COVER PAGE

Official Study Title: **Title of Study:** In-person vs. Remote Wellness Support (study sub-title: Remote Cognitive Adaptation Training to improve medication follow through in managed care (R-CAT))

NCT number: NCT04526067

IRB Approval Date: 11/09/2020

Unique Protocol ID: HSC20200525H

Form CT
UTHSA Clinical Trial Description

This form is not mandatory. Other documents are acceptable if equivalent information is provided.

UTHSCSA Tracking Number *(internal use only)*	HSC20200525H	**1. Original Version Date**	V1.1 2020-07-21
		1.1. Revision Date(s) *add rows as needed*	

Official study title: In-person vs. Remote Wellness Support (study sub-title: Remote Cognitive Adaptation Training to improve medication follow through in managed care (R-CAT))

2. Background

Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.

Poor adherence to prescribed medications is a major public health problem across chronic illness such as (SMI), cardiovascular disease, diabetes, and COPD and has been called "America's other drug problem" by the National Council on Patient information and Education.10 Data support that poor adherence leads to increased risk of hospitalizations, and poor recovery outcomes. In SMI, a gap as short as 10 days in which medication is not available to the individual has been associated with a two-fold increase in hospitalization.11 Up to $300 billion of avoidable health care costs have been attributed to nonadherence in the US annually, representing 10% of total US health care costs. **Problem adherence is arguably one of the most important modifiable risk factors leading to poor outcomes in multiple chronic medical conditions.** In fact, according to the World Health Organization, **"increasing adherence may have a greater effect on health than any improvement in specific medical treatments."** In SMI, we know that problem adherence contributes to a wide variety of poor outcomes including symptom exacerbation, hospitalization, suicide, homelessness, victimization, and unemployment. A primarily remotely delivered workable adherence intervention used by managed care is the low-hanging fruit in improving outcomes across multiple conditions. If successful, a remote, easy to deliver intervention such as R-CAT in managed care has the potential to improve adherence and outcomes for those with SMI and other chronic medical conditions and to substantially reduce the costs of care. It is important to learn about preferences satisfaction, and follow-through for remote versus home-delivered CAT. This will allow managed care and treatment organizations to determine which approach may fit best for the individuals they serve.

3. Objectives and Endpoints *All data points collected in the study should support an objective or have a regulatory purpose.*

Complete the table – add rows as needed.

3.1. Objective(s) *Clearly and concisely define the primary and secondary outcomes.*	3.2. Endpoint *Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).*	3.3. Justification for Endpoint *Briefly explain why the endpoint(s) were chosen.*
Aim 1: Examine the reach and acceptance of R-CAT and CAT for MCO members meeting entry criteria. Barriers and facilitators for initial acceptance and those identified during treatment as well as treatment satisfaction, rates of dropout and reasons for dropout will be examined.	Descriptive qualitative data regarding barriers / facilitators to initial acceptance; Proportion of drop out	Pilot data to inform future trials and community adoption of interventions Pilot data to inform future trials and community adoption of interventions

Aim 2: Examine pre-implementation parameters of CAT and R-CAT including case load differences for full time staff, provider and MCO assessment of barriers and facilitators and treatment related costs.	Cost of treatment including mail, supports, provider time in visit, prep time, mileage.	Pilot data to inform future trials and community adoption of interventions
Aim 3: Examine preliminary efficacy of R-CAT. We hypothesize that both CAT and R-CAT will improve adherence to medication over time and that changes within each group will be of similar magnitude. We expect increases over time in automaticity/habit strength and decreases in the overall level of psychiatric symptomatology.	Descriptive qualitative data regarding barriers and facilitators from provider perspective Pill count percent (primary) Medication possession Ratio from prescription refill data Automaticity subscale score on self-reported habit index Symptoms rated from the BPRS	Pilot data on efficacy Pilot data on efficacy Pilot data on mechanism of action Pilot data on efficacy

4. Rationale

Briefly state the reason for conducting the clinical trial.

Cognitive Adaptation Training (CAT) is an evidence-based psychosocial treatment using environmental supports such as signs, alarms, pill containers, and the organization of belongings established in a person's home on weekly visits to cue adaptive behaviors and establish healthy habits. We have demonstrated that CAT improves adherence and outcomes for individuals with SMI. Improved adherence with CAT is maintained for at least 6 months following treatment discontinuation, suggesting that environmental supports lead to habit-formation. In response to PA-18-722 Improving Patient Adherence to Treatment and Prevention Regimens to Promote Health, we propose an R56 to collect pilot data on the delivery of a remote intervention based upon CAT—Remote-CAT (R-CAT) for improving medication follow-through. We found a telephone/mail adaptation of CAT improved both automaticity and medication adherence. Habit-strength/automaticity—the proposed mechanism of action for CAT and R-CAT—is based upon dual process theory which distinguishes controlled processes, those under the person's awareness, intention, and conscious control, from automatic processes which occur outside of the person's awareness, and are highly efficient, and minimally labor intensive. 95% of daily behaviors are automatic; but few adherence interventions target habit-formation in a systematic way. Automatic processes rely less on the resources that are known to be impaired in SMI including memory, problem-solving and motivation. The proposed mechanism of action has not been tested.

We will use components of the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework to compare Cognitive Adaptation Training (CAT) to Remotely delivered Cognitive Adaptation Training (R-CAT) 1-9 within a managed care organization (MCO), targeting members with serious mental illness (SMI) needing assistance with the regular taking of medication. In Part 1 of the research, **to assess both pre-implementation parameters and potential effectiveness, we will survey approximately 200-400 MCO members identified as having difficulty with medication follow through. CAT or R-CAT will be described in a randomized way and asked about acceptance, participants will then be told about the other intervention and asked about acceptance. Participants will than rate a series of statements covering dimensions of these treatments on the extent to which they agree/disagree with each statement. After the survey, participants will be offered the opportunity to participate in a research study examining CAT and R-CAT. Those who prefer one treatment over the other will get that**

treatment and those with no preference will be randomized 1:1 to CAT or R-CAT. This procedure will be followed and then altered as needed until 50 have accepted or been randomized to each group. Treatment will be offered for 6 months. In R-CAT interventions will be delivered primarily by remote and electronic means. Medication follow-through will be assessed using monthly unannounced pill counts. Automaticity (Habit formation), treatment satisfaction, barriers and facilitators to treatment and psychiatric symptoms will be assessed at baseline and every other month. Costs of providing CAT and R-CAT will be recorded including driving time, assisting with technology use, shipping, mileage, time in direct contact with member, time preparing for visits, and supports provided. Outcomes will be evaluated using within group repeated measures analyses. In sum, we are proposing to assess acceptability, feasibility, treatment satisfaction, pre-implementation parameters such as caseloads and costs, and preliminary efficacy of R-CAT compared to traditional home-delivered CAT.

Rationale for home visits. Home visits are required for CAT intervention, in order to deliver its treatment components and complete treatment assessment. This is the primary variable for the study, which nearly half if items rated are observational in nature (e.g. blunted affect). We have attached the SOP for home visits to protect both participants and UT staff during COVID-19 pandemic.

Special considerations for COVID-19: Due to the current pandemic, the CAT treatment group start date may be delayed until a time it is safe for UT staff to resume participant home visits. In the event pandemic safety precautions lead to a continued delay, additional remote treatment data may be collected and compared to historical CAT data in order to meet grant aims. [An amendment will be submitted to the IRB and approval will be sought prior to implementation, should this change be necessary.]

5. Study Design

5.1. Number of Groups/Arms	2	**Group name(s)**	Remote Cognitive Adaptation Training (R-CAT) Cognitive Adaptation Training (R-CAT)

5.2. Overall Design
Select all applicable

☒	**Randomization**			☐	**Cluster Randomized**						
☐	**Group-Sequential**			☐	**Adaptive Design**						
☒	**Parallel Design**			☐	**Placebo-Controlled**						
☐	**Superiority**			☐	**Equivalence**			☐	**Non-inferiority**		
	Device	☒	Pilot	☐	Pivotal			☐	Post-Approval		
	Drug/Biologic	☐	Phase 1	☐	Phase 1/2	☐	Phase 2	☐	Phase 2/3	☐	Phase 3	☐	Phase 4
☐	**Dose escalation**	*If yes, details →*									
☐	**Dose ranging**	*If yes, details →*									
☐	**Sub-studies**	*If yes, details →*									

5.3. Other Design Details:

We will use components of the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework to compare R-CAT to home-delivered CAT. To assess both pre-implementation parameters and potential effectiveness, we will offer CAT or R-CAT in a randomized fashion to approximately 200-400 MCO members identified as having difficulty with medication follow through. CAT or R-CAT will be offered as an add on to the treatment they receive from community providers. Following baseline assessment, 100 MCO members will choose or be randomized to CAT or R-CAT for a 6-month period. Medication adherence will be assessed using monthly unannounced pill counts and claims data. Service use and costs will be obtained from the MCO. Automaticity (Habit formation) and symptomatology will be assessed monthly during treatment and follow-up.

6. Study Population

6.1. Study Population(s) Label/Name *To add more populations – select a row, copy & paste*	6.2. Identify the criteria for inclusion *The criteria that every potential participant must satisfy, to qualify for study entry.* All individuals in this study population must meet all of the inclusion criteria in order to be eligible to participate in the study	6.3. Identify the criteria for exclusion *The characteristics that make an individual ineligible for study participation.* All individuals in this study population meeting any of the exclusion criteria at baseline will be excluded from study participation.
Serious Mental illness (Major Depressive Disorder, Bipolar Disorder, Schizophrenia/Schizoaffective Disorder)	1. Able to give informed consent. 2. Between the ages of 18 and 65. 3. Clinical Diagnosis of Major Depressive Disorder, Bipolar disorder, Schizophrenia, or Schizoaffective Disorder 4. Receiving treatment with oral psychiatric medications. 5. Have had a hospitalization or emergency department visit in the past year 6. Have a Medication Possession Ratio (MPR) based upon electronic refill data below 80% at least 1 of the past 4 quarters with at least 1 psychiatric medication 7. Responsible for taking their own medications 8. Report on telephone prescreen call with researcher team that they have missed at least 2 doses of medication in the past 3 weeks, that they are willing to take medication and would like remote assistance to take medication more regularly 9. Report on telephone prescreen call with research team that they have a stable living environment (individual apartment, family home, board and care facility) within the last three months and no plans to move in the next year 10. Report on prescreen research call with research team that they have no plans to change their MCO in the next 12 months 11. Have a working smart phone 12. Able to understand and complete rating scales and assessments. 13. Agree to home visits for intervention and to count pills and conduct assessments	1. Substance dependence within the past 2 months 2. Currently being treated by an ACT team 3. Documented history of violence or threatening behavior on initial assessment 4. Receive home visits to assist with medication adherence 5. Unable to complete baseline assessments

6.4. Will screen failures be allowed to re-screen at a later date?	☐	No	☒	Yes	*If yes, describe criteria below ↓*
We will re-screen when they initiate a follow-up call or we will call them in 3 months.					

7. Study Intervention(s) being tested or evaluated

This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)

Cognitive Adaptation Training (CAT) (completed at baseline and once weekly for 6 months or until study completion; when allowable).

Individuals choosing or assigned to CAT will continue to see all their current treatment providers and have CAT as an added service. CAT is a manual-driven, evidence based psychosocial treatment developed to bypass impairments in controlled

processes such as directed attention, problem solving, memory and motivation which often characterize individuals with SMI. CAT uses environmental supports such as signs, calendars, alarms, pill containers, and checklists to cue and sequence adaptive behaviors such as taking medication, socializing with others, and taking care of independent living skills. CAT environmental supports are established and maintained on weekly home visits. CAT has been disseminated to multiple countries and is a billable service for many community mental health centers in the U.S.

R-CAT (completed at baseline and once weekly for 6 months or until study completion).
Individuals choosing or assigned to R-CAT will continue treatment as usual with their health care team and R-CAT will be added. R-CAT is a remotely delivered version of CAT focused on medication adherence using a series of manual-driven compensatory strategies and environmental supports (signs, checklists, electronic cueing devices) based upon a streamlined assessment of executive function impairment and barriers to habit formation including forgetfulness, difficulties in problem-solving, disorganization, apathy or amotivation, disinhibition. and home environment. Initial R-CAT goals are to 1) ensure that medications listed as prescribed are available 2) to assess current cognitive, behavioral and environmental facilitators and barriers to habit-formation 3) to set up customized CAT supports to address the barriers and use facilitators to build habits to take medication. Rare home visits may occur if issues cannot be resolved remotely. Based upon the pilot, we don't anticipate any more than 5-10% of individuals to need face-to-face visits. No one had home visits as part of our pilot intervention. A structured R-CAT treatment note with places for pictures of CAT interventions is used for home visits. Support and reminder calls use a brief checklist modified from the Healthy Habits Program to address issues in use of supports, placement of supports and habit formation. Examples of CAT interventions to promote taking medication regularly appear above. All home visits and phone calls will be audio-taped (with consent) for quality assurance.

8. Protocol-Directed procedures, items, services or tests
List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

8.1. Drugs *(trade and generic, dosage, route of administration)*

8.2. Devices

8.3. Biologics

8.4. Laboratory Tests

8.5. Imaging Procedures

8.6. Other Research Procedures *(e.g., other safety and efficacy assessments.)*

Part 1:
Telephone interviews: based upon a list provided by Superior Medicaid as possibly meeting inclusion criteria for the pilot study, the research team will call individuals to invite them to participate in a telephone interview. Verbal consent will be obtained from those interested in participating, and the interviews will be recorded over the phone. The interview will involve the researcher describing the R-CAT and CAT programs and after a description of each, participants will be asked a series of questions to assess their attitudes and acceptance of each program. Those who complete the telephone interview will be informed about the clinical trial (Part 2) and will undergo a general screening (described below) if interested.

Part 2:
Telephone Pre-screening (screening visit) - based upon a list from superior Medicaid we will call individuals to determine whether they meet inclusion criteria outlined above and ask them about their interest in participating**. Diagnosis**. Will be based upon the clinical diagnosis (DSM-5) of the treating prescriber. This is done to improve ease of implementation in health maintenance organizations.

Acceptability/Feasibility (ongoing) - will be based upon numbers of individuals accepting initial offers of CAT or R-CAT, numbers with and without preferences for either treatment, and reasons for choosing / not choosing one add on treatment versus another. In addition, we will examine drop-out rates by treatment group and reasons for drop out. Barriers and facilitators to the selected or assigned treatment and treatment satisfaction will be queried at routine assessments.

Symptomatology (baseline and at Months 2, 4 and 6) - Symptoms will be assessed by a trained rater using the Brief Psychiatric Rating Scale-Expanded version.[65] A total score reflects an overall level of symptomatology. (20 minutes).

Medication Adherence (baseline and once monthly until 6 months or study completion) - based upon our own work and recent publications, medication adherence will be assessed using unannounced in-home pill counts conducted every other month (months 0, 2, 4, 6) with video counts done in the intervening months (1, 3, 5). We will also have electronic claims data provided by the MCO. The primary measure will be in-home pill counts due to evidence that this measure is more sensitive to treatment changes. An initial visit prior to randomization [or initiation of chosen intervention] is conducted to count and bag all old pills, identify current bottles, count current pills in the bottles and any medication containers used by the individual. A box is set up with a sign to remind participants not to throw out empty bottles. Counts are conducted monthly in an attempt to capture all prescription refills and medication changes. Adherence percent is calculated as the number of pills missing and presumed taken/ the number of pills prescribed for the time period X100. Percentage of all mental health medications and a percentage for all medications will be calculated. The latter being the primary measure. We used these procedures in two R01's previously. We will also obtain prescription refill data from MCO records. We will calculate Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) as secondary measures of adherence. MPR is calculated as the day's supply for all fills of a medication in the time period divided by the number of days in the time period X 100. PDC is calculated by the number of days "covered" divided by the number of days in the time period X 100. PDC is less commonly used but is endorsed by the Pharmacy Quality Alliance and is now incorporated into Medicaid and Medicare services in their plan ratings. Moreover, for individuals on multiple medications, PDC better characterizes overall adherence. (20-40 minutes depending upon person's organization and number of medications).67

Automaticity (Habit Strength) (baseline and at Months 2, 4 and 6) - the Self–Report Habit Index (SRHI) 68 is a 12-item scale assessing three proposed characteristics of habit;1) automaticity (e.g., I take medication without thinking), 2) frequency ('. . .I take medication frequently), and 3) relevance to self-identity ('taking medication is a behavior that's typically "me"').The SRHI has good reliability and convergent, discriminant, and predictive validity as a measure of habit.22,69 Four items of this scale, items 2,3,5 and 8 represent the Self-Reported Behavioral Automaticity Index (SRBAI).This index is based upon research suggesting that automaticity also called habit strength is the active ingredient in habit.23 The SRBAI has been found across studies to be related to habit and to predict future behavior. Lower scores indicate greater habit strength and greater automaticity. A mean Habit score will be computed using the entire scale. Automaticity (SRBAI score) will be the primary measure used to examine the paths among the target behavior (adherence) and habit strength. The mean SRHI will be used in secondary analyses. (10 minutes)

Functional Outcome (baseline and at Months 2, 4 and 6) - Functional outcome will be rated using the Social and Occupational Functioning Scale (SOFAS).70 The SOFAS rates functioning on a scale from 0 to 100 based upon all the data collected in the assessment. Higher scores reflect better functional outcome. Symptoms are not taken into account in the rating. (0 minutes).

Remote monitoring/remote visits will occur using UTHSCSA licensed Zoom. Audio-recording of remote visits will be conducted through the Zoom platform with participant consent. Therefore, privacy and confidentiality is not guaranteed due to the nature of the electronic conferencing platforms that will be used.

8.7 Attach a Schedule of Activities (SOA) Excel File [Download the Template here: *Schedule of Activities*]	*Check to indicate that the SOA Excel File is attached →*	☐

9.	**Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device**
☒	*N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)*
☐	*N/A - An Investigator Brochure is attached*
☐	*N/A - A Drug/Device Manual is attached*

9.1. Acquisition and accountability

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.

9.2. Formulation, Appearance, Packaging, and Labeling

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

9.3. Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

9.4. Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.

10. Study Intervention Additional Details

10.1. Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

Those with no preference for CAT or R-CAT will be Randomized, 1:1 done by statistician who has no patient contact through a random allocation program. If blinds are broken accidentally, new raters can be assigned, but blinds are kept by having raters and pill counters unaware of treatment group or study design.

10.2. Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).

All CAT and R-CAT providers will be UT Personnel and will receive regular supervision, audio taping of sessions for fidelity (5% reviewed per therapist), and photos of supports in home to complete quality assurance forms. Feedback will be provided to R-CAT providers to ensure high fidelity.

10.3. Permitted Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).

All concomitant therapies are allowed during the study.

10.4. Rescue Medicine

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.

☒ *N/A, no rescue medicine*

11. Study Intervention Discontinuation

11.1. Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.

None-- all individuals remain in standard community treatment with providers whether or not in this study.

11.2. Continued Follow-up Discontinuation of Study Intervention

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).

None-- all individuals remain in standard community treatment with providers whether or not in this study.

12. Statistical Considerations

12.1. Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

Aim 1: Examine the reach and acceptance of R-CAT and CAT for MCO members meeting entry criteria. Barriers and facilitators for initial acceptance and those identified during treatment as well as treatment satisfaction, rates of dropout and reasons for dropout will be examined.

Aim 2: Examine pre-implementation parameters of CAT and R-CAT including case load differences for full time staff, provider and MCO assessment of barriers and facilitators and treatment related costs.

Aim 3: Examine preliminary efficacy of R-CAT. We hypothesize that both CAT and R-CAT will improve adherence to medication over time and that changes within each group will be of similar magnitude. We expect increases over time in automaticity/habit strength, and decreases in the overall level of psychiatric symptomatology.

12.2. Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

This is a pilot study and not powered for testing efficacy. Given that, we examined power for proportions using PASS (Aims 1 and 2). We will approach a minimum of 200 individuals to examine the acceptance rates of an initial offer of CAT versus R-CAT. We will be able to detect a 20% difference in proportions in acceptance with a power greater than .80; two-tailed alpha =0.05. We don't expect dropout rates to vary greatly between the 2 treatments but with 100 individuals and 50 in each of 2 treatment groups we will be able to detect a difference in drop out of at least 10% versus 30% at a power of .80; alpha=0.05. A smaller difference in dropout across 6 months would not be likely to impact decisions about which treatment to adopt and is not important to detect. Aim 3 examines differences from baseline within 4 groups (those with a preference for CAT; those with a preference for R-RCAT; those with no preference randomized to CAT and those with no preference randomized to R-CAT). With 25 per group for the randomized samples within each treatment SAS Power indicates that the smallest detectable effect would be for pill count adherence going from 70% to 85%. We would have power of .80 to detect difference of about 25% in pill count adherence proportions that that correlate .48 with probabilities of adherence from 60-85% in with a one tailed test at alpha of .05. http://statulator.com/SampleSize/ss2PP.html. This was verified using a simulation using 5000 replications. A one-tailed test is used as we are not interested in whether the intervention makes adherence worse.

12.3. Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

All participants with a baseline and at least one follow-up visit will be included in the analyses

12.4. Statistical Analyses

Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses

Aim 1

We will use X2 analyses to examine differences in proportions. We are interested in the rate of acceptance of CAT versus R-CAT when only one treatment is offered as an ecologically valid way of looking at acceptance rates in a real-world situation. In addition, we will examine acceptance of the 2nd treatment when the first is declined. We will also look at overall acceptance once both treatment options are explained (CAT, R-CAT, Neither) and whether the order in which the treatments were offered impacts acceptance. Finally, after both treatment options are presented, we will examine stated preference given an offer of both treatments (CAT, R-CAT, no preference, no

treatment desired). We will compare dropout by treatment group (CAT/R-CAT) using X2 analyses examining randomized and self-selected groups both combined and separated.

We will compare treatment satisfaction between groups using t-tests comparing CAT versus R-CAT examining randomized and self-selected groups both combined and separated.

Aim 2

Descriptive statistics will be used to examine treatment related costs and we will organize qualitative data thematically using NVivo software.

Aim 3

The primary variable is in-home pill count percent established on each monthly visits or virtual visits. Secondary variables are MPR, PDC, SRHI automaticity SRHI total score, Symptoms and SOFAS scores. We will examine within group change and effect sizes using a likelihood-based population-averaged (marginal) generalized linear regression model with repeated measures as implemented in the SAS GLIMMIX procedure specifying binomial (proportions) or normal (scales) as appropriate. A-likelihood based regression model with repeated measures makes the best use if all the information including cases with incomplete or missing data. The. primary hypothesis tests planned contrasts at the final assessment of within-arm change and the difference between arms.

We will examine trajectories for 4 groups; the 2 groups with a preference (for either R-CAT or CAT) that were self-selected the 2 groups who did not indicated a preference and were randomized to either CAT or R-CAT. We will examine differences in baseline characteristics between the two groups with preferences as these differences may be related to outcome in the self-selected samples.