PROTOCOL

TITLE: USING LATENT VARIABLES AND DIRECTLY OBSERVED TREATMENT TO IMPROVE THE DIAGNOSIS AND MANAGEMENT OF DEPRESSION AMONG HEMODIALYSIS PATIENTS

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ABSTRACT

Depression is present in about 20-30% of hemodialysis patients and is associated with morbidity and mortality. However, depression is inadequately diagnosed and treated among dialysis patients. This is due in part to the overlap between depressive symptoms (e.g. appetite change, trouble sleeping, feeling tired) and symptoms related to persistent metabolic derangements in hemodialysis patients (e.g. nausea, nocturnal cramps, feeling washed out after treatment). The overlap between depressive symptoms and dialysis-related complications makes it difficult to diagnose and therefore to treat depression. In addition, prescription of antidepressant medication may increase an already high pill burden and result in poor adherence. Moreover, the evidence base to guide depression treatment among hemodialysis patients is limited. In our previous work, we developed methods to use latent variables and structural equation modeling to isolate depressive symptoms. Other investigators have demonstrated that directly observed treatment enhances the effectiveness of tuberculosis and HIV treatment.

We now propose a cross-sectional study (Phase 1) followed by a randomized controlled trial (Phase 2) at 17 dialysis facilities. The cross-sectional study will involve assessments of depressive symptoms (using the PHQ-9 screening instrument) as well as dialysis-related complications (KDQOL) in about 1083 patients. We will then use structural equation modeling to develop and validate a hemodialysis-specific PHQ-9 (hdPHQ-9) that will isolate depressive symptoms. The trial will involve 216 patients with confirmed depression who will be randomly assigned to (a) directly observed weekly antidepressant treatment with fluoxetine or (b) referral to their nephrologists, their primary care physicians, or nearby mental health providers. The primary outcome of the trial will be remission of depression at 12 weeks. The trial results will also be used to compare the responsiveness of the PHQ-9 and the hdPHQ-9. We anticipate that the hdPHQ-9 will be a valid and responsive instrument that will isolate depressive symptoms in hemodialysis patients and ultimately improve the screening and diagnosis of depression. We also expect that directly observed weekly fluoxetine treatment will be an effective way to manage depression among hemodialysis patients.

Innovative features of the proposed project include the use of latent variables to address overlap, administration of a long acting weekly antidepressant, directly observed treatment, and a rigorous randomized controlled trial design. The project has the potential not only to improve the diagnosis and management of depression among hemodialysis patients but also to improve their morbidity and mortality. Furthermore, it may serve as a model for future studies to isolate symptoms among overlapping medical conditions.

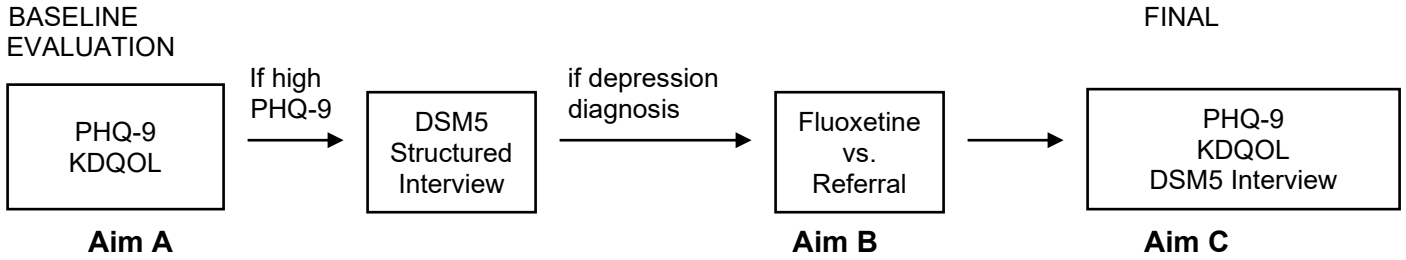
Participating dialysis facilities

FACILITY NAME	FREE-STANDING?	FOR PROFIT?	NUMBER OF PATIENTS	% FEMALE	% AFRICAN-AMERICAN
CDC Eliza Bryant	No	Yes	117	48	86
CDC East	Yes	No	343	39	92
CDC Euclid	Yes	Yes	240	46	64
CDC Mentor	Yes	No	175	42	7
CDC Shaker	Yes	Yes	196	52	85
CDC Warrensville	Yes	Yes	186	46	80
CDC West	Yes	No	113	34	47
CDC Canfield	Yes	No	88	43	38
CDC Heather Hill	No	No	72	40	5
CDC Jefferson	Yes	No	17	60	7

CDC Beachwood	No	Yes	62	38	32
CDC Garfield	Yes	Yes	96	54	66
CDC Painesville	Yes	Yes	42	45	37
CDC Oakwood	Yes	Yes	92	46	55
CDC Park East	No	Yes	39	60	69
CDC Warren	Yes	Yes	55	46	30
CDC Youngstown	Yes	Yes	31	57	25

We propose to conduct our trial at the 17 facilities affiliated with the Centers for Dialysis Care (CDC), a greater Cleveland dialysis chain. The median facility size is 92, 47% of patients are female, 48% are African-American, and 3% are Hispanic. These facility and patient characteristics are roughly comparable to national figures, except that there are more African American and fewer Hispanic dialysis patients in the Cleveland area compared to the United States as a whole. **We have previously conducted several NIH-funded randomized controlled trials at these facilities**.[43-46]

Study design overview and timetable



After a development and training period, we propose a cross-sectional study followed by a randomized controlled trial. The cross-sectional study will involve assessments of depressive symptoms (PHQ-9) and quality of life for **1083 patients**. These data will be used to address Aim A (diagram above). The trial will involve **216 patients** with DSM5-confirmed depression who will be assigned to **2 groups** using envelopes for randomization.

- Approximately 108 patients will be randomized into the intervention/fluoxetine group over the duration of the entire study. Patients randomized to fluoxetine will be prescribed 2 weeks of short-acting fluoxetine 20 mg and will be instructed to take the prescription daily for 2 weeks. After the approximately 2 weeks of daily fluoxetine is completed, patients will receive a filled prescription of long-acting fluoxetine 90 mg to be taken weekly (observed during dialysis) for 10 additional weeks. The first dose of fluoxetine 90mg will be 5-8 days after the last dose of daily 20mg fluoxetine based on FDA guidelines. During each week, the nurse practitioner or research assistant will review possible adverse effects and response to treatment. At the end of the 12-week study period, participants will be provided 4 additional weeks of 90 mg fluoxetine in order to provide sufficient time to follow up with their primary care physician or nephrologist.

- Approximately 108 patients will be randomized into the control/referral group over the duration of the study. Patients randomized to referral will be informed about their diagnosis and asked to follow-up with their nephrologists or primary care physicians and will also be given a list of nearby mental health providers. Details about their study

evaluation will be shared with their nephrologists, primary care physicians, and any mental health providers.

- After 12 weeks, patients in both groups will undergo repeat assessments of the PHQ-9, KDQOL, and DSM5 structured diagnostic interview. These data will be used to address Aims B and C.

We anticipate beginning the project at 2-3 dialysis facilities and estimate it will take about 4-5 months to complete the cross-sectional study and randomized controlled trial at these facilities. We will then involve another 2-3 facilities in the project. This process will continue until we reach our target sample size. Based on our previous work, we anticipate that it will take approximately 45 months to complete the trial. We considered involving more study personnel to shorten the time necessary to complete the trial but felt that this would impair our ability to maintain study quality and intervention fidelity. Intervention fidelity will be maintained through initial training, in-person meetings, monitoring of study notes, and direct observation. Trial results will be reported in accordance with CONSORT recommendations.[51]

Note that we will use the PHQ-9 and the DSM5 structured interview to screen for depression, confirm the diagnosis, and determine response to treatment. While the overlap between dialysis complications and depressive symptoms may affect the accuracy of these methods, they are currently standard practice in depression intervention trials. **Until we have assessed the validity and responsiveness of the hemodialysis-specific PHQ-9 (hdPHQ-9), it would be premature to use this new instrument for screening or for determining response to treatment.**

Year	1	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4	5	5	5	5
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
DEVELOPMENT & TRAINING																				
Finalize study protocol, instruments	x	x																		
Train study personnel	x	x																		
Refine conceptual model	x	x																		
RANDOMIZED CONTROLLED TRIAL																				
Recruit eligible patients			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Baseline evaluation			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Fluoxetine vs. referral trial			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Final evaluation				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ANALYSIS & MANUSCRIPTS																				
Develop, validate new screening instrument																	x	x		
Impact of directly observed weekly fluoxetine																		x	x	
Responsiveness of new instrument																			x	x

Screening & Study sample

Patients will be screened from the previously mentioned CDC dialysis units. Appropriate approval including credentialing, electronic medical record (Clarity) training and access, as well as the appropriate letter of support from the CDC medical director have all been secured. Study team staff will access the Clarity system remotely at MetroHealth. Staff will use the chart

abstraction form to look for eligible participants (see study sample above). A note will be made in the patient's Clarity chart deeming them "eligible" or "ineligible" based on screening. For Aim A, we will restrict the study to patients age ≥ 18 who have been on dialysis for ≥ 3 months, speak English, are not cognitively impaired, and are not currently being treated for depression. We will exclude children age < 18 because the performance of the PHQ-9 and the DSM5 criteria for depression are slightly different among children compared to adults.[24,52] We will exclude new patients because the first 3 months of dialysis treatment is often a time of multiple adjustments in dialysis prescriptions which may in turn affect dialysis complications. We will also exclude patients with the following comorbid conditions: Alzheimer's, Dementia, Bipolar Disorder, Psychotic Disorder, Substance Use Dependence. This will be assessed by cross referencing diagnosis in Clarity as well as the patient's medication list. Eligible participants will be assigned a study ID. A screening interview form will be partially completed to note the study ID and dialysis shift. In this way, no Protected Health Information (PHI) will leave MetroHealth. The research assistant will take the coded screening form to the dialysis facility and log onto Clarity to confirm patient identity and initial eligibility. The research assistant will then approach the patient and ask if they would be willing to answer a few brief screening questions to see if they qualify for a research study. Interested participants will be asked the questions in the screening interview. The screening interview will exclude non-English speaking patients because we are not budgeted to have study documents in both English and Spanish. It will also exclude cognitively impaired patients because they will be unable to reliably report on depressive symptoms and dialysis complications.[53] Patients who meet eligibility criteria will be invited to participate in the first Phase of the study and to provide written informed consent. The informed consent process will take place and participants will be given a chance to ask any questions they have regarding the study. A copy of the signed informed consent will be given to them. After consenting, the research assistant will administer the PHQ-9 followed by the KDQOL. Patients scoring under a 10 on the PHQ-9 will have completed their part in the study and will receive a $20 clincard. Only de-identified data (utilizing the subject ID) will be transported back to MetroHealth for data entry.

Patients with a PHQ-9 score ≥10 will be told that the psychiatric nurse practitioner will first perform a DSM5 structured diagnostic interview. Patients with a diagnosis of depression based on the DSM5 structured interview will then be further evaluated by the nurse practitioner to confirm the diagnosis prior to randomization to fluoxetine or referral. This will involve an approximately hour-long standard clinical mental health assessment and will exclude individuals with bipolar or psychotic disorders, individuals who are at immediate risk of harm to themselves or others, individuals who have a history of intolerance or failure to respond to fluoxetine, individuals with substance use dependence, and individuals who have any comorbid conditions that would make them unable to comply with study procedures. Patients diagnosed as depressed based on the MINI assessment will then be asked to participate in Phase 2 of the study (the randomized controlled trial). Willing participants will be consented and subsequently randomized into one of the 2 following groups:

Fluoxetine (Intervention) group

The study psychiatric nurse practitioner will write a prescription for 2 weeks (14 days) of short-acting fluoxetine 20 mg and order the prescription from the MetroHealth Research Pharmacy. The short-acting fluoxetine prescription will be picked up from the MH Research Pharmacy the following day by either the study coordinator or the nurse practitioner. The prescription will be transported by the nurse practitioner or other study team member to the dialysis facility and

given to the participant by the nurse practitioner. The nurse practitioner will instruct them to take one capsule daily for the next 14 days. The nurse practitioner will meet with patients at day 3, end of week 1, and end of week 2 to assess adverse effects (such as insomnia, headache, nausea, weakness), adherence, and response to treatment based on interviewing the patient and re-administering the PHQ-9. After consultation with Drs. Sehgal and Sajatovic, the nurse practitioner may encourage adherence (if patient has missed fluoxetine doses at home), or discontinue fluoxetine (if moderate-severe adverse effects). After the successful completion of the 2 weeks of daily fluoxetine, a prescription of weekly (90 mg) fluoxetine will be ordered by the nurse practitioner from the MetroHealth Research Pharmacy. The weekly fluoxetine will be filled and transported to the participant's upcoming dialysis visit by the nurse practitioner or other study team member. The participant will be instructed by the nurse practitioner to take the weekly/long-acting once weekly at the dialysis facility while observed by the nurse practitioner or other study team member starting 5-8 days after the last dose of daily 20mg fluoxetine. If a patient misses the dialysis treatment that fluoxetine should be taken at, the nurse practitioner or other study team member will remind him/her by telephone to take the medication. The nurse practitioner will then meet with patients every two weeks for the next 10 weeks and make necessary medication adjustments.

Beginning with daily short acting fluoxetine and then transitioning to weekly long-acting fluoxetine is the recommended approach for using long acting fluoxetine.[34,36] A recent systematic review concluded that 12 weeks is an appropriate period of time to determine if depression treatment is effective in kidney disease patients.[28] If a patient is suicidal at any time during the trial (e.g. based on response to the last question in the PHQ-9 or as ascertained from other interactions with the patient), we will immediately administer the MINI suicidality module. If the participant is determined to have low risk, we will notify the dialysis facility social worker or charge nurse and document in the progress note. If the participant is determined to have moderate to high risk, we will call the study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed) then notify the dialysis facility social worker and/or charge nurse so they can arrange for urgent evaluation and treatment. This will also be documented in the progress note.

Patients who discontinue fluoxetine due to severe adverse effects will be referred to their nephrologists or primary care physicians for consideration of alternative depression treatments. Based on studies in the general population, we estimate that about 65% of patients will respond to daily fluoxetine and that 80-90%% of responders will continue to do well with weekly fluoxetine (at 90 mg or, if necessary, 180 mg).[34-36,40] We further estimate that about 5% of all fluoxetine group patients will need to discontinue fluoxetine because of adverse effects.[34-36,40] Because of the short duration of the trial, we will not simultaneously provide other pharmacologic or non-pharmacologic treatments for depression. Moreover, long-acting fluoxetine is the only treatment that allows for weekly directly observed administration. At the end of 12 weeks, participants will be given a filled prescription of 90 mg fluoxetine for 4 additional weeks. They will also be given a set of instructions to follow up with their nephrologists or primary care physicians for decisions about ongoing depression treatment.

Referral (Control) group

Patients will be informed about their diagnosis and asked to follow-up with their nephrologists or primary care physicians and will also be given a list of nearby mental health providers. A written summary of their study evaluation will be shared with their nephrologists and primary care physicians. A research assistant will see referral group patients at the same frequency that the nurse practitioner will see fluoxetine group patients (i.e. day 3 and weeks 1, 2, 4, 6, 8, 10). At

these visits, the research assistant will administer the PHQ-9 and inquire about any depression treatment that the patients' providers have initiated (such as specific antidepressant medications or cognitive behavioral therapy). If a patient is suicidal at any time during the trial (e.g. based on response to the last question in the PHQ-9 or as ascertained from other interactions with patient), we will immediately administer the MINI suicidality module. If the participant is determined to have low risk, we will notify the dialysis facility social worker or charge nurse and document in the progress note. If the participant is determined to have moderate to high risk, we will call the study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed) then notify the dialysis facility social worker and/or charge nurse so they can arrange for urgent evaluation and treatment. This will also be documented in the progress note.

Data elements

Baseline (week 0) and final (week 12) data on patient characteristics, PHQ-9 and KDQOL will be obtained by a research assistant. Patients will be interviewed during dialysis to obtain the data elements listed below. In previous trials, we found that many patients are unable to complete self-administered questionnaires such as the PHQ-9 because of visual problems or low health literacy. Other patients are not allowed to move their dominant arm during dialysis treatment because tubing from the dialysis machine is connected to blood vessels in the arm. The combination of sitting next to the patient and the ambient noise in the dialysis facility allows for a relatively private interview. If patients prefer, they may be interviewed in a separate room following completion of dialysis treatment. It is not possible to blind study personnel to assessments of depression treatment, adherence, response, and adverse effects during the trial (day 3, weeks 1, 2, 4, 6, 8, 10). Patients will be given a $20 clincard at the end of each interview to thank them for participation. The nurse practitioner and other study team members will have a lock box for transporting consent and clincard receipts. Other study documents will be devoid of PHI. Patients will be assigned a study ID that is linked only by a secure RedCap database. A study ID system utilizing patient initials and codes for dialysis facility will be employed to keep track of patients. Below is a chart outlining the various instruments that have been either developed or utilized for the purposes of this study:

Form Name	**Summary**	**Study Group**	**Type**	**When to Be Administered**
Chart Abstraction Eligibility Form	Chart review to gather demographic info and determine initial eligibility for study	Both	Data entry Form	Screening (via CDC medical record)
Screening Interview	Interview with patient to determine final eligibility for Phase 1 of the study	Both	Data entry Form	Screening

Phase 1 consent form	To consent patients to first phase of the study if eligible (1083 patients)	Both	Consent	After eligibility for study confirmed
Enrollment Checklist	Checklist to ensure completion of all baseline tasks	Both	Administrative Document	After baseline surveys are complete
Phase 2 consent form	To consent patients to second phase of the study if eligible (216 patients)	Both	Consent	After Mini reviewed and diagnosis of depression assessed
Patient Instructions for Daily Fluoxetine	To direct intervention patients in first part of filling prescription and taking fluoxetine daily	Intervention	Patient Information	After randomization into intervention group
Daily Adherence Form	To use to assess adherence to daily fluoxetine	Intervention	Administrative Document	Visits 1, 2, 3 & 4 (Fluoxetine)
Patient Instructions for Weekly Fluoxetine	To direct intervention patients in 2nd part of filling their prescription and taking fluoxetine (weekly)	Intervention	Administrative-Patient Info	After daily fluoxetine is completed (Visit 4)
Advanced Practice Nurse Study Note	To track the patient's response to fluoxetine treatment; to record any adverse events	Intervention	Source Document	Visits 1,2, 3, 4, 5, 7,9,11,13
Patient Instructions for Control Group	To let patients know that they may be depressed and to seek outside help	Control	Patient Information	After randomization into control group (Visit 1)
List of Mental Health Providers for Control Group	To be used in tangent with Patient Instructions for Control Group	Control	Patient Information	After randomization into control group (Visit 1)
Referral Group Follow Up Checklist	To record ongoing PHQ-9 scores and monitor for adverse events	Control	Source Document	Visits 1-9

Fluoxetine Group Adherence Checklist	To record ongoing PHQ-9 scores and observations of fluoxetine administration	Intervention	Source Document	Visit 1-13
Patient Letter for End of Study (Intervention Group)	To be used after study is over to direct patients to speak with their physician to continue treatment	Intervention	Patient Information	Visit 13: after all follow up surveys have been completed
Close-out Checklist	To capture administration of all follow up surveys, instructions & payment	Both	Data Entry Form	Visit 13
PHQ-9	9-item questionnaire that asks about depressive symptoms	Both	Questionnaire	Baseline, Visits 2,3,4,5,7,9,11,13
Dialysis Symptoms Index	Addresses complications in dialysis	Both	Questionnaire	Baseline and Final (Week 12)
Kidney Disease Quality of Life	Addresses quality of life and complications in dialysis	Both	Questionnaire	Baseline and Final (Week 12)
MINI (Mini International Neuropsychiatric Interview)	Gold standard for depression diagnosis	Both	Structured Interview	Baseline and Final (Week 12)

Patient characteristics. Captured by "Chart Abstraction Eligibility." Included on these forms are demographic variables to be obtained by chart abstraction include age, gender, race/ethnicity. Medical variables will be cause of renal failure, number of years on dialysis, and possible depressive treatment and/or medications.[18,59] Also, a "Screening interview" will be done to ensure cognitive ability and confirm no current depression treatment.

Patient Health Questionnaire (PHQ-9). The PHQ-9 is a 9-item questionnaire that asks about depressive symptoms (listed in section 3.01). In the general population, the PHQ-9 has good internal reliability (Cronbach's α of 0.89) and validity (sensitivity and specificity both 88% for major depression diagnosed by structured diagnostic interview).[26] A small study of dialysis patients found similarly high sensitivity and specificity (both 92%).[3] **However, it is not surprising that PHQ-9 scores correlate strongly with structured interview diagnoses of depression because both address the same 9 symptoms**. The main difference between them is that the structured interview tries to determine if symptoms may be due to another

psychiatric condition such as bipolar disorder. We selected the PHQ-9 (rather than other depression screening instruments) because it is brief, is commonly used, and will allow us to build on our previous work on symptom overlap in multiple sclerosis.[14]

Quality of life. We will also use the KDQOL assess quality of life. This widely used instrument includes both general scales on health-related quality of life as well as scales that target specific areas relevant to end stage renal disease.[19,60,61] 10 additional dialysis complication symptoms have been added to the KDQOL-36

DSM5 structured diagnostic interview. The gold standard for depression diagnosis is a structured diagnostic interview based on DSM5 criteria. This semi-structured interview involves an introductory overview followed by several modules that represent the major axis I psychiatric diagnostic classes. The output of the interview is the presence or absence of the disorders being considered.[63,64] As in our previous work, we propose to utilize the Mini International Neuropsychiatric Interview (MINI) as opposed to other structured interview instruments because the MINI is much shorter but still reliable and valid.[47,65] The MINI has excellent inter-rater agreement (kappa 0.84) and diagnostic accuracy (sensitivity 0.96 and specificity 0.88 compared to much longer diagnostic interviews).[66] In addition, the diagnostic stability of the MINI is superior to unstructured assessments conducted by clinicians.[65]

Depression treatment, adherence, response, and adverse effects. To be captured by a combination of: “Enrollment Checklist”; “Daily Adherence Form”; “Fluoxetine Group Follow Up Checklist”; “Control Group Follow Up Checklist”; “Progress Note.” The psychiatric nurse practitioner will meet with fluoxetine patients at day 3 and at weeks 1, 2, 4, 6, 8, and 10 during the trial to assess adherence, response to treatment, and adverse effects (see section 4.05 for details). Adherence will be assessed by pill counts and by using an adherence question from the Brief Medication Questionnaire that asks participants how consistently they took their medication during the prior week. This questionnaire has been used to assess adherence to antidepressants and is correlated with pharmacy fill records.[67,68] Patients who miss two or more daily doses will be categorized as nonadherent.[69,70] Note that adherence will only be assessed in this manner when fluoxetine patients are taking short-acting fluoxetine since administration of long-acting fluoxetine will be directly observed by the research assistant. Adverse effects will be assessed by the nurse practitioner. The nurse practitioner will complete a written study note listing the fluoxetine dose, adherence, response, and adverse effects.

In a similar manner, the research assistant will meet with referral patients at day 3 and at weeks 1, 2, 4, 6, 8, and 10 during the trial. The research assistant will inquire about any depression treatment that has been initiated by each patient’s nephrologist, primary care physician, or other provider. The research assistant will complete a study note listing any depression treatment including new medication or cognitive behavioral therapy.

For detailed visit flow, please see **Attachment A**.

Training and intervention fidelity

Quality control and fidelity during the trial will be maintained through a combination of i**nitial trainings, weekly meetings, monitoring of study notes, and direct observation**. Initial training will take place over multiple days addressing specifics related to research ethics, the

study protocol, psychiatric interviewing and dialysis unit etiquette. All staff will be CREC certified and receive additional training on the importance of confidentiality, specific to research in a community setting. The psychiatric interview training will be cover issues related to inter-rater reliability, as well as how to handle various situations when dealing with depressed patients (specifically the topic of suicidality). The other training will be an introduction to dialysis unit etiquette and safety that will include a site visit to a local unit. As the study progresses, the research assistants and nurse practitioner will meet weekly with other research team members to review study progress, adherence to the protocol, and address any challenges in carrying out study tasks. Ms. Dolata will review all study notes to identify any deviations from specified tasks. To further ensure intervention fidelity and consistency across research assistants, she will also directly observe a randomly selected 5% of research assistant interactions with patients. She will use a fidelity checklist to verify that specific tasks are carried out properly. In a similar manner, Dr. Sehgal or Sajatovic will observe a randomly selected 5% of nurse practitioner interactions with patients. Any problems noted from review of study notes or from direct observation will be addressed at our weekly group meetings. If a research assistant or the nurse practitioner is unable to complete the trial, we will identify and train a replacement.

Data and safety monitoring plan

We propose several methods to ensure safety and to monitor our intervention. First, our intervention is theoretically sound and based on our prior work and that of others. Second, we will refine and pre-test our approach prior to beginning the clinical trial. Third, Dr. Sehgal will meet weekly with other study personnel in order to trouble-shoot any potential areas of concern regarding the safety of the study protocol. Fourth, all study personnel will undergo rigorous training. Fifth, we will closely monitor study personnel through a combination of weekly meetings, monitoring of study notes, and direct observation. Sixth, project data will be reviewed quarterly by the entire study team. Any indications of potential threats to patient safety or a pattern of refusal by patients to participate in specific interactions with study personnel will be responded to immediately by a careful review conducted by the study team. When appropriate, involvement of the patient's nephrologist or dialysis facility medical director, reporting to our Institutional Review Board, reporting to End Stage Renal Network 9 (a regional Medicare quality oversight organization), and adjustment of the project protocol will occur. Although risk to subjects is considered low, any adverse events will be reported to our Institutional Review Board and the National Institutes of Health.

Confidentiality

We will do several things to protect the participant's privacy. First, we are assigning study IDs to all data so that PHI is not being regularly written down or collected throughout the study. Also, we will be utilizing the lock box in order to ensure confidential transport of consent forms and clincard receipts. Third, if a participant wishes to discuss the study in a more private area than the dialysis chair, we will offer to wait until their dialysis session is over and move to a private room in the unit. All data at Metro will be stored on a secured drive, will be password protected and will have no PHI (other than the Key in RedCap).

ATTACHMENT A: VISIT FLOW SHEET

VISIT TYPE	TASKS
PRE-SCREEN	• Identify CDC unit(s) to begin project at • Introduce study staff to CDC unit staff
SCREENING (Part 1-remote at Metro)	• Screening for that unit to take place off site by study staff • Complete *Chart Abstraction Eligibility Form* • Enter note in CDC research tab that patient was "successfully screened" or a "screen fail" • Weekly report of potentially eligible patients will be generated at Metro through use of CDC Clarity EMR • Participant is assigned a study ID to be used in future visits
SCREENING (Part 2-at dialysis facility)	• Research assistants (RA) will bring coded list of eligible patients and blank study documents • RA will log into CDC Clarity to confirm patient ID (via note in research tab) • RA will begin approaching participants based on screening report • *Screening Interview* administered by RA and is filled out at the unit via patient interview
ENROLLMENT (Part 1-at dialysis facility)	• Eligible participants will be asked to be in the "Phase I" of the study • Obtain Informed consent #1; given a copy of consent, another stays at unit; another copy goes back to Metro
ENROLLMENT (Part 2-at Metro)	• Consented patients' name and Study ID entered into REDCAP Key • Baseline info entered into master tracking spreadsheet
BASELINE (day 1)	Baseline surveys via patient interview • PHQ-9 • KDQOL Score PHQ-9 at unit (other survey does not need to be scored at that time) • If Score is less than 10, patient receives CLINCARD, is thanked for participation • If Score is greater than or equal to 10, participant is told that a nurse practitioner will be back on next dialysis day to conduct the MINI interview • If patient is suicidal based on PHQ-9 RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study NP on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • Surveys, Clincard receipt, and consent are transported back to Metro in lock box

BASELINE	PC enters all info to date into main tracking database at Metro
BASELINE (part 2-at dialysis facility)	Nurse practitioner conducts MINI interview (on next dialysis day) • MINI is scored and assessed by NP • If NOT diagnosed as depressed, participant is given Clincard and thanked for their time • If diagnosed as depressed, participant is asked to be in Randomized Controlled Trial (RCT) • If patient consents to RCT, they are then randomized by the NP via envelopes • If patient is randomized to Fluoxetine (intervention group), the NP orders prescription of daily (20 mg) fluoxetine from the MetroHealth Research Pharmacy (2 weeks worth)
BASELINE (part 2-at Metro)	PC or RA creates participant folder (all de-identified info) • Enrollment checklist • Blank PHQ-9 forms • Daily Adherence Form • Follow Up Checklists • Progress Notes • Participant Calendar • Close-Out Checklist
VISIT 1 **FLUOXETINE** (DAY 1)	• NP or study staff picks up prescription of daily fluoxetine at research pharmacy • NP transports prescription to dialysis unit to meet with participant • NP fills pill holder with participant • Participant is given *Daily Fluoxetine Instructions* • Participant calendar is generated based off first dose
VISIT 1 **REFERRAL** (Day 1)	• Participant given referral group instruction sheet • Participant given list of nearby mental health providers
VISIT 2 **FLUOXETINE** (DAY 3 of Daily)	• NP meets with participant • Checks for adverse events (*Progress Note*) • Administers *Daily Adherence Form* • Administers *PHQ9* • If patient is suicidal based on PHQ-9, NP immediately performs the MINI suicidality module. *If participant determined to have low risk the NP will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, contact SW or charge nurse; then note in progress note • Clincard payment • PHQ9, Daily Adherence Form & study note back to Metro before next check in • Chart relevant info in CDC Clarity EMR
VISIT 2 **REFERRAL** (DAY3)	• RA meets with participant • Administers *Control Group Follow Up Checklist* and inquires re: any depressive treatment (medication or cognitive therapy)

	• Administer *PHQ9* • If patient is suicidal based on PHQ-9, RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • PHQ9 & Study notes back to Metro before next check in
VISIT 3 **FLUOXETINE** (End WEEK 1 Daily)	• NP meets with participant*; Fluoxetine Group Follow Up Checklist* • Checks for adverse events & response to treatment (Study note) • Administers *Daily Adherence Form* • Administers *PHQ9* • If patient is suicidal based on PHQ-9, NP immediately performs the MINI suicidality module. *If participant determined to have low risk the NP will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, contact SW or charge nurse; then note in progress note • Clincard payment • PHQ9, Daily Adherence Questionnaire & study note back to Metro before next check in • Chart relevant info in CDC Clarity EMR
VISIT 3 **REFERRAL** (End WEEK 1)	• RA meets with participant; *Completes Control Group Follow Up Checklist* • Inquires re: any depressive treatment • Administer PHQ9 • If patient is suicidal based on PHQ-9, RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • PHQ9 & Study notes back to Metro before next check in
VISIT 4 **FLUOXETINE** (End WEEK 2 Daily/Begin Weekly)	• NP meets with participant • Completes *Fluoxetine Group Follow Up Checklist* • Checks for adverse events (Study note) • Administers *Daily Adherence Form* • Administers *PHQ9* • If patient is suicidal based on PHQ-9, NP immediately performs the MINI suicidality module. *If participant determined to have low risk the NP will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress

	note. **If participant determined to have moderate to high risk, contact SW or charge nurse; then note in progress note • Clincard payment • PHQ9, Daily Adherence Questionnaire & study note back to Metro before next check in • Chart relevant info in CDC Clarity EMR
VISIT 4 **REFERRAL** (WEEK 2)	• RA meets with participant; *Completes Control Group Follow Up Checklist* • Inquires re: any depressive treatment • Administer *PHQ9* • If patient is suicidal based on PHQ-9, RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • PHQ9 & Study notes back to Metro before next check in
Visit 5 **Fluoxetine** (week 3)	• NP fills new prescription for 90 mg (weekly Fluoxetine) prior to visit • NP meets with participant and observes first dose of weekly treatment • Study note back to Metro • Chart relevant info in CDC Clarity EMR
VISITS 7, 9, 11, 13 **FLUOXETINE** (weeks 5, 7, 9, 11)	• RA observes ongoing doses of weekly fluoxetine on odd weeks (i.e. weeks that participant is not meeting with NP) • Completes *Fluoxetine Group Follow Up Checklist*
VISITS 6, 8, 10, 12 **FLUOXETINE** (Weeks 4, 6, 8, 10)	• NP observes participant administration of fluoxetine (*Fluoxetine Group Follow Up Checklist*) • Checks for adverse events & response to treatment (*APN Study Note)* • Administers *PHQ-9* • If patient is suicidal based on PHQ-9, NP immediately performs the MINI suicidality module. *If participant determined to have low risk the NP will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, contact SW or charge nurse; then note in progress note • Clincard payment • PHQ9 & study note back to Metro • Chart relevant info in CDC Clarity EMR
VISITS 5,7, 9, 11 **REFERRAL** (Weeks 4, 6, 8, 10)	• RA meets with participant • Inquires re: any depressive treatment (Completes *Control Group Follow Up Checklist*) • Administer *PHQ9*

	• If patient is suicidal based on PHQ-9, RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • PHQ9 & Study notes back to Metro
VISIT 14 **FLUOXETINE** (WEEK 12)	• NP observes participant administration of fluoxetine (completes *Fluoxetine Group Follow Up Checklist*) • Checks for adverse events & response to treatment (*APN Study Note*) • NP fills prescription (at MH Research Pharmacy) for 4 more weeks of 90 mg fluoxetine and give to patient • Patient is given participant instructions • *PHQ-9, KDQOL & MINI* administered • Final Clincard payment • Complete *Closeout Checklist* • Chart relevant info in CDC Clarity EMR • Surveys & study note back to Metro
VISIT 13 **REFERRAL** (WEEK 12)	• RA meets with participant • Inquires re: any depressive treatment (*Control Group Follow Up Checklist*) • *PHQ-9*, *KDQOL & MINI* • If patient is suicidal based on PHQ-9, RA immediately performs the MINI suicidality module. *If participant determined to have low risk the RA will notify the social worker at dialysis facility that this occurred and that it appears to be low risk; document in progress note. **If participant determined to have moderate to high risk, call study nurse practitioner on study cell (216-339-9244) or Dr. Sajatovic (if needed); then contact SW or charge nurse; then note in progress note • Complete *Closeout Checklist* • Surveys & study note back to Metro