Prospective 12-week randomized controlled trial (RCT) of remotely- delivered Customized Adherence Enhancement for poorly adherent individuals with schizophrenia (CAE-S) vs Enhanced Treatment as Usual (eTAU)

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Objectives

This project aims to evaluate the feasibility, acceptability and preliminary efficacy of remotely delivered CAE among patients with schizophrenia (CAE-S). The project will be operationalized in 3 specific aims.

Aim 1: To determine the feasibility and acceptability of administering CAE-S via videoconferencing to patients with schizophrenia. Based on this team's previous work in developing and delivering CAE to individuals with SMI who are poorly adherent with prescribed oral antipsychotic medication[10] and the team's previous work in remotely-delivered engagement and adherence promotion approaches[15], we expect that patients with schizophrenia will be able to receive CAE-S via a telehealth platform and find it highly acceptable.
H1: We expect that CAE-S participants will attend an average of at least 4 CAE sessions.
H2: We expect that at least 75% of participants will agree or strongly agree that the intervention was useful.

Aim 2: To test the pragmatic, clinical effects of CAE-S vs. Enhanced Treatment as Usual (eTAU) on schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) in a randomized control trial (RCT) of 36 poorly adherent patient with schizophrenia.
H3: We expect that patients randomized to CAE-S will have greater improvement from baseline to 12 weeks on PANSS improvement vs. individuals randomized to eTAU.

Aim 3: To explore the effects of CAE-S in improving self-reported medication adherence as measured by the Tablets Routine Questionnaire (TRQ) and validated by electronic pill monitoring (eCAP). We expect that individuals who have improved symptoms of schizophrenia will also have psychotropic medication adherence (TRQ) improvements and improvements in other secondary health outcome measures that are relevant to people with schizophrenia at 12 weeks compared to those randomized to eTAU.

Background

Psychotropic medications are a cornerstone of treatment for individuals with schizophrenia, but rates of full or partial non-adherence exceed 60%[1-3]. There is direct correlation between non-adherence and rates of relapse in schizophrenia[4]. On average, non-adherent patients have a risk of relapse that is 3.7 times greater than their adherent counterparts[5]. Second generation oral antipsychotic medications are effective and better tolerated than first generation but adherence remains low due to both intentional and non-intentional non-adherence[6].

This study team has completed a series of studies showing the feasibility and efficacy of a relatively brief, patient-centered customized psychosocial adherence enhancement intervention (CAE) in various patient populations including individuals with schizophrenia[7-9]. In-person administration of CAE as an adjunct to standard medical care has been shown to improve psychotropic medication adherence, psychiatric symptoms and functioning[7-12]. CAE targets an individual's specific barriers to medication adherence, has been manualized for broad scale-up and appears acceptable to individuals with serious mental illness. An effective behavioral program that targets common reasons for missing medication with customized modules has the potential to modify long-term medication attitudes, behaviors and outcome trajectories.

Inclusion and Exclusion Criteria

	Inclusion Criteria
1.	Individuals age 18 and older with schizophrenia as confirmed by the Mini International Psychiatric Inventory (MINI).
2.	Prescribed an antipsychotic medication for treatment of schizophrenia.
3.	Have medication treatment adherence problems as identified by the Tablets Routine Questionnaire (TRQ, 20% or more missed medications in past week or past month).
4.	Ability to be rated on psychiatric rating scales.
5.	Currently in treatment or scheduled to receive treatment at a Community Mental Health Clinic (CMHC) or other clinical setting able to provide mental health care during and after study participation.
6.	Able to provide written, informed consent to study participation
7.	Has access to electronic device and internet to complete sessions conducted on videoconferencing platform.

	Exclusion Criteria
1.	Prior or current treatment with clozapine (clozapine therapy includes additional medication-related monitoring and clinical visits that may impact medication adherence)
2.	Medical condition or illness, which in the opinion of the research psychiatrist, would interfere with the patient's ability to participate in the trial.
3.	Physical dependence on substances (alcohol or illicit drugs) likely to lead to withdrawal reaction during the course of the study in the clinical opinion of the treated research psychiatrist.
4.	Immediate risk of harm to self or others.
5.	Female who is currently pregnant or breastfeeding.

Study Design

The project will be implemented as a prospective 12-week RCT of CAE-S vs. enhanced treatment as usual (eTAU) in 36 poorly adherent individuals with schizophrenia. Patients with schizophrenia will be randomly assigned to receive either CAE-S or eTAU following the baseline assessment. The primary feasibility outcomes will be attendance and patient satisfaction (Aim 1) and change from baseline to 12 weeks in schizophrenia symptoms as measured by the Positive and Negative Symptom Scale (PANSS) (Aim 2). An exploratory evaluation (Aim 3) will examine the posited mechanistic underpinnings of the CAE-S intervention by assessing change from screening to 12 weeks in psychotropic medication adherence as measured by the Tablets Routine Questionnaire (TRQ) and validated by eCAP (objective bottle openings). Secondary measures will include the Clinical Global Impression (CGI), functional status, quality of life and attitudes towards medication. Findings will be summarized in at least one manuscript submitted for peer-reviewed publication, paving the way for a larger-scale trial, and will help inform clinicians on care approaches which may optimize antipsychotic medication response in their patients with schizophrenia.

Customized Adherence Enhancement (CAE) Intervention: CAE is an adjunctive (to standard medication treatment) behavioral intervention delivered virtually (real-time one on one video-conferencing) in 6 individual sessions. Because the CAE manual does not target any specific oral antipsychotic medication or group of antipsychotic medications, (it is unbranded) positive

findings from the proposed trial will enhance potential usability across a broad variety of oral antipsychotic medications.

All participants will receive content from the 4 currently existing CAE modules delivered over a 6-session series spaced out over approximately 6-10 weeks. The material from the 4 modules will be broken down into predetermined sub-sections and delivered in 6 sessions. The modules themselves are delivered in sections (thematic units within the module) and do not correspond to a specific session. For example, units of the Psychoeducation module are delivered in multiple CAE sessions. The reason for this is threefold:

1) To limit the amount of psychoeducational (or other) material in any one session;
2) To reinforce material that is presented in one session in subsequent sessions, and
3) To provide patients with the opportunity to absorb and practice strategies in between sessions.

While previous studies targeting other patient populations have delivered CAE in 4 core sessions and 1 booster session, given the fact that this population is expected to be more impaired and the fact that we are delivering the intervention remotely, it is even more important that sessions not be too long and that material is both repeated and reinforced. The slower-paced virtual delivery of the existing CAE content to patients with schizophrenia represents a reduction in content –per-session as compared to the in-person version. Each session, delivered by a mental health counselor (such as a licensed social worker, mental health counselor or advanced trainee supervised by PhD level clinician scientist) lasts from 30-45 minutes. It has been our experience that longer video-delivered /telehealth sessions are more challenging to implement vs. in-person visits due to lagging of attention and "zoom fatigue", especially among people with serious mental illness who may already be experiencing cognitive difficulties and/or sedation due to psychotropic medication treatments.

While previous studies based module selection on self-reported items completed at screen, in the schizophrenia trials, most patients received the majority of modules[7]. The 4 CAE modules are Psychoeducation, Communication with Providers, Medication Routines, and Substance Use. Based on the screening evaluation of substance use/abuse as a potential impediment to adherence, individuals will receive either a more intensive (MI) vs. less intensive (LI) content version of this module.

a. MI version: This is for individuals who are currently using a substance and will include an interactive discussion on the person's current and past substance use history. The MI version targets identifying problems experienced as a result of substance use, information on the effects of excessive drug/alcohol use generally and on medication treatment and adherence specifically, assessment for the person's readiness for change, the completion of a decisional balance worksheet, as well as a change plan worksheet (2 be carried out in 2-3 different sessions).
b. LI version: This is for individuals who either do not use substances at all (perhaps because they are in recovery), or individuals deemed to use only moderately. In the former case, there will be an interactive discussion on the person's substance use history including a review of problems caused by substance use and its impact on psychiatric symptom management. This is then followed by information on the effects of excessive drug/alcohol use generally and on medication treatment and adherence specifically, and reinforcement for changes that could be implemented. For those who report that they have never had an issue with substance use, the interactive discussion on substance use will be briefer, however information on the effects of excessive

drug/alcohol use generally and on medication treatment and adherence specifically will be presented. The low intensity version will be completed in a single session.

Enhanced Treatment as Usual (eTAU): Individuals in eTAU will receive an eCAP for their foundational antipsychotic medication and continue to receive care, including prescribed antipsychotic medication with their current non-study providers. Medication adherence behavior typically transiently improves during early phases of focused monitoring (Hawthorne effect), but this wanes over time[16] with expected regression to behaviors existing prior to study enrollment unless otherwise reinforced with an approach like CAE. To optimize control intervention rigor, the eTAU participants will view a pre-taped series of videos (based on NAMI or DBSA general wellness guidelines) 1:1 with a therapist who has similar credentials and competency as the CAE mental health clinician during 6 one-on-one sessions lasting at least approximately 30 minutes. The therapist will view the videos with the participant and field questions the patient may have. This controls for attentional effects, an important consideration in behavioral clinical trials. As an additional consideration to optimize rigor, while study staff are not blinded to intervention assignment, outcomes assessments are collected by non-interventionist research staff, and outcomes data analysts are blinded to the nature of intervention assignment.

Concomitant medications: This project will not involve the administration of any study drug. CAE is intended to be an adjunct to any standard medication treatment for patients with schizophrenia, and, to increase potential for scale-up and generalizability, CAE can be administered during any phase of medication treatment, including when treatment first begins, during any medication cross-tapers or in the case of polypharmacy treatment. All patients will be receiving treatment with an FDA-approved oral antipsychotic medication, a first-line treatment for schizophrenia as prescribed by their non-study prescribing clinicians. An essential component of CAE is to empower patients and encourage them to communicate with their prescribing clinician when they encounter common roadblocks to staying on track with medications such as side effects or problems with remembering to take the dosing regimen. Participants will also remain on any concomitant medications prescribed by their non-study clinician. The study team will assess medication treatments (drug categories, dosage) and adherence with antipsychotic drugs and all other maintenance treatment with psychotropic medications (TRQ for all prescribed psychotropic treatments, eCAP assessment of foundational antipsychotic drug and directly-observed pill counts done via videoconference) at each research assessment study visit.

Study Procedures

Outcome measures:
Study Measures: As part of the initial clinical evaluation, information will be collected on participant previous illness history including duration of psychiatric illness, previous hospitalizations, previous suicide attempts, medication treatment history (including history of previous treatment-related adverse events), previous history of legal problems and incarcerations and cumulative medical burden as evaluated by the self-reported Charlson Index.

Primary Outcomes:
For Aim 1, primary outcomes for feasibility and acceptability will be assessed via CAE-S attendance (number of sessions attended out of all scheduled sessions) and self-reported patient satisfaction with CAE-S respectively.

For Aim 2, primary outcomes will be schizophrenia symptoms using a standardized, validated measure.

Attendance and Patient Satisfaction: Attendance will be evaluated as the number of attended CAE sessions (out of a total possible attendance of 6 sessions). This will be a simple count of ranging from 0 (no attended session) to 6 (attended all sessions). In previous work, using CAE to promote oral antipsychotic medication adherence among seriously mentally individuals who were poorly adherent, average attendance was 76% with in-person sessions[10]. While we believe that attendance will be greater for remotely-delivered vs. in-person, we conservatively estimate that the average attendance with CAE-S will be at least 4 sessions.

Treatment satisfaction will be assessed using a series of self-report items measured on a 5-point Likert Scale from strongly disagree to strongly agree regarding different aspects of the intervention (e.g. the length of sessions, # of sessions, content covered, etc.). This method has been used successfully by our team in multiple treatment outcome studies.[7-12] In previous work using CAE to promote oral antipsychotic medication adherence among poorly adherent individuals with serious mentalillness, 90% felt that the benefit of the intervention exceeded the burden, most (90%) felt that CAE was "about right" in the number of sessions and timing, and all strongly agreed or agreed that CAE addressed all important issues specific to their situation.[10]

Schizophrenia Symptoms: Symptoms of schizophrenia disorder will be assessed using the Positive and Negative Syndrome Scale (PANSS) developed by SR Kay et al[17]. The PANSS is very widely in research settings. Alpha-coefficient analysis has indicated high internal reliability and homogeneity among PANSS items, with coefficients ranging from 0.73 to 0.83 ($p < .001$) for each of the scales. The split-half reliability of the General Psychopathology Scale was demonstrated to be 0.80 ($p < .001$). The authors have also demonstrated the discriminate and convergent validity of the PANSS dimensional assessment in relation to independent clinical, genealogical, psychometric, and historical measures.

Adherence Behavior: Adherence will be evaluated with the self-reported Tablets Routine Questionnaire (TRQ) for the past week and the past month. Self-reported adherence will be validated with eCaps, an automated pill-monitoring system. While it is true that the literature on measurement of adherence, including the co-PIs' work in this area notes limitations with all methods of adherence assessment, both self-report and automated pill-caps appear valid and practical for use in schizophrenia studies.[16,18] In addition to the TRQ, using the videoconference platform, research staff will also conduct a directly-observed pill count to augment the eCAP real-time bottle opening record.

Tablets Routine Questionnaire (TRQ): TRQ is a measure which quantifies the proportion of days with missed doses over the past week and the past month. A total combined adherence score (proportion of days with missed doses out of total medications prescribed) will be calculated as an average of the TRQ values of all orally-prescribed medications. The TRQ has been noted by other investigators to be reliable and responsive to change in seriously mental ill populations including in individuals with schizophrenia[7,19-21]. The TRQ is not dependent upon timing of medication provided that medication is consumed within the required day/24 hour period.

eCaps: Electronic monitoring of pill container openings is an important method of measuring adherence. The methodology employed in this study will be an eCAP™.[22] Pill bottles equipped with eCAPS are capable of storing a 90-day supply of one medication. The eCAP records openings. This provides a precise, objective assessment of the timing of each dose and the

patient's pattern of pill-taking behavior. Although many patients with schizophrenia take multiple antipsychotic medications, we will monitor the antipsychotic dosed most often (index drug). If more than one drug is dosed at the same frequency, the antipsychotic most recently added to the regimen will be the index drug. As-needed or "prn" drugs will not be monitored. In previous work by this study team, the correlation between a single "index" drug and all drugs was 0.95 providing support for measuring one medication as proxy for medication adherence.[23] The method of choosing an index drug also limits participant burden. To ensure that the data collected represent pill-taking behavior as accurately as possible, patients will be instructed to (1) dispense doses of their monitored medication only from the eCAP equipped bottle, (2) remove only one dose at a time, and (3) remove a dose only at the time that they plan to swallow the medication. Adherence is defined as the % of pills missed, and a ratio of number of doses missed to number prescribed will provide a percentage, with a higher value indicating poorer adherence. While just assessing adherence behavior may temporarily increase adherence (e.g., the Hawthorne effect), it is expected that any potential impact on adherence behavior will wane over the 3 month follow-up. A large recent clinical trial demonstrated limited long-term adherence advantage for passive medication aids (e.g., 7-day pill organizer, pill cap displaying time since last dose), a category into which eCAP would fall.[24] Experience with eCAP conducted by this team yielded substantially less missing data using the eCAP than the MEMS. Adding an extra financial incentive for bringing in the eCAP ($10 per visit) optimizes use of automated pill-monitoring. Notably, in a recent pilot study, 31/38 participants (81.6%) brought their eCAP to all 3 study visits over a 6-month period.[25] To optimize generalizability, individuals who use medisets or pill-minders to manage multiple medications will not be excluded from the study. We will follow the same procedure that we did for a recent study which was very effective. Only one medication will be tracked via eCAP. All other medications can remain in the pill-minder or other medication tracking device. The medication is placed in the eCAP by the research assistant (RA) when setting up the device if in person or the RA will instruct the participant to do so during their video-conferencing meeting. Participants will be trained on the use of eCAP and will have the opportunity to practice opening the cap before it is activated. Other outcomes of interest:

Adherence Attitudes:
The Drug Attitude Inventory (DAI), is used to measure attitudes towards medication among individuals with serious mental illness[26] and is known to be relatively unaffected by psychiatric symptom severity[27]. The DAI was originally developed to assess the attitudes and subjective experience of patients with schizophrenia being treated with antipsychotic medications. The DAI is a simple, true-false format questionnaire that assesses domains of patient's attitudes including positive and negative experience, locus of control, and attitudes towards health. Responses are scored on a euphoric-dysphoric continuum (alpha= 0.93).

Patient-Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS)[28] is a 9-item self-report measure which targets the multiple potential reasons patients with various chronic health conditions may not adhere to their medications. The measure was developed using rigorous methodology[28] and can be used to compare to other adherence studies.

Health Resource Use: Resources that are typically utilized by the most severely ill individuals with schizophrenia include emergency care and hospitalization. Resource use in the 3-month period prior to study enrollment and during the 3-month study period will be evaluated.

Global Psychopathology: Global psychopathology will be measured with the Clinical Global Impressions (CGI)[29] a widely used scale which evaluates illness severity on a 1 to 7 point

continuum. Severity of illness ratings on the CGI have reported reliability scores ranging from 0.41-0.66[29] and correlate with the BPRS[30].

Social Functioning: Life and Work Functional status will be evaluated using the GAF and the Strauss-Carpenter Level of Functioning Scale (SCLFS). The GAF is a 100-point single-item scale which measures global functioning of psychiatric patients and is widely utilized in clinical studies involving Seriously Mentally Ill patients.[31] The reliability of the GAF ranges from 0.62-0.82. Additionally we will use the SCLFS which measures functioning in four areas: symptoms in the previous month, hospitalizations, work, and social contacts in the previous year.[32] Functioning in each area is rated on a scale from 0, worst functioning, to 4, best functioning.

Alcohol and Substance Use: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a widely used and validated 8-item measure of alcohol and drug use (World Health Organization ASSIST Working Group, 2002).[33]

Quality of Life (QoL): The Short Form Health Survey (SF-12) will be used to assess health related quality of life.[34] This 12-item self-report Health-related Quality of Life measure has an index for mental health and an index for physical health and has been validated in individuals with serious mental illness.[35]

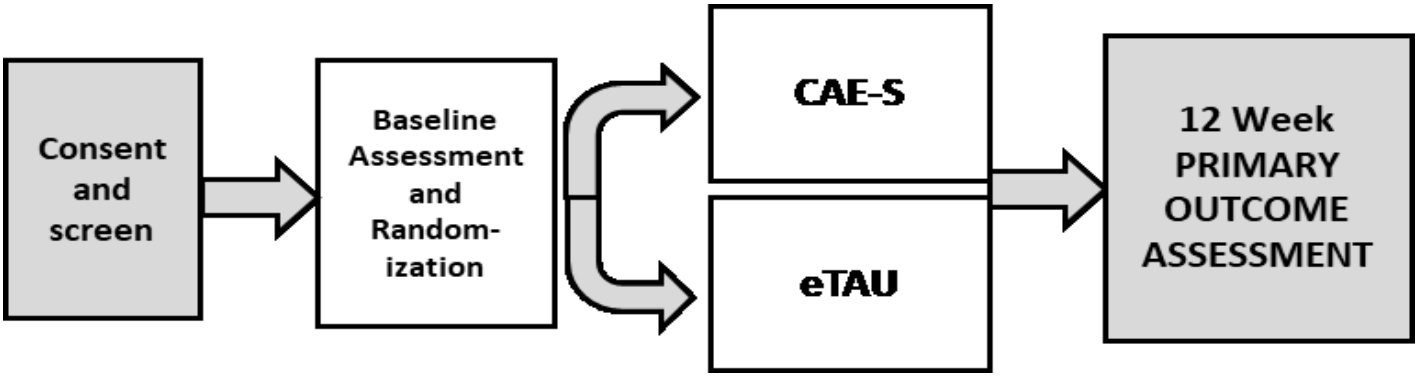
Schedule of Events

	Screen	Baseline (~1 week after screen)	Weeks 2-8	12 weeks
Screening, Informed consent	**X**			
Inclusion/Exclusion	**X**			
Demographics	**X**			
Diagnostic Interview (MINI)	**X**			
Medical burden (Charlson)	**X**			
Randomization		**X**		
eCAP administration and training	**X**			
Primary Outcome: Schizophrenia Symptoms - PANSS		**X**		**X**
Secondary outcomes: Adherence Behavior: TRQ, directly-observed pill counts and eCAP*	**X**	**X**		**X**
Secondary outcomes:		**X**		**X**

Adherence Attitudes: DAI, PROMIS Global Psychopathology: CGI Social Functioning: Strauss-Carpenter Alcohol/Substance Use: ASSIST Quality of Life: SF-12 Health Resource Use				
CAE sessions/attendance **ETAU sessions/attendance**			**X**	
Participant satisfaction				**X**

*eCAP data collection will start at baseline following distribution at screen

Figure 1: Study Design



Data Analysis Plan

Statistical Analysis: Our study proposes to assess the primary outcome of change from baseline to week 12 on the PANSS. Expected magnitude of change is informed by results of 2 previous studies using CAE in schizophrenia by these PIs (Sajatovic 2013, Sajatovic 2017). We will conduct descriptive analysis of baseline variables (i.e., age, gender, ethnicity, and level of education). The PANSS total will be a sum of global symptoms of schizophrenia. First, we will compare the changes in PANSS from baseline to 12 weeks, respectively, for the CAE-S and eTAU groups using a non-parametric Wilcoxon rank-sum test to determine whether the subgroup medians differ. Should baseline-covariates differ between subgroups, we will conduct the appropriate multivariable linear regression for normalized outcome measures, to account for residual confounding. Analysis of the secondary outcomes will be conducted in a similar manner. An intent-to-treat analysis will be conducted. We will assess the missing at random assumption for the mixed models for missing data due to dropout or missed assessments.

We project a sample size of 36 subjects, randomized in equal numbers (CAE=18, eTAU= 18). In our previous study using CAE and long-acting injectable antipsychotic medication in homeless individuals with schizophrenia, 10 (33%) out of 30 subjects dropped out after 24

weeks, including 3 (10%) due to incarceration (thus, 23% due to other discontinuation reasons). This study will not specifically enroll homeless individuals, but rather those who are on oral antipsychotics prescribed by the patient's outpatient clinician; thus, we believe the attrition proportion will be substantially smaller for the proposed study. Additionally, since the duration of observation in the proposed study is 12 rather than 24 weeks, this is expected to optimize study retention. Nonetheless, for the power calculation we hypothesize an attrition of up to 23% (N=8), a one-sided alpha of 0.05 (because we hypothesize CAE will result in improvements based on our pilot studies) For PANSS, we previously observed an average decrease in the composite score from baseline of 6.7 (SD = 7.1), there is 77% power for a sample size of 28. Thus the sample size of 36 individuals enrolled is appropriate for this conservative estimate of attrition. For our exploratory aim, adherence is calculated as a percentage of self-reported proportion of oral medications missed. Automated pill monitoring (eCAPS) will be used to validate the TRQ and we expect that CAE will improve adherence at week 12 from screen at least as comparably as it did in our study of homeless iandividuals[7] (average TRQ improvement past week = 37%; SD = 36.9%). For a Wilcoxon rank-sum test, we expect there will be minimal change in adherence in the eTAU group at week 12 – for which we have 81% power to detect a difference; even if the eTAU group reports a 5% change, there is still 71% power to detect a difference.

Risks to Research Participants

Any time information is collected, there is a potential risk for loss of confidentiality. There are no other known risks of harms or discomforts associated with this study beyond those encountered in normal daily life. Some of the activities we will ask you to complete might make you feel uncomfortable or tired. Participants may refuse to answer any of the questions, take a break, or stop your participation in this study at any time.

Provisions to Protect the Privacy Interests of Research Participants

Confidentiality of research data will be protected in several ways. Patient identifiers at the analytic level will not be the same as the patient's clinical medical record number. The files that link the patient identifiers to the study numbers will be kept in locked cabinets in the PIs office. Only aggregate data will be presented or published and will be presented such that individual patients cannot be identified. The proposed project's research personnel who will have access to subject identities are the study PI, co-investigators, and the study research assistants. All study personnel will be required to be certified in the protection of human subjects throughout the study.

Potential Benefit to Research Participants

There is no direct benefit from participation in this study.

Participant may find it helpful to participate in the educational sessions and/or watch the wellness videos. It is possible that the interventions may help participant remember to take their medication. Information obtained in this study may help improve care for other patients

Withdrawal of Research Participants

Participation is voluntary. There is no penalty or loss of benefits for not participating or for discontinuing your participation.

Participant is free to withdraw from this study at any time. The research team may also end participation in this study if they do not follow instructions, miss scheduled visits, or if safety or welfare are at risk.

Alternatives to Participation

Alternative to participation is to not participate

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