Northwell Health

RESEARCH PROTOCOL

Protocol Title:	Early-phase Schizophrenia: Practice-based Research to Improve Outcomes (ESPRITO) - Using Artificial Intelligence to Measure Adherence to Oral Medication
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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*.
  - Your study is a registry or repository for data and/or samples, In this case, use *Protocol Template – Registry Studies.* .
- If a section of this protocol is not applicable, please indicate such.
- Do not delete any of the text contained within this document.
- Please make sure to keep an electronic copy of this document. You will need to use it, if you make modifications in the future.
- Start by entering study information into the table above, according to these rules:
  - Protocol Title: Include the full protocol title as listed on the application.
  - Investigator: include the principal investigator's name as listed on the application form
  - Date Revised: Indicate the date at which the protocol was last revised
  - IRB Number: Indicate the assigned IRB number, when known. At initial submission, this row will be left blank.
- Once the table information in entered, proceed to page 2 and complete the rest of the form.

↓ Continue to next page to begin entering information about this study ↓

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*

Our network Early-phase Schizophrenia: Practice-based Research to Improve Outcomes (ESPRITO) is one of five collaboratives selected by the NIMH to advance the treatment and outcomes of patients with early phase schizophrenia. As part of this collaborative, two research projects will be conducted within the ESPRITO network.

Direct Observation of Treatment (DOT) represents an approach to adherence assessment that has not been utilized previously in this population in any clinical setting in mental health care except substance abuse. No one can expect FEP patients to come to a central clinic or have clinic staff come to them daily to do DOT. The unique AiCure suite of technological innovations is provided to the user via a smart phone and includes HIPAA compliant facial recognition, medication identification, medication ingestion confirmation as well as dashboard delivery to the provider (https://aicure), The AiCure model makes it possible to evaluate the potential benefit of DOT for individuals receiving Coordinated Specialty Care (CSC) services. This pilot study will enable us to determine acceptability, usability and sustainability in this context, and will also provide an initial evaluation of whether technology-provided adherence assessment impacts on hospitalization/ER visits

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*

The previously completed RAISE ETP study showed that a CSC model could be feasibly delivered in community mental health clinics in multiple states and was effective [1]. Since then, with the support of SAMSHA block grants to states, there are CSC programs across the nation [2]. NAVIGATE, the CSC developed for RAISE-ETP, is manual driven and incorporates clinical services that promote recovery in first-episode psychosis (FEP) participants. Since the RAISE-ETP study was completed, 48 CSC teams across the US have been trained in NAVIGATE by our team. Participating sites will be drawn from four states, Florida, Michigan, Oklahoma and South Carolina and are currently operating certified NAVGATE programs. They vary in populations served, levels of funding available and research experience.

Many FEP patients are ambivalent about taking medication, and even if they are not, medication adherence is a challenge in any chronic illness. Technological strategies to improve assessment of medication adherence are increasingly employed in industry sponsored clinical trials in schizophrenia, and many areas in general medicine, but have yet to be employed in CMHC's or freestanding CSC programs as part of "real world" care.

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.*

Aim 1: **To determine acceptability to E-NAVIGATE participants of an AI smart phone app to support medication adherence assessment – target of engagement**. The artificial intelligence (AI) platform (AiCure) uses software algorithms on smartphones to visually and automatically confirm participant identity, medication identity, and medication ingestion. Clinical staff has access to real-time data for review.[3,4]

Aim 2: To compare the effect of AiCure to "usual" E-NAVIGATE services on hospitalization and Emergency room visits – primary outcome. Participants will be randomly assigned to AiCure added to E-NAVIGATE treatment versus continuation of E-NAVIGATE without AiCure for 12 months.

Exploratory Aim: To explore the feasibility in community treatment settings of extending the measurement capabilities of the AiCure platform to include measurement of the disease markers facial expressivity, verbal acoustics, content of speech and patterns of movement.

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*

Each CSC site involved in the protocol will employ a part-time research assistant to the enrollment of participants into the protocol. This dedicated research assistant will be trained by the central team on all required research procedures. The central team has previous experience in the training and oversight of site research assistants. By employing a dedicated resource, the sites should have sufficient time to engage all current and future eligible CSC participants allowing us to meet our enrollment goals. Sites will have the option of having ESPRITO staff other than the research assistant participate in the consent process. These staff will also receive training by the central team on consent procedures.

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*

The source of participants will come from the site's existing and future CSC participants. The research assistant will be responsible for insuring that all existing, eligible CSC participants will be informed about the protocol. Informed consent will be obtained in a shared decision making context and reasons for agreement or refusal will be documented. Consenting participants will be randomly assigned to receive the AiCure app or continue with usual E-NAVIGATE care for 12 months. The AiCure DOT model provides monetary micro-incentives for successful use of the app for documenting adherence/non-adherence. Maximum compensation participants can receive over 12 months is $150 if they are randomized to use the app and $50 if they are not randomized to use the app.

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:

1. All participants enrolled into the CSC program who are participating in the Learning Health System component of the ESPRITO project
2. Ages between 15 and 39
3. Prescribed oral antipsychotic medication
4. Have a smartphone (Android or iOS) with the capability to download the AiCure app
5. Have sufficient proficiency in English language to be able to use the app
6. Have at least 12 months of remaining treatment eligibility

Exclusion Criteria:
Participants unable to download and use the app or those who do not have a functioning smartphone camera will be excluded..

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.*

One hundred participants who are already enrolled in a CSC program and 100 newly enrolled participants who are prescribed an oral antipsychotic medication and have smart phones (Android or IOS) will be included. Informed consent will be obtained in a shared decision making context and reasons for agreement or refusal will be documented. Consenting participants will be randomly assigned to receive the AiCure app or continue with usual E-NAVIGATE care for 12 months. Randomization will be on a 1:1 basis to AiCure or usual E-NAVIGATE care. The study statistician will prepared a computer generated randomization list prior to study initiation which will only be available to central team members. Randomization will be stratified by the clinic status (intervention or control site) in the separate disengagement study. When a site enrolls a new AiCure study participant, the site research assistant will notify an unmasked central team member who will inform the site of the participant's randomized study condition as

determined by referral to the randomization list prepared by the study statistician. The site research assistant will provide documentation to the central team of receipt of the randomized condition for the participant.

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*

Participants enrolled in the protocol will participate for 12 months.

10. ENDPOINTS

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

The primary endpoints will be (1) acceptability and rate of utilization of AiCure and (2) a composite measure of ER visits and hospitalization.

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*

Those randomized to AiCure will receive training on the use of the app. Use of the app allows for the collection of data (to measure medication taking and to understand participant engagement. Data are encrypted and transmitted in real time to clinician dashboards. Sites will receive no instruction on what they should do with the information provided and any actions taken will be based upon their judgment and not any direction from the protocol. Demographics, will be collected at baseline; whereas a self-administered questionnaire covering usability and sustainability, and a form to collect hospitalization and ER visits data will be collected at baseline and then at every 3 months (3,6,9, 12 months). Participants will also be completing an interactive questionnaire within the AiCure app (described below). The study outcomes will be acceptability and rate of utilization

of AiCure and a composite measure of ER visits and hospitalization. Other relevant assessments information will be collected from the Learning Health System (parent protocol IRB# 19-0935). The schedule of assessments for both the groups (people who are randomized to AiCure and those not randomized) is as follows:

Assessments	Baseline	1 Month (not in the clinic. In-app check in)	3 Month	6 Month	9 Month	12 Month
For ALL Study Participants:						
Demographic Information	X					
Hospital and ER Visits Information	X		X	X	X	X
For Participants Using AiCure:						
AiCure Experience Questionnaire			X	X	X	X
Tasks of describing some pictures, smiling and saying "aaahhh" done on the smartphone app.	X	X	X	X	X	X

Participants randomized to use the AiCure app will be asked to use the app each time they are taking their prescribed oral medication. Participants will use the app daily by holding up the phone to their faces and record themselves ingesting the medication.

Exploratory Aim procedures: The AiCure Digital Biomarker Platform is a mobile data capture tool that provides objective measurement of known visual and auditory markers of disease. It is built on the understanding that disease manifests itself in observable ways that can be measured using advances in computational science. AiCure has the ability to securely record, store, and process both video and audio of patient behavior. Hence, it is able to measure both visual and auditory biomarkers of disease. This includes capturing facial expressivity, verbal acoustics, content of speech, and patterns of movement. Data are collected during patient participation in interactive tasks within the AiCure app. These tasks allow for

calculation of digital biomarkers from active patient behavior. They are designed to be brief, simple, engaging, and can be deployed regularly for assessment of disease severity.

The task battery takes 2 minutes to complete and will be done by participants randomized to AiCure at baseline and study months 1, 3, 6, 9 and 12. Tasks include: tell what you have been doing for the past few hours (both tasks capture spontaneous facial expressivity and free speech behavior); describe what you see in a picture and how it makes you feel (two pictures from the OASIS image set to capture spontaneous facial expressivity and speech behavior); make a smile and hold for 3 seconds and make a sad face and hold for 3 seconds (to calculate emotional expressivity during non-spontaneous evoked expressivity) and say "aaahhh" for 3 seconds (to calculate the acoustic properties of the voice).

The study is part of an NIMH funded grant (1R01MH120594-01; IRB# 19-0935). We will begin enrollment for this study in month 7 of the ESPRITO project and complete enrollment by month 25. We are recruiting 100 participants who are already enrolled in the CSC program and 100 participants newly enrolled in the CSC program to be able to generalize the results between people who have been in treatment for some time and participants receiving treatment for the first time. Each of our 11 sites enrolls at least one new participant a month (n = 198) in the LHS. Thus, 18 months of enrollment for this research study will easily provide 100 who will be newly enrolled in LHS and who consent to the study. The sites already have over 400 patients in ongoing treatment; recruitment of 100 such patients who are already in treatment over 18 months will be feasible

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.*

Statistical design: The primary outcome will be a binary variable indicating if a participant had an ER visit or a hospitalization. The target of engagement will be a measure of acceptability of AiCure that is only available in the experimental treatment arm. If the study confirms target engagement, this will provide evidence for further studies that use DOT methods to assess adherence. Descriptive statistics (proportions and 95% CI's for binary outcomes and means (SDs) for continuous measures) will be calculated. Comparisons of proportions between groups will be done using χ^2tests.
Power Analysis: The outcome used for power analysis was the composite ER/hospitalization rate. We estimated this rate to be 40% over 12 months given that between a quarter and a third of participants in CSC studies are hospitalized

and ER visits are frequent. With 100 participants in each treatment group (AiCure and E-NAVIGATE-as-usual) in an individually randomized trial, a two-group χ^2test for proportions will be able to detect a treatment difference at 80% power and α = 5%, if the hospitalization rate for AiCure is 21.7% or lower. This difference is clinically meaningful.

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.*

None

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.*

The data collected utilizing the AiCure technology is reviewable only through a roles- and rules-restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information. Phone numbers of the patients may also be collected and stored in an encrypted manner. At no time is the phone number visible to healthcare providers or monitoring personnel. Use of this system will in no way supersede or change patients' prescriptions—the goal is to monitor adherence to the treatments decided upon by the prescriber and the patient.

The self-administered questionnaire covering usability and sustainability and the hospitalization information will be collected utilizing a data system called CSC-ONE.

Participant PHI will not be shared/obtained with the CSC-ONE system or with the central team at Northwell. Subject data for CSC-ONE and Northwell will be identified only via non-informative IDs.

CSC-ONE will be implemented in Microsoft Azure (https://docs.microsoft.com/en-us/azure/). Azure Key Vault will be used for storing and retrieving sensitive key value secrets required for various layers and tiers provisioned with Azure Paas stack. Secure Web access will be facilitated by issuance of SSL certificate (tied to domain name). SSL integration with the CSC-ONE application allows for data encryption in transit.

The CSC-ONE informatics system will be customized at each site (based on specific needs and preferences). Individual logins for users will be setup and managed by site leads. Industry standard password conventions are used to gain access, including automatic logouts. The core system for the hub will be hosted on a Microsoft Azure HIPAA compliant cloud-based server. Each clinical site will opt into having a partition of this server or an on-premises server (adherent with their local implementation team will design and support the implementation of CSC-ONE at each site.

CSC-ONE has already undergone and passed extensive Security Data Review at Yale University and is being used in the context of both a NIMH funded grant and working clinical service at this site. Technical details of this extensive security data review can be made available upon request (john.cahill@yale.edu). The informatics infrastructure has been approved to the highest standards set at this site for high risk data (https://cybersecurity.yale.edu/minimumsecuritystandards). These standards will represent the minimum security standards for this project, as the team accommodates each individual sites data security requirements.

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.*

N/A. The study involves use of a method to assess medication adherence and in an exploratory manner the use of the AiCure app to obtain digital biomarkers. The protocol does not provide any guidance/suggestions about patient care.

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.*

Participants will only be withdrawn from the protocol if they terminate their participation in the CSC program (or requests withdrawal from the study). Once a participant completes or terminates their participation in the CSC treatment, they will stop all data collection for this protocol..

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 risk to participants participating in the DOT protocol is minimal. Participants may become annoyed or upset while responding to a data questionnaire or because they are being video recorded. Participants will be given the opportunity to take a break or skip an assessment if desired. Furthermore, patient will be connected with the clinical team to provide therapeutic support. Patients will also be reminded that their participation is voluntary and they may choose to withdraw at any time.

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 who become upset during the data collection will be treated by the local study team who can provide therapeutic support.

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*

The AiCure app may provide a better method than standard methods to assess medication adherence. If this occurs, better information may facilitate clinician decision making by patients and their clinicians which in turn may lead to better patient outcomes.

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).*

The participants in the protocol will only include those participants already receiving services in one of the selected CSC treatment programs. All participants already enrolled or who will be enrolled into a CSC program's Learning Health System (LHS) who are eligible for the protocol will be considered for participation.

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 is no cost to the participant not to the participants' insurance carrier.

22. PAYMENT TO SUBJECTS

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

All study participants will receive payment to compensate them for their time and effort doing study procedures. Payment depends upon what assessments you do. All participants will be asked to provide some background information at the study start and be asked at 4 other times about whether they have been to an emergency room or been hospitalized. Participants will be given $10 for each of these study assessments (total of 5 assessments for $50 over the 12 months). If they are randomized to use AiCure, they will be asked to use the AiCure app to document their medication taking in addition to the assessments described above. If they use the AiCure app daily they will be paid an additional $25 at 3 months, at 6 months, at 9 months and at 12 months (total of an additional $100 over the 12 months). If they do not complete the entire study or do not use the app every day, we will deduct 27 cents per day for the number of days that they don't use the app. If they leave the study before 12 months, their last payment will be given to them at the time they leave the study. Thus, if they use the AiCure app consistently and complete the other assessments, participants will receive $150 in total. .

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.*

Recruitment and consent/assent will follow procedures that are IRB approved. Referrals for the study will come from clinicians or self-referral by patients. If a clinician referral, the clinician will first seek permission from the patient for referral. The consent process begins with an assessment of the patient's ability to give informed consent. Patients who on initial evaluation by the study investigator are deemed not to be capable of giving informed consent will not be evaluated further. Patients 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. A parent or legal guardian will be asked for consent on behalf of minors along with the assent of the minors. If the minor does not agree to participate, while the parent or legal guardian agrees to their participation, the minor's decision will be respected.

To ensure that subjects understand the fundamental aspects of the study, we require that they demonstrate this by correctly answering a series of specific questions about the study covering key aspects of the study. These Study Information Reviews are IRB approved. The format of the Study Information Review is a question followed by two possible answers. The answers are written in a parallel sentence structure to minimize reading difficulty. We employ the parallel answer format instead of a true false format because of our experience that subjects with limited education and test taking skills better comprehend the parallel answer format.

An example of part of a Study Information Review is presented below.

DIRECTIONS: Below are questions that people frequently have about the study. Each question is followed by 2 answers. One answer is correct and the other answer is wrong (or false). Please put a check mark next to the correct answer.

Example question: Do you have to stay in the study until it ends?

a) I have to stay in the study until it ends. I cannot leave early.

OR

b) I do not have to stay in the study until it ends. I can leave early.

Subjects must answer correctly all the questions on the Study Information Review before providing informed consent for the study. Informed consent will be documented when the subject signs the consent form that has been approved by the Institutional Review Board.

Consent will be obtained at local site where the study is being conducted. In case participants or parent/legal guardian are unable to come in-person to sign consent, consent may be obtained via email, mail or fax. In case of remote consent, a member of the research team 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 select the witness signature waiver box in the consent form before emailing, mailing, or faxing the form back to the site.

A copy of the consent/assent will be provided to the participant and/or parent or legal guardian.

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 CSC programs participating in the ESPRITO collaborative include the enrollment of adolescents into their CSC program. These participants will not be excluded from the protocol, as there is no anticipated additional risk for this population.
Our ESPRITO network includes sites in 5 states. Please note that none of the sites are in New York State (only the central team that provides study co-ordination but no direct clinical or research activities with participants is in New York). State law differs among the 5 states regarding which individuals under the age of 18 years are independently able to give consent for research (e.g. some states have a general age for independent consent of 16 years, other 18 years). For the protocol, sites will follow the legal standards for their jurisdiction. Individuals under 18 years of age who can legally consent to research independent of a parent or guardian will provide written informed

consent for the protocol using the process described immediately above. Individuals under 18 years of age who cannot legally consent to research independent of a parent or guardian will provide written informed assent and their parents or guardians written informed consent. The number of parents or guardians needed to provide written informed consent will be one unless state law would require more for consent for a minor to participate in research. Criteria for guardianship that allows consenting to research to minors vary across states. Guardians providing consent for study participation will have to meet the criteria for being able to give informed consent for research to minors and their eligibility documented by the site.

Individuals who enter the trial based upon providing assent with parental/guardian consent who later meet state law criteria for providing consent will then be required to provide full written informed consent to continue participation in the trial.

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*

N/A

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*

N/A

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:

- [x] *Children or viable neonate*
- [ ] *Cognitively impaired*
- [x] *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- [ ] *Prisoners*
- [ ] *NSLIJ Employees, residents, fellows, etc*
- [x] *poor/uninsured*
- [x] *Students*
- [x] *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.

All patients who are being seen for CSC treatment at the ESPRITO sites are eligible for participation. The protocol does not provide any guidance about treatment and sites will provide their best choice of treatment to women who are pregnant whether the woman is or is not participating in the study. Similar considerations hold for the poor, students and minorities.

The CSC programs participating in the ESPRITO collaborative include the enrollment of adolescents into their CSC program. These participants will not be excluded from the protocol, as there is no anticipated additional risk for this population. Consent procedures for adolescents have been described above.

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.

This protocol will include 12 sites across the United States. The central team at Northwell who coordinate the study meets weekly via conference call to review all aspects of project progress and performance. The central team has significant experience managing community mental health centers (CMHCs) participating in research projects with early phase psychosis patients. The central team will provide administrative support and oversight for the protocol which includes oversight of the data collection, problem solving barriers to ensure timely data collection

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.

1. Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, Addington J, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Meyer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Pipes R, Kurian BT, Miller AL, Azrin ST, Goldstein AB, Severe JB, Lin H, Sint KJ, John M, Heinssen RK. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 2016 Apr 1;173(4):362–372. PMCID: PMC4981493
2. Snapshot_of_State_Plans-Rev5._508 compliant.pdf [Internet]. [cited 2018 Oct 22]. Available from: https://www.nasmhpd.org/sites/default/files/Snapshot_of_State_Plans-Rev5._508%20compliant.pdf
3. Labovitz DL, Shafner L, Gil MR, Virmani D, Hanina A. Using Artificial Intelligence to Reduce the Risk of Nonadherence in Patients on Anticoagulation Therapy. Stroke [Internet]. 2017 May [cited 2018 Oct 8]; Available from: https://www.ahajournals.org/doi/full/10.1161/strokeaha.116.016281
4. Bain EE, Shafner L, Walling DP, Othman AA, Chuang-Stein C, Hinkle J, Hanina A. Use of a Novel Artificial Intelligence Platform on Mobile Devices to Assess Dosing Compliance in a Phase 2 Clinical Trial in Subjects With Schizophrenia. JMIR Mhealth Uhealth. 2017 Feb 21;5(2):e18. PMCID: PMC5340925