This is an optional study component and participants may opt out of this component at the time of consent or at any other later time.

CoPilot allows participants to record good experiences in their lives. In this process, they may inadvertently enter material that may include personal information (participants are specifically warned not to enter personal information into CoPilot.). This information may be transferred to the automated Healios server as part of the CoPilot app functioning. This is an automated process with no planned review or data capture by Healios. If such personal information was sent to the Healios server, it would not be included in any data transmissions to Northwell or any other entity besides communication with the participant's smartphone.

The CoPilot app emphasizes positive aspects of participants' lives (e.g., the recording of Good Things that have happened to the participant). Nevertheless, it is possible that participants may become distressed during use of app functions. If this happens, participants can stop using CoPilot at any time. Another option follows from the design feature of CoPilot that allows users to choose among different sections of the app based upon participant preferences. Thus, participants can decline to use a section that caused distress while using other parts of CoPilot. Further, participants can delete the entire CoPilot app from their smartphones at any time. Finally, NAVIGATE staff at the clinical sites are available to provide support and counseling if participants wish that option.

For participants at sites not randomized to use the copilot app, the main risk is discomfort from answering the MTBQ. To reduce this risk, participants will be reminded that participation in this research study is voluntary and they can choose to not answer questions at any time. There is also the risk of breach of confidentiality.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

Participants will have access to their NAVIGATE treatment team for any psychological distress associated with protocol participation.

19. **POTENTIAL BENEFIT TO SUBJECTS**

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

Study participants at sites randomized to provide NAVIGATE without CoPilot will not receive any direct benefit from the app, however, they are contributing to the testing of a smartphone app that if successful could support NAVIGATE treatment in the future. Participants at sites randomized to provide NAVIGATE plus CoPilot will receive the above benefits in addition to use of the CoPilot app which may increase their likelihood of staying in their current treatment and reduce the risk of relapse or disengagement..

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Potential participants will be participants in NAVIGATE treatment at each site subset to those who are eligible for 6 months or longer of continued treatment and those who are not court-mandated for treatment. With these minimal criteria, sites will be able to identify potential participants with the knowledge that they have from ongoing treatment of their patients and not need to access other sources.

Site trained Research Assistants will briefly present the study to potential participants. Participants who express an interest in the study will then be provided a complete description of the study. Before providing informed consent (written assent by participants and consent from family/guardians for participants younger than the age to provide consent in the jurisdiction in which their clinic site is located) participants (or family/guardians depending upon who provides consent) will demonstrate knowledge of key aspects of the study. All discussions of the study will be done in settings that maintain full confidentiality of potential participants. All site personnel have been trained on maintaining confidentiality of study participation.

All site study personnel will follow the guidelines at their clinic for privacy protections in communication with participants.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

There are no costs to participants.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Participants will receive $10 for completion of each Multimorbidity Treatment Burden Questionnaire. Multimorbidity Treatment Burden Questionnaires will be administered 3 times during the protocol.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

Consent will be obtained by site study research staff. Consent will follow procedures that are IRB approved.

As described in prior sections of this application, sites will identify potential participants (patients in their NAVIGATE program who have 6 or more months remaining eligibility for clinic treatment and who are not court-mandated for treatment). Research staff will briefly present in a confidential manner the study to potential participants. Participants who express an interest in the study will then be further evaluated for study participation.

The consent process begins with an assessment of the participant's ability to give informed consent. Participants who on initial evaluation by the study investigator are deemed not to be capable of giving informed consent will not be evaluated further. Participants who are deemed capable of giving informed consent will then be provided with a full and complete description of the study. Informed consent will be obtained in a shared decision-making context and reasons for agreement or refusal will be documented.

Before providing informed consent (written assent by participants and consent from family/guardians for participants younger than the age to provide consent in the jurisdiction in which their clinic site is located) participants (or family/guardians depending upon who provides consent) will demonstrate knowledge of key aspects of the study. Copies of the questions used to demonstrate understanding are included with the informed consent document included in this application.

All discussions of the study will be done in settings that maintain full confidentiality of potential participants. All site personnel have been trained on maintaining confidentiality of study participation.

Informed consent will be documented when the participant signs the consent form that has been approved by the Institutional Review Board. Signature can be either by writing on a paper consent document or by IRB electronic signature procedures.

The usual means of documenting consent are paper forms used during in-person meetings between the potential participant and study staff or remote electronic signature procedures. However, there are potential situations when paper consent forms must be used but in-person meetings using the paper forms is not possible (e.g. the clinic only provides remote treatment due to COVID or other issues and the potential participant does not have the equipment/means to do electronic documented consent). The research staff will review the consent form with the participant and/or parent/legal guardian over the phone or via telehealth. Participants and/or parent/legal guardian will then be asked to sign the consent form before emailing, mailing, or faxing the form back to the site. Participants and/or parent/legal guardian will then be asked to select the witness signature waiver box in the consent form before emailing, mailing, or faxing the form back to the site or completing the consent form in the Learning Health System (ESPRITO-One) with an electronic signature.

Once the study team receives the signed copy, the research staff will sign the consent form and a copy will be made and sent to the participant and/or parent or legal guardian for his/her records.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

The NAVIGATE programs participating in the study allow the enrollment of adolescents into their program. These participants will not be excluded from the study, as there is no anticipated additional risk for this population.

Participants under the age for providing consent for research in the site jurisdiction will have their parent or legal guardian sign an informed consent utilizing the process described above

and the participant will sign an assent form. If the participant reaches the age for providing consent while in the study, re-consent from the participant will be obtained. If the participant declines to provide re-consent, further study participation will end.

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*
  - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

Not applicable

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

Not applicable

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS ☒ N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *Explain why it is not possible to conduct this research without using the information or biospecimens in an identifiable form*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

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25. WAIVER OF HIPAA AUTHORIZATION ☒ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*
- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)*

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☒ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☒ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☒ *poor/uninsured*
- ☒ *Students*
- ☒ *Minorities*
- ☐ *Elderly*
- ☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

The age of onset of first episode psychosis is usually in adolescence and the early years of adulthood so individuals younger than 21 years of age are included in the study to allow study findings to be generalizable to the patient populations served by NAVIGATE clinics. Similarly, NAVIGATE programs provide services to the poor/uninsured, students, minorities and pregnant women and these groups are included in the study.

Participation in the study by children, pregnant women, the poor, students, and minorities will have no additional risks beyond those of any study participant. Study consent for participation by an individual who is younger than the age for consent for study procedures in the jurisdiction of the relevant site will require consent by a parent or legal guardian in addition to the assent of the participant. In order to maintain economic equity of study participation, poor participants who do not have a smartphone will be supplied one for use during their study participation.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

Northwell will be the coordinating center for the study. Our central study team has extensive experience coordinating large multi-site investigations and specifically studies involving first episode psychosis populations. The central study team coordinates the EPINET project and provided the oversight for phase 1 of this study. Any modifications or annual reports that may need to be submitted to the Northwell IRB will be submitted by the Northwell central team and will be approved for submission by the external site PI.

The Northwell central team monitors on a regular schedule the recruitment, retention, and completion of all required study procedures at each site. Monitoring is facilitated by access to the ESPRITO ONE data management system which provides the Northwell central team oversight of the collection of all study data. Issues can also be detected through regularly scheduled calls to study site personnel and on-site monitoring visits when needed. Issues identified at any site will be brought to the attention of the local site PI and other site personnel when appropriate. The Northwell central team will also be holding monthly group calls with the local site coordinators to provide oversight, identify best practices, and problem solve any issues that may arise.

The Northwell central team will provide training to each site's coordinator on the definition and collection of unanticipated problems, including the completion and submission of the Unanticipated Problem Form to the IRB. In the event that a site does identify an unanticipated problem, the Northwell central team will assist the site in the completion and submission of the Unanticipated Problem Form to the IRB as well as alert the Operations Core of the event.

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

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