STUDY TITLE: Social Reward and Its Effect on Brain Functions in Psychotherapies for Mid- and Late-Life Depression

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Statement of Compliance

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

For multi-site IIT only. Remove signature lines if single site study.

Weill Cornell Medicine

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Institution Name

Nili Solomonov, PhD		4/14/2020
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

All abbreviations used throughout the protocol must be defined. Add additional abbreviations specific to protocol.

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

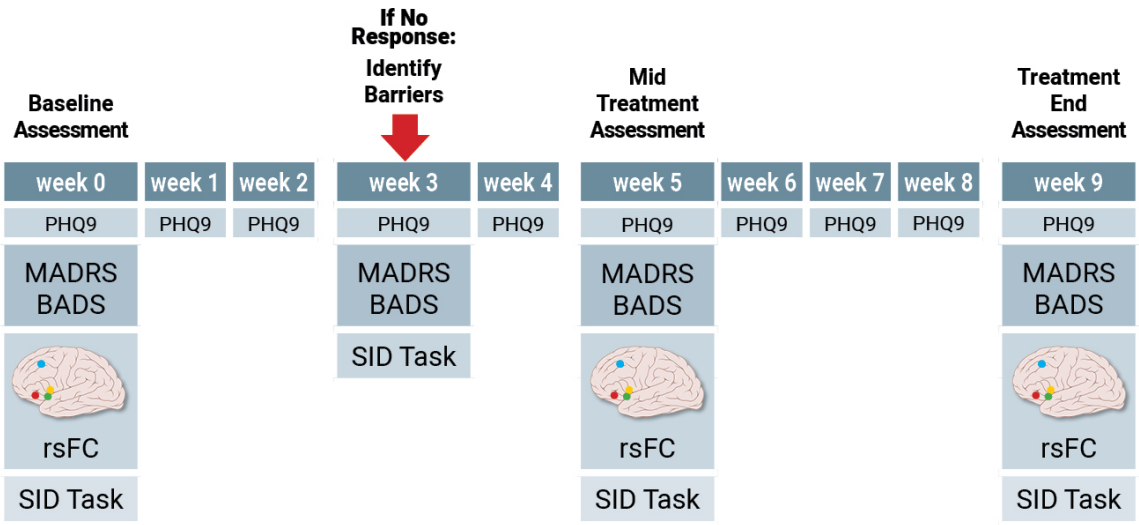
1. Protocol Summary

Full Title:	*Social Reward Psychotherapy and its Effect on Brain Functions in Mid- and Late-Life Depression*
Short Title:	*Social Reward in Late-life Depression*
Clinical Phase:	*I, II, III, or IV*
Principal Investigator:	*Nili Solomonov, PhD*
Study Description:	*Major depression in mid- and late-life is characterized with abnormalities in the Positive Valence System (PVS). Exposure to rewarding experiences can target these abnormalities and in turn, reduce depression severity. Given the high prevalence of loneliness and social isolation in late life, socially rewarding interactions are especially important. Engagement in social interactions with significant others during reward-based psychotherapy reduces depression and increases behavioral activation. The aim of the study is to examine if exposure to meaningful social rewards during psychotherapy, engages PVS circuitry and improves mid- and late-life major depression. The "reward exposure" of this study will consist of meaningful social activities with significant others ("Engage & Connect"). The study will be a pilot RCT that will compare 9-week "Engage & Connect" vs. a Symptom Review and Psychoeducation condition (SRP) for adults older than 50 years with major depression. We will investigate changes in resting-state functional connectivity, social reward processing during an fMRI-based social reward task, and changes in behavioral outcomes over the course of treatment.*
Sample Size:	*N= 60*
Enrollment:	*This study will enroll 60 subjects and screen up to 90 subjects.*
Study Population:	*Individuals aged 50-85 with major depression*
Enrollment Period:	*The study will recruit participants over 5 years*
Study Design:	*This is a randomized controlled trial comparing two psychosocial interventions. We will assess target engagement of the PVS through functional connectivity at rest (rsFC), a self-report measure of behavioral activation (BADS), and performance on a novel fMRI social reward paradigm, during two psychotherapies for middle-aged and older adults with major depression, i.e., "Engage & Connect" therapy (n = 30) and a comparison condition of Symptom Review and Psychoeducation (SRP; n = 30). Participants will receive nine weekly therapy sessions. We will administer research assessments at baseline, Weeks 3, 5, and 9 and MRI scans at baseline, Week 5 and 9. All participants will provide informed consent prior to enrolling in the study.*
Description of Sites/ Facilities Enrolling	

Participants:	*Participating sites will be the Weill Cornell Medicine Psychiatry Department in Manhattan and the Weill Cornell Institute of Geriatric Psychiatry in Westchester.*
Study Duration:	*July 31, 2027*
Participant Duration:	*Participation duration is estimated for approximately 9 weeks, which is the duration of the psychosocial intervention provided. Study enrollment is expected to last 5 years; we propose an additional 2 years for data analysis and manuscript preparation. The projected end date of this study is July 31, 2027.*
Study Agent/Device Name	
Intervention Description:	*Participants will be randomized to one of two psychosocial interventions, each consisting of 9 weekly sessions: 1) "Engage & Connect" – a reward-based psychotherapy aimed to increase engagement in rewarding social activities; 2) Symptom Review and Psychoeducation (SRP) aimed to track patients' depressive symptoms and provide education regarding depression.*
Primary Objective:	*The principal aim of this pilot study is to examine if exposure to meaningful social rewards during psychotherapy engages reward circuitry and improves mid- and late-life major depression. We will test whether "Engage & Connect" leads to: 1) increase in resting state functional connectivity of the Positive Valence System (PVS)*
Secondary Objectives:	*We will test whether "Engage & Connect" leads to: 2) increase in behavioral activation (BADS scale); 3) reduction in depression severity (MADRS scale)*
Exploratory Objectives:	*Evaluate whether in "Engage & Connect" treated participants, change in rsFC of the PVS and behavioral activation (BADS) predicts subsequent reduction in depression severity (MADRS). Investigate changes in social reward processing over the course of psychotherapy using a novel Social Incentive Delay (SID) fMRI task*
Primary Endpoints:	*Change in resting state functional connectivity of the PVS over 9 weeks;*
Secondary Endpoints:	*Change in BADS scores and MADRS scores over 9 weeks*

1.1 Schema

*The time point(s) indicated in the schematic should correspond to the time point(s) in **Section 6.1, Schedule of Assessments**, e.g., Visit 1; Visit 2; etc.*



Note. 60 patients will be randomly assigned to 9-weeks of either "Engage & Connect" (N=30) or "SRP" (N=30); BADS = Behavioral Activation for Depression scale; MADRS = Montgomery-Asberg Depression Rating Scale; rsFC = resting state functional connectivity; PHQ9 = Patient Health Questionnaire; SID Task = Social Incentive Delay Task

1.2 Study Objectives and End Points

1.2.1 Primary Objectives

Examine if exposure to meaningful social rewards during psychotherapy, engages reward circuitry and improves mid- and late-life major depression. The "reward exposure" of this study will consist of meaningful social activities with significant others ("Engage & Connect"). We will test whether "Engage & Connect" leads to change in resting state of the PVS over 9 weeks. The study will be a pilot RCT that will compare 9-week "Engage & Connect" vs. a Symptom Review and Psychoeducation condition (SRP) for adults 50-85 years old with major depression

1.2.2 Secondary Objectives

We will test whether "Engage & Connect" leads to: 2) increase in behavioral activation (BADS scale); 3) reduction in depression severity (MADRS scale).

1.2.3 Exploratory Objectives

Evaluate whether in "Engage & Connect" treated participants, change in rsFC of the PVS and behavioral activation (BADS) predicts subsequent reduction in depression severity (MADRS).

Investigate changes in social reward processing over the course of psychotherapy using a novel Social Incentive Delay (SID) fMRI task

1.2.4 Primary Endpoints

Change in resting state functional connectivity of the PVS over 9 weeks.

1.2.5 Secondary Endpoints

Change in BADS scores and MADRS scores over 9 weeks.

2. Background

2.1 Disease

Depression in late life is common[1] and associated with suffering, reduced quality of life,[2] increased risk of cognitive dysfunction,[3] dementia,[4] disability, cardiac, cerebrovascular, peripheral diseases,[5] suicidality, all-cause mortality,[6,7] and economic burden.[8]

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Antidepressants have modest efficacy in late-life depression.[9,10] The public health impact of antidepressants is attenuated by poor adherence, inadequate dosages and duration, and infrequent follow up of older patients, most of whom are treated in primary care practices.[11,12] Psychotherapies are efficacious in late-life major depression[13–15] and well-liked by older adults.[16,17] However, too few community therapists are able to offer evidence based psychotherapies, mainly because of their complexity.[18–21] Therefore, there is a need for streamlined efficacious psychotherapies that can match the skill set of community therapists.

Our group developed “Engage”, a streamlined, stepped psychotherapy for mid- late-life depression, whose principal intervention is “reward exposure”.[22] In patients with negativity bias, apathy, or inadequate emotional regulation interfering with “reward exposure”, “Engage” offers additional interventions so that “reward exposure” proceeds unimpeded. “Engage” is based on the view that dysfunction of Positive Valence Systems (PVS) perpetuates late-life depression.[22]

“Engage” reduces late-life depression and disability.[23,24] Early increase in resting state functional connectivity (rsFC) in PVS structures during “Engage” predicts increase in behavioral activation.[25] Change in behavioral activation is followed by reduction of depressive symptoms.[26] In order to further streamline “Engage” and guide its personalization, we examined whether specific types of “reward exposure” have higher therapeutic value. Activities involving social interactions with significant others (but not solitary activities) predicted subsequent increase in behavioral activation and reduction of depression.[27] We have also documented that high perceived social support predicts early response to psychotherapy.[28] Exposure of socially isolated older adults to social rewards during “Engage” led to greater reductions of depression than a ‘care as usual’ condition.[29] The above findings underscore the therapeutic role of rewarding social interactions with significant others. Based on this work, we developed “Engage & Connect”, a streamlined version of “Engage”, whose principal intervention is exposure to meaningful, rewarding social activities with significant others. “Engage & Connect” aims to recondition PVS functions, increase behavioral activation, and lead to reduction of symptoms of depression.

2.3 Rationale

The proposed study will be the first study to test target engagement of “Engage & Connect”, a social reward-focused intervention for mid- and late-life depression. “Engage & Connect” is innovative because: 1) It is directly informed by neurobiological research and designed to address dysfunction of PVS, a core component of depression; 2) It is based on data

demonstrating that exposure to social rewards has the highest probability to improve depressive symptoms; 3) It is streamlined so that it can potentially be used by community clinicians. The NIMH Strategies 3.1; 3.2 encourage the development of novel streamlined treatments informed by advances in neuroscience.

To our knowledge, the proposed study will be the first to examine neural processing of social rewards in mid- and late-life depression. It is based on computational modeling, which identified perceived social support as the strongest predictor of early response to psychotherapy and examines whether PVS changes by mid-treatment predict response of depression to “Engage & Connect”. Along with other PVS function measures, it uses a novel social reward fMRI paradigm to examine PVS change and its relationship to “Engage & Connect” response. Behavioral tasks and clinical scales across multiple units of analysis are quick, cost-effective, and easy to administer, making them feasible to use in future large-scale studies and as screening tools in clinical settings.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Participants and family/caregivers participating in this study may be exposed to the following risks:

1. The burden of responding to standardized assessments.
2. The distress associated with discussing personal concerns with research personnel.
3. The discomfort of an MRI scan (approximately 60 minutes per session).
4. Worsening of patients’ depression.
5. Skin irritation from the optional study wearable device (smartwatch).
6. Suicide risk.

2.4.2 Known Potential Benefits

Enrolled participants will accrue the following benefits at no cost:

1. A structured evaluation of psychopathology and an assessment of functional limitations for which interventions are needed.
2. Nine weekly sessions of psychotherapy intervention aimed to reduce depression severity.
3. Ongoing monitoring of clinical status and appropriate referral for clinical care in the event of deterioration.

Additionally, some participants find research participation to be a meaningful experience.

2.4.3 Assessment of Potential Risks and Benefits

The risks for study participants are minimal. We anticipate that a portion of the participants will benefit from the psychotherapies delivered in our study and experience improvement in depression severity. Additionally, the potential knowledge to be gained in this study and its clinical implications are substantial. The study could provide evidence for a novel streamlined social reward-based psychotherapy which targets

network abnormalities central in mid- and late-life major depression and could potentially benefit patients with mid- or late-life depression in the future.

2.5 Correlative Studies Background

NA

3. Study Design

3.1 Overall Design

The aim of the proposed study is to examine whether exposure to socially rewarding activities in a reward-based psychotherapy ("Engage & Connect") leads to changes in Positive Valence Systems (PVS) in middle-aged and older adults with major depression. We will assess target engagement of the PVS through functional connectivity at rest (rsFC), a self-report measure of behavioral activation (BADS), and performance on a novel fMRI social reward paradigm, during two psychotherapies for middle-aged and older adults with major depression, i.e. "Engage & Connect" therapy (n = 30) and a comparison condition of Symptom Review and Psychoeducation (SRP; n = 30). Participants will be randomized to nine weekly therapy sessions. Participants may be asked to use a wearable device during their participation in the study. The device allows for passive sensing of movement (steps), heart rate,and sleep daily. Participants and therapists may be able to review their activity for the week to augment the sessions. We will administer research assessments at baseline, Weeks 3, 5, and 9 and MRI scans at baseline, Week 5 and 9. All participants will provide informed consent prior to enrolling in the study. All participants will be recruited at Weill Cornell Medicine.

The "reward exposure" of this study will consist of meaningful social activities with significant others ("Engage & Connect"). The study will be a pilot RCT that will compare 9-week "Engage & Connect" vs. a Symptom Review and Psychoeducation condition (SRP) for adults older than 50 years with major depression and test the following hypotheses:

During the 9 week course of "Engage & Connect" treatment there will be an:
H1. *Increase in rsFC of the PVS.*
H2. *Increase in behavioral activation (BADS scale)*
H3. *Reduction in depression severity (MADRS scale).*

SH. *In "Engage & Connect" treated participants, change in:* ***SH1a)*** *rsFC of the PVS and* ***SH1b)*** *behavioral activation (BADS) will predict subsequent reduction in depression severity (MADRS). These relationships will not be observed in the SRP treated group. The rationale of this hypotheses is based on the theory that the "Engage & Connect" mechanism of action is reconditioning the PVS, while SRP relies on non-specific mechanisms of action.*

3.2 Scientific Rationale for Study Design

The proposed study will be the first study to test target engagement of "Engage & Connect", a social reward-focused intervention for mid- and late-life depression. "Engage & Connect" is innovative because: 1) It is directly informed by neurobiological research and designed to address dysfunction of PVS, a core component of depression; 2) It is based on data demonstrating that exposure to social rewards has the highest probability

to improve depressive symptoms; 3) It is streamlined so that it can potentially be used by community clinicians. The NIMH Strategies 3.1; 3.2 encourage the development of novel streamlined treatments informed by advances in neuroscience.
To our knowledge, the proposed study will be the first to examine neural processing of social rewards in mid- and late-life depression. It is based on computational modeling, which identified perceived social support as the strongest predictor of early response to psychotherapy, and examines whether PVS changes by mid-treatment predict response of depression to "Engage & Connect". Along with other PVS function measures, it uses a novel social reward fMRI paradigm to examine PVS change and its relationship to "Engage & Connect" response. Behavioral tasks and clinical scales across multiple units of analysis, are quick, cost-effective, and easy to administer, making them feasible to use in future large-scale studies and as screening tools in clinical settings.

3.3 Justification for Dose

Selection of 9 weeks of treatment as "dosage" is based on our previous published work showing that this length of treatment in similar "Engage" psychotherapy studies reduces depressed older adults depression severity and increases their behavioral activation.[23,26,27]

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

4. Subject Selection

4.1 Study Population

We will recruit 60 non-demented middle-aged and older adults (aged 50-85; stratified so that 50% are older than 65) with Major Depressive Disorder (MDD) without psychotic features, determined by the Structured Clinical Interview for DSM-5 (SCID). Based on previous studies we expect a 1.6:1 female: male ratio, reflecting higher rates of major depression among women. We expect an attrition rate of ~10%, comparable to previous "Engage" psychotherapy trials conducted at the Weill Cornell Institute of Geriatric Psychiatry. Included participants will not receive other psychotherapeutic or pharmacological treatments and will either be off antidepressants or will be on a stable dose of antidepressants for ≥ 8 weeks at study entry. We will exclude participants with intent or plan to attempt suicide in the near future, as well as those diagnosed with antisocial or borderline personality disorder (DSM-V); dementia [Mini Mental Status Exam (MMSE) ≥ 1 SD below the mean score for patient's age and education, or DSM-5 criteria]; delirium, severe or acute medical illness, i.e. metastatic cancer, decompensated organ failure, major surgery, recent stroke, or myocardial infarction.

4.2 Inclusion Criteria

1. Ages aged 50-85 [stratified so that 50% are older than 65]
2. Diagnosis of unipolar major depressive disorder without psychotic features, determined by the SCID
3. Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 20.

4. Mini Mental Status Exam (MMSE) ≤ 1 SD below the mean score for patient's age and education
5. Off antidepressants or on a stable dose of an antidepressant for 8 weeks and do not intend to change the dose in the next 10 weeks.
6. Capacity to provide consent for research assessment and treatment.

4.3 Exclusion Criteria

1. Intent or plan to attempt suicide in the near future.
2. History or presence of psychiatric diagnoses other than major depressive disorder without psychotic features, generalized anxiety disorder, persistent depressive disorder, or specific phobia.
3. Use of psychotropic drugs or cholinesterase inhibitors other than use of ≤ 0.5 mg of lorazepam daily up to seven times per week.
4. Neurological disorders (dementias, history of stroke, multiple sclerosis, Parkinson's disease, epilepsy, etc.); cardiac, renal, or respiratory failure; severe chronic obstructive pulmonary disease; metastatic cancer; or debilitated states or less common medical illnesses that may either influence brain systems of interest or ability to participate in the study. A senior clinician at the institute will review any medical illnesses that does not appear in the list above and determine whether it interferes with the study of positive valence system functions in depression.
5. Contraindications to MRI scanning including cardiac pacemaker, heart valve replacement, vascular stent, insulin pump, cochlear implant, any other metallic biomedical implant contraindicating to MRI, and claustrophobia.

4.4 Lifestyle Considerations

Not Applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of low depression severity or exclusion criteria related to recent change in medication may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Participants will be recruited from the outpatient clinic of the Weill Cornell Institute of Geriatric Psychiatry, community-based mental health services, community-based medical practices, and other community organizations.

Additionally, participants may be recruited through the Epic MyChart subject pool, protocol #18120119822 ("Collecting Patient Consent to be Contacted for Research"). Patients in this subject pool have given consent to be contacted about research studies based on the information in their electronic medical record.
We will also recruit participants through social media ads on Facebook and Instagram. We have used a similar approach in two active protocols #1802019007 and #1708018441. Participants who press on our social media ad will be presented with a brief Qualtrics survey, managed in collaboration with JCTO specialist, Megan Kavy, where participants can fill in their information and contact details if they choose to be contacted by a research assistant to discuss voluntary participation. Participants will also receive a link to the JCTO page of the study, as previously noted. Qualtrics is used via Weill Cornell's approved resources. The PI will monitor responses to the survey.

Eligible individuals will be invited to participate in the study after providing informed consent. Individuals who do not meet criteria may be offered participation for other research studies or given referrals for treatment in the community if desired.

Recruitment of WCM clinicians:

We will recruit four Masters-level therapists from those working on other psychotherapy projects at the Weill Cornell ALACRITY Center. Therapists will be certified to provide "Engage & Connect" or SRP and will be unaware of study hypotheses. Training will follow the Institute's training procedures and fidelity standards. Our previous work has shown that therapists with this level of training and clinical experience can be trained in "Engage" and maintain high fidelity.[30] Training procedures are described below. Therapists and research assistants administering clinical rating will remain unaware of study hypotheses. Therapists will be responsible for completing the Patient Health Questionnaire (PHQ-9) at the beginning of each session to monitor patients' clinical states. At the end of each session, they will complete the "Working Alliance Inventory-12" (WAI-12) to evaluate the quality of the working relationship at each session. Additionally, they will complete the MULTI at Baseline, Week 3, 5 and 9 to evaluate their use of therapeutic techniques.

All therapists are service providers on this protocol and are employed by Weill Cornell Medicine's Geriatric Psychiatry Institute or participate in activities at the Geriatric Institute either full-time, part-time, or on a contract basis. Thus, they are all paid for their time regardless of whether they participate in this research study or not. Therapist service providers are given the option to participate in this or any other research study that aligns with their interests, skills, schedule, and the clinical training it provides. If they are not interested, they are welcome to continue working on other services and research projects at the Institute. Therapists' involvement is voluntary and in addition to their primary duties at the Weill Cornell ALACRITY Center. We are seeking informed consent from the therapists to collect basic data related to their training background (e.g., training history, years of experience, theoretical orientation), completion of research assessments, and use of study interventions. Their participation will be voluntary, and their information will be kept confidential. Information regarding the therapists' performance in the study will not be shared with employers outside of the study. Of particular importance is the need to ensure that the therapist understand that their decision to participate (or to withdraw participation as therapists on the study) will have no job ramifications.

WCM clinicians working on other similar psychotherapy trials will be offered the opportunity to

participate in the study as therapists. They can choose not to participate without any negative consequences to their employment or benefits. Clinicians' direct supervisor will not be involved in the study activities and thus the main supervisory relationship will not be affected by study participation. Participating therapists are not the subjects of the research intervention per se, and we will not collect medical or psychiatric information about them. We consent the providers because they are administering clinical scales to monitor patients' progress during the study period when they are delivering the study interventions (e.g. depression symptoms, suicide risk).

Patients participating in this study will be compensated approximately $345 for completion of the study. This amount is equivalent to similar ongoing studies in our department:

- $30 for each research assessment ($120 total)
- $75 for each MRI assessment ($225 total)
-

Participants could be reimbursed for travel to and from study visits if needed.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration. Data will be tracked on RedCap. Clinical notes by clinicians will be tracked in Epic.

5.2 Subject Registration (Sub-sites)

For multicenter studies with a WCM as the coordinating site, please contact JCTOIIT@med.cornell.edu for template language for participate site registrations

6. Study Procedures

6.1 Schedule of Assessments

Patient participants will be randomized to receive a 9-week course of either weekly Engage & Connect therapy or SRP, and research assessments will be conducted at baseline and weeks 3, 5, and 9.

Week	Baseline	1	2	3	4	5	6	7	8	9
Therapy Session		x	x	x	x	x	x	x	x	x
Research Assessment	x			x		x				x
MRI Scans	x					x				x

Trained research assistants unaware of study hypotheses will collect weekly clinical and self-report ratings at each study time point.

Instrument	Baseline	Week 1	Week 3	Week 5	Week 9
Demographics					
Demographic questionnaire	x		x	x	x
Brief Antidepressant Questionnaire (BAQ)	x		x	x	x
Intent to Complete	x				
Depression Severity and Anhedonia					
Montgomery Åsberg Depression Rating Scale (MADRS)	x		x	x	x
Hamilton Depression Severity Scale (HAMD)	x		x	x	x
The Dimensional Anhedonia Rating Scale (DARS)	x		x	x	x
Behavioral Activation and Reward Measures					
Behavioral Activation for Depression (BADS)	x		x	x	x
Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIP)	x		x	x	x
Clinical Characteristics	x				
Mini-Mental State Examination (MMSE)	x				
Interpersonal Problems Inventory – 32 items (IIP-32)	x				x
Duke Social Support Index	x		x	x	x
Revised UCLA Loneliness scale	x				x
Treatment Rationale Scale		x			
MRI tasks	x			x	x
Probabilistic Reversal Learning task	x			x	x
Social Incentive Delay task	x			x	x
Adverse Event Evaluation		x----------x			

Trained research assistants unaware of study hypotheses will collect weekly clinical and self-report ratings at each study time point via zoom, and in person assessments will be offered if needed.

- **Demographics:** Our demographics questionnaire includes age, gender, race, religion, living conditions, marital status, occupation, birth place, and education.
- **Medication List and History of Antidepressant Treatment:** The medication list will also help the RA assess medical comorbidity. The Brief Antidepressant Questionnaire (BAQ) is used to evaluate frequency, dosage, and duration of antidepressant treatment for the past 3 months.
- **Intent to Participate:** At baseline, the participants will be asked about their intent to complete the study.
- **Mini-Mental State Examination (MMSE):** This brief cognitive screen will be used to screen for the presence of cognitive impairment. Participants will need to receive a score equal or above 1 SD below the mean score for patient's age and education, or DSM-5 criteria.
- **Working Alliance:** The Working Alliance Inventory (WAI) is an assessment of the

working relationship ("alliance") between the patient and the therapist [31]. The WAI is administered to the patient at baseline and to both the patient and the therapist after each session.

- **The Multitheoretical List of Interventions:** The MULTI is an assessment of use of therapeutic techniques delivered by the therapist.[32] The MULTI will be filled out by the therapist at Baseline, Week 3, Week 5, and Week 9.
- **Anhedonia:** The Dimensional Anhedonia Rating Scale (DARS) is a self-report scale assessing hedonic response over the previous few days.[33]
- **Behavioral Activation:** The Behavioral Activation for Depression Scale (BADS) is designed to measure behaviors related to rewarding experiences that are targeted in therapies like Engage. [34]
- **Depression Severity:** The Montgomery-Asberg Depression Rating Scale [35], a 10-item severity scale, will be used to measure symptom severity. The MADRS is sensitive to change and is appropriate for depressed elders. It also allows us to assess suicidal ideation and level of risk. We will also use the Hamilton Depression Severity Scale, a 17-item measure that is widely used and well validated.[36]
- **The Dimensional Anhedonia Rating Scale (DARS):** The DARS is a 17-item measure which will be used to measure severity of anhedonia and changes in severity over time.[33]
- **Interpersonal Problems:** The Interpersonal Problems Inventory – 32 items (IIP-32) assesses difficulties in interacting with other people [37].
- **Social Support:** The Duke Social Support Index will be used to assessed patients' subjective and instrumental support and amount of social interaction.[38]
- **Loneliness:** The Revised UCLA Loneliness Scale will be used to measure patients' perceived sense of loneliness.[39]
- **Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIP).** A 17-item questionnaire aimed to evaluate patients' anticipatory and consummatory pleasure associated with social and interpersonal interactions with others
- **Treatment Rationale Scale:** A 4-item measure will be used to evaluate patients' expectations of the potential benefits of treatment.[40,41]

MRI Tasks

- **Probabilistic Reversal Learning (PRL) Task:** This task is aimed to measure prediction error and affective salience. In this task, participants select between two simultaneously presented stimuli and receive positive or negative feedback following their response selection. They must learn, through trial and error, which stimulus dimension (color or category) is more likely to lead to positive feedback.[42,43] This task is widely used in the literature and is a component of NIMH's RDoC matrix learning criterion.
- **Social Incentive Delay Task (SID):** We developed a novel SID task, modeled after the Monetary Incentive Delay task (MID), which we will use for our exploratory analyses.[44,45] The SID examines social reward anticipation and receipt (Figure 7). On incentive trials, the participant sees a cue stimulus, human face silhouette, indicating an anticipated social reward. Then, he/she responds as quickly as possible with a button press during target stimulus presentation (White Square). Fast response time is rewarded with 'thumbs up' and happy face. Slow response is punished 'thumbs down' and sad face. On neutral trials, all performance is followed by a neutral face. The SID includes two social reward conditions: a) Standard: feedback from a stranger; b) Personalized: feedback from the patient's therapist (i.e. an individual with likelihood of a high social reward

value).

6.1.1 Screening Visit + Baseline (*several days before start of treatment*)

Screening will include the Major Depression Module and the Screener from the SCID-V to ensure the participant meets the clinical criteria (see exclusion and inclusion criteria section)

- Informed consent
- Medical history and medication history
- Demographic questionnaire
- Brief Antidepressant Questionnaire (BAQ)
- Intent to Complete
- Depression Severity and Anhedonia
- Montgomery Åsberg Depression Rating Scale (MADRS)
- The Dimensional Anhedonia Rating Scale (DARS)
- Behavioral Activation for Depression (BADS)
- Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIP)
- Mini-Mental State Examination (MMSE)
- Interpersonal Problems Inventory – 32 items (IIP-32)
- Duke Social Support Index
- Revised UCLA Loneliness scale

MRI tasks

- Probabilistic Reversal Learning task
- Social Incentive Delay task

6.1.2 Treatment Phase

Monitoring of Clinical State

Study participants' clinical state will be monitored by their study therapists. Therapists and their supervisor will discuss symptoms that may require treatment other than that provided by the study. The supervisor will also be available for phone calls with therapists between supervision sessions. If a participant requires additional care, the therapist and supervisor will collaborate on a referral.

Therapists will administer the Patient Health Questionnaire (PHQ-9) during each therapy session. If a participant endorses suicidal ideation or behavior on item 9 of the PHQ-9 ("Thoughts that you would be better off dead, or of hurting yourself"), the therapist will conduct a thorough safety evaluation. If the therapist determines that the participant is at risk, the therapist will consult with a supervisor and/or with the director of the Weill Cornell Institute of Geriatric Psychiatry to determine a course of action.

Additionally, research assistants will administer the MADRS during research assessments. If a participant endorses suicidal ideation or behavior on item 10 of the MADRS ("This past week, have you felt like life isn't worth living?"), the research assistant will complete the Suicide Risk Assessment protocol (see attachments), which has been approved by NIMH for determining an increase in suicidal ideation. The research assistant will then report the results of the Suicide Risk Assessment to the

participant's study therapist or another clinician in the Institute of Geriatric Psychiatry, who will conduct a thorough safety evaluation if warranted.

Depending on the level of risk, the participant may be encouraged to speak to his/her own clinician; the PI or therapist may call the participant's clinician and/or family member; or the participant may be referred for an evaluation by a clinician who will conduct a thorough assessment via phone or video. . Other urgent risks may necessitate calling 911 or having a family member bring the participant to a local emergency room for evaluation.

6.1.2.1 Visit 1 (baseline; Cycle 1 Day 1)

Assessments will be administered based on assessment schedule above over the course of 9 weeks (See SoA above).

6.1.2.2 Visit 2 (± X day(s))

Assessments will be administered based on assessment schedule above over the course of 9 weeks (See SoA above).

6.1.3 Follow-up Phase

Not Applicable

7. Study Intervention

7.1 Study Intervention/Device Description

We will randomize participants to 9-weeks of either weekly "Engage & Connect" therapy or Symptom Review and Psychoeducation (SRP) provided by licensed or license-eligible clinicians (at least Masters-level social workers or mental health counselors). Therapists will receive training and weekly supervision from the PI in collaboration with a licensed clinical psychologist and member of our research team, to ensure adherence to treatment protocols and address clinical issues. Trained research assistants, unaware of study hypotheses, will assist in administration of ratings and scanning procedures.. Interventions will be delivered via video or phone, in accordance with the institutional policy.

Participants may be lent a tablet during their participation in the study to facilitate remote sessions if they do not have adequate technology at home. When possible, participants may be asked to use a wearable device that we provide during their participation in the study. The wearable device allows for passive sensing of movement (steps), heart rate, and sleep daily. Participants and therapists may be able to review their activity for the week to augment the sessions. Data will be collected from the device's corresponding mobile app (e.g., device-linked app commercially used to extract steps, sleep, and heart rate as described above). No investigational devices or apps will be used to collect or extract data, and the device will be used in accordance with its approved and marketed use.

At the end of the study, participants are required to return the mobile and/or wearable devices. This technology and platform are being used successfully in the other IRB-approved studies at our

ALACRITY center (19-09020810; 19-09020854).

"Engage & Connect"
"Engage" targets the PVS system using 'reward exposure' intervention – engagement in rewarding activities implemented in weekly 'action plans' developed by the depressed patient and the therapist.[22] In patients with negativity bias, apathy, or inadequate emotional regulation, therapists provide targeted interventions so that reward exposure proceeds unimpeded. "Engage & Connect", a modified adapted version of "Engage", focuses on exposure to rewarding activities with significant others. During sessions, the therapist and patient will select a social activity (i.e. interaction with a significant other) and formulate a stepped plan to complete this goal. By week 3, therapists will assess patients' barriers to reward exposure – negativity bias, apathy, inadequate emotion regulation, as well as interpersonal conflicts and social skills deficits, which may hinder social interactions – and address barriers through targeted strategies.

Symptom Review and Psychoeducation (SRP)
SRP is a comparison condition that resembles *what a good clinician does in evaluating, reassuring, and educating a depressed patient*. Each session begins with reviewing the depressed patient's symptoms, then assessing patient's knowledge base about depression. Identifying patient's misconceptions about depression will guide the selection of educational material to be presented in each session. Comprehending depression-related information is *contaminated* by pessimism, denial, misconceptions, and stigma. The role of SRP therapist is to impart valuable information, despite these complexities. Conveying information is a *process*. The SRP therapist needs to be aware of "where the patient" is and offer information for which he/she has *readiness to accept*. SRP therapists do not engage in other interventions. Arguably, SRP is a condition with: 1) *non-specific active therapeutic ingredients*; 2) *little overlap* with the therapeutic ingredients of "Engage & Connect"; and 3) *exposure* of patients to therapists equal to that of "Engage & Connect". We used a similar comparison condition in a recently completed psychotherapy study of post-stroke depression and found that SRP leads to reduction in depression severity (R01 MH096685, PI: Alexopoulos).

7.2 Availability

Not Applicable

7.3 Acquisition and Accountability

Not Applicable

7.4 Formulation, Appearance, Packaging, and Labeling

Not Applicable

7.5 Product Storage and Stability

Not Applicable

7.6 Preparation

Not Applicable

7.7 Dosing and Administration

All participants will receive 9- weeks of psychotherapy, either “Engage & Connect” or “SRP”, as indicated above.

7.7.1 Dosing Delays/Dose Modifications

Not Applicable

7.8 General Concomitant Medication and Supportive Care Guidelines

Not Applicable

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), psychosocial interventions will continue for a period of 9 weeks.

7.10 Duration of Follow Up

Participants who choose to discontinue the study will be asked and encouraged to complete research assessments for the remaining weeks per their agreement.

7.11 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomly assigned to 9-weeks of either “Engage & Connect” psychotherapy or “SRP” psychotherapy. Therapists and research assistants administering clinical rating will remain unaware of study hypotheses. Trained research assistants unaware of study hypotheses will collect weekly clinical and self-report ratings at each study time point.

7.12 Study Intervention/Follow-up Compliance

Adherence to intervention will be monitored through therapist training and supervision: Training will include: a) Review of treatment manual (1 hour) and videotaped training session describing the treatment protocol and therapeutic techniques (1 hour), followed by video or in-person Q&A session with a trainer (either the PI or a licensed clinical psychologist with expertise in “Engage”); b) role-play session with the trainer to practice skills; c) 3 practice sessions with an actor-patient to evaluate adherence to treatment using the “Engage Adherence Scales” adapted to Engage & Connect and “SRP Adherence Scale” adapted from previous psychotherapy trial which used a similar intervention (R01 MH096685, PI: Alexopoulos); d) Therapists will be required to achieve a ‘good’ fidelity score (≥4) on at least 3 sessions; e) Weekly supervision will focus on prevention of skill drift and maintenance of fidelity.

Therapy sessions will be video or audio-recorded for the purposes of supervision and evaluation of therapist adherence to the therapy protocol (e.g., therapist interventions, therapeutic interactions, etc.). These recordings will not be labeled with information such as participants’ name, date of birth, or other identifying information. Therapists will meet with a supervisor weekly for supervision, during

which corrective feedback will be provided to therapists that show "skill drift" (i.e. fidelity scores < 4). Recordings samples may be processed by a transcription service in order to obtain research grade transcriptions while maintaining privacy and data safety regulations. The files will only be labeled by an alphanumeric code and remain completely separate from any identifying information documentation. Because these recordings may include personal identifiable information (PII) or protected health information (PHI), we treat all samples as confidential data. Samples may be transcribed by study staff, TranscribeMe, or Speech to Text Watson IBM software. If needed, files will be transferred using Secure File Transfer protocols managed by WMC ITS. Speech to Text Watson IBM follows strict data safety regulations stores data on an encrypted cloud that requires user authentication for access, and all data are secured by encryption both while stored in the cloud and in transit.

Patient adherence to intervention (i.e. attendance) will be monitored by the PI and staff: We have developed procedures to minimize risk to our participants, increase retention, and create conditions that make study participation as comfortable as possible. To this end, we will educate participants regarding study procedure and commitment during the informed consent process. We will schedule appointments early in the day or at the participants' convenience. Our team will call participants prior to each appointment to provide reminders and assist with transportation arrangements. Funds for transportation are included in our budget in order to increase accessibility. The PI or staff member will accompany participants to all MRI scans and be present during scanning sessions in order to maximize comfort and address any questions or concerns that may arise. The PI will collaborate with trained and experienced technicians at our MRI Center to reduce wait time and optimize efficiency of the MRI procedures. The PI will train study personnel in recruitment and data collection procedures with an emphasis on clear communication, sensitivity, and multicultural competence. These measures have led to high retention rates and participant satisfaction in our Institute's randomized clinical trials. Based on data collected in previous psychotherapy trials at the Institute, we anticipate an attrition rate of ~10%, which has been incorporated into our power analyses.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Efforts will made to increase retention and reduce dropout (see above). In the event that a participant chooses to discontinue the study, the PI and the clinician will discuss with the participant, identify reasons for discontinuation and invite the participant to continue to attend the remaining research assessments. The PI and staff will provide the participant will an appropriate referral for alternative treatment if needed and/or requested by the participant. In the event of an emerging suicide risk, the PI will follow procedure for suicide risk management (See Section 13 for full description of procedures). The study may be discontinued and the participant may be referred for outpatient or inpatient treatment based on clinical indication. If a patient is at imminent risk for harming themselves and unwilling to agree to psychiatric hospitalization, involuntary admission may be needed.

8.2 Participant Discontinuation/Withdrawal from the Study

- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Worsening of depression symptoms and/or emerging suicide risk that warrants a higher level of care than provided within the study (e.g. psychiatric hospitalization).
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who give informed consent and are randomized but do not receive the study intervention may be replaced. Subjects who give informed consent, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may be replaced.

8.3 Lost to Follow Up

Not Applicable

9. Correlative/Special Studies

Not Applicable

9.1 Laboratory Correlative Studies

Not Applicable

9.1.1 Title – Laboratory Correlative Study #1

9.1.1.1 Collection of Specimen(s)
9.1.1.2 Handling of Specimen(s)
9.1.1.3 Shipping of Specimen(s) (if multicenter)
9.1.1.4 Site(s) Performing Correlative Study (if multicenter)

9.2 Special Studies

Not Applicable

9.2.1 Title – Special Correlative Study #1

9.2.1.1 Assessment
9.2.1.2 Method of Assessment
9.2.1.3 Timing of Assessment

10. Measurement of Effect

Treatment effect will be measured by change in depression severity, resting state functional connectivity in PVS regions, and behavioral activation over the course of treatment.

10.1 Response Criteria

Reduction in depression severity over the course of 9 weeks of treatment (slopes of change in MADRS scores will be calculated within mixed-effects model approach, see Statistical Analysis).

10.2 Duration of Response

Duration of response will be evaluated as reduction in depression severity (measured by the MADRS scale) over the course of 9 weeks of treatment.

10.3 Progression-Free Survival

Not Applicable

10.4 Other Response Parameters

Other endpoints and the criteria for their measurement should be entered below or reference should be made to the protocol section where these criteria may be found.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be

submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document. Due to COVID-19, informed consent will be obtained over the phone. In our experience, many older adults do not have access to technology that would allow them to consent electronically. An information sheet will be emailed to the participant so that it can be viewed by the participant (or mailed if email is not used). This will allow the participants to review the form thoroughly. Participants will be encouraged

to discuss any concerns or questions they may have with the member of the research team who is conducting the consent. Members of the research team will ensure there is sufficient time to pose questions and will be in contact with the Principal Investigator regarding any potential concerns that need to be addressed. When possible, consent will be conducted over video call within a HIPAA-compliant platform (i.e. Zoom) and the participant could review the consent, presented over video, during the process. Zoom invitations will be sent to participants via email, collected at the initial phone screen phase as contact information and stored in a secured folder that only authorized study team members can access. The same procedures will be used for consent of therapists participating in this study. After the consent form has been reviewed, if informed consent is obtained, the research will sign the "Researcher's statement" portion of the consent form digitally through RedCap in order to have documentation on file.

Participants may opt for an in-person informed consent meeting, which will be conducted in a private interview room located in the Weill Cornell Medicine Psychiatry Department. Participants will have the opportunity to discuss the study in detail with a member of the research study team, ask any questions they may have, and provide their written informed consent by signing the physical consent form. Only the participant and the researcher obtaining consent will be present for the in-person consent procedures.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

*All investigator-initiated trials **must** include a study statistician assigned by the Division of Biostatistics and Epidemiology or approval to use alternate biostatistician personnel. Please contact Dr. Paul Christos (pac2001@med.cornell.edu) for additional information and assignment*

of a study statistician.

Describe the statistical methods that will be used to analyze the data (chi square, t-test, correlation, etc.)

12.1 Study Design/Endpoints

The principal aim of this pilot study is to examine if exposure to meaningful social rewards during psychotherapy, engages reward circuitry and improves mid- and late-life major depression. The "reward exposure" of this study will consist of meaningful social activities with significant others ("Engage & Connect"). The study will be a pilot RCT that will compare 9-week "Engage & Connect" vs. a Symptom Review and Psychoeducation condition (SRP) for adults older than 50 years with major depression and test the following hypotheses:

During the 9 week course of "Engage & Connect" treatment there will be an:
H1. *Increase in rsFC of the PVS.*
H2. *Increase in behavioral activation (BADS scale)*
H3. *Reduction in depression severity (MADRS scale).*

SH. *In "Engage & Connect" treated participants, change in:* ***SH1a)*** *rsFC of the PVS and* ***SH1b)*** *behavioral activation (BADS) will predict subsequent reduction in depression severity (MADRS). These relationships will not be observed in the SRP treated group. The rationale of this hypotheses is based on the theory that the "Engage & Connect" mechanism of action is reconditioning the PVS, while SRP relies on non-specific mechanisms of action.*

To further investigate the PVS correlates of social reward, we developed a social reward fMRI paradigm, modeled after a monetary incentive delay task[44] and plan to use it in analyses for hypothesis generation.

Analysis Plan
H1, H2, H3: *During the 9-week course of "Engage & Connect" there will be an:*
H1. *Increase in rsFC of the PVS*
H2. *Increase in behavioral activation (BADS)*
H3. *Reduction in depression severity (MADRS).*
We will implement mixed-effects models using the *lme4* package in R.[46] For **H1**, **H2**, and **H3** we will include subject-specific random intercept and fixed effects for time-related parameter(s). For **SH**, We will estimate a separate mixed-effects model for each of the four a-priori PVS ROIs. Models of PVS ROIs will include change from baseline to Week 5, Week 5 to 9 and models of behavioral activation (BADS scale) and depression severity (MADRS scale) and will include change from baseline to Week 3 to Week 5 and Week 5 to Week 9 as independent variables. Dependent variables will be depression severity at Weeks 5 and Week 9 for PVS ROI models and at Weeks 3, 5, and 9 for BADS model. We will include fixed effects for age, gender, antidepressant use, or any other variable that will be unbalanced between the groups. We will explore in all models the inclusion of higher order(s) of the time variable (e.g., quadratic, cubic, etc.) and choose the final model based on Bayesian Information Criterion (BIC).[47] We will control the overall Type I error rate at 5% using Holm's stepdown procedure to adjust for four post-hoc multiple comparisons (four PVS ROIs) in **H1** and five comparisons (four PVS ROIs and BADS) in **SH**.
SH. *In "Engage & Connect" treated participants, change in:* ***SH1a.*** *rsFC of the PVS; and* ***SH1b.***

Behavioral activation (BADS) will predict subsequent reduction in depression severity (MADRS). These relationships will not be observed in the SRP treated group. Five mixed-effects models (as described above) will investigate whether change in the predictor is associated with subsequent change in depression severity (MADRS).

Power Analysis

Our primary outcome is change over 9 weeks of "Engage & Connect" in resting state functional connectivity (rsFC) of the Positive Valence System (PVS) (**H1**). Our secondary outcome measures are change in behavioral activation measured by the Behavioral Activation for Depression Scale (BADS) (**H2**); and depression severity, measured by the Montgomery-Asberg Depression Rating Scale (MADRS) (**H3**). Our secondary hypothesis (**SH**) investigates whether early change in the predictors (i.e. rsFC of the PVS and BADS change) predict subsequent change in depression severity (MADRS). We will measure rsFC at baseline, Week 5, and Week 9 and behavioral activation and depression severity at baseline, Week 3, Week 5, and Week 9.

12.2 Sample Size/Accrual Rate

The annual participant recruitment plan is as follows: 11 participants in Year 1 (5 SRP, 6 "Engage & Connect"), 14 in Year 2 (7 per group), 17 in Year 3 (9 SRP, 8 "Engage & Connect"), and 18 in Year 4 (9 per group). MRI scans and clinical assessments at Weeks 5 and 9 for 10 participants will be completed in the first four months of Year 5. Statistical analyses will be conducted in Year 6 and Year 7.

12.3 Stratification Factors

The sample will be stratified by age so that 50% of participants recruited are between ages 65-85 and 50% are between ages 50-65. The stratification is aimed to allow investigation of the research questions in a balanced sample of middle-aged and older adults with major depression.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

We will implement mixed-effects models using the *lme4* package in R.[46] For **H1**, **H2**, and **H3** we will include subject-specific random intercept and fixed effects for time-related parameter(s).

12.4.2 Analysis of Secondary Endpoints

For **SH**, We will estimate a separate mixed-effects model for each of the four a-priori PVS ROIs. Models of PVS ROIs will include change from baseline to Week 5, Week 5 to 9 and models of behavioral activation (BADS scale) and depression severity (MADRS scale) and will include change from baseline to Week 3 to Week 5 and Week 5 to Week 9 as independent variables. Dependent variables will be depression severity at Weeks 5 and Week 9 for PVS ROI models and at Weeks 3, 5, and 9 for BADS model. We will include fixed effects for age, gender, antidepressant use, or any other variable that will be unbalanced between the groups. We will explore in all models the inclusion of higher order(s) of the time variable (e.g., quadratic, cubic, etc.) and choose the final model based on Bayesian Information Criterion (BIC).[47] We will control the overall Type I error

rate at 5% using Holm's stepdown procedure to adjust for four post-hoc multiple comparisons (four PVS ROIs) in **H1** and five comparisons (four PVS ROIs and BADS) in **SH**.

12.5 Interim Analysis

Interim Analysis will be conducted periodically to ensure adequate data collection and protocol procedures in accordance with NIMH policy and reporting requirements.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

Not Applicable

12.6.2 Evaluation of Response

All subjects included in the study will be evaluated for treatment response at treatment end (See analysis plan above)

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

Adverse event (AE) monitoring and reporting is a routine part of clinical research. Safety is monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical over-read of all MRI scans, etc.

Protocols for Addressing Adverse Events: All participants will have access to the telephone number of the PI and can call in an emergency. The Department of Psychiatry and the Weill Cornell Institute of Geriatric Psychiatry is located in within New York-Presbyterian Hospital, which has a 24-hour emergency call system, should participants require urgent evaluation and care. Information how to use the hospital's call system will be provided to all participants. The strategy for reporting adverse events is as follows:

1. Clinical or study personnel will immediately notify the PI.
2. The PI will consult with a senior clinician at the Institute to discuss potential risks and decide on a plan of action.
3. The PI will notify the Weill Cornell IRB about adverse events (AEs).
4. If the adverse event is serious (SAE), the NIMH will be informed.

Procedures for management of suicide risk: We will exclude participants who endorse intent or plan to attempt suicide in the near future at screening. During the study, participants' clinical state will be monitored by their therapists. Therapists and their supervisor will discuss symptoms that may require treatment other than that provided by the study. Therapists will administer the Patient Health Questionnaire (PHQ-9) during each therapy session. If a participant endorses suicidal ideation or behavior on item 9, the therapist will conduct a thorough safety evaluation. If the participant is at risk, the therapist will consult with a supervisor to determine a course of action. Additionally, the research assistant (RA) will administer the MADRS during research assessments. If a participant endorses suicidal ideation or behavior on item 10, the RA will complete the Suicide Risk Assessment protocol, approved by NIMH for determining an increase in suicidal ideation. The research assistant will then report the results to the study therapist, the PI, and the supervisor, who will conduct a thorough safety evaluation if warranted. Depending on the risk, the PI or therapist may call the participant's clinician and/or family member; or the participant may be referred for an evaluation by a study clinician available at the time via phone or video. Other urgent risks may necessitate calling 911 or having a family member bring the participant to a local emergency room for evaluation.

Procedures for managing incidental clinically significant MRI findings: All MRI scans will be read by a board-certified Weill Cornell Medicine neuroradiologist. If a clinically significant finding is identified, an MD clinician investigator on the study protocol will notify the participant (in person or via phone call) and discuss the finding. With the participant's permission, his/her primary care physician will be notified by the PI, and the participant will be informed and advised to take clinically appropriate action. The proposed MRI scan sequences are not optimized for diagnostic purposes and might not reveal all clinically significant abnormalities. Participants are informed that the MRI scan is not intended for diagnostic purposes, thus, undergoing the MRI scanning session is not comparable to receiving a clinical MRI exam.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

(Include additional sections as needed for all agents of devices being utilized in the research study.)
Include expected risks for agent or device.

13.1.2 Adverse Event Characteristics and Related Attributions

Reportable events for this study are based on relevant NIMH-defined designations:
Adverse event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).
External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.
Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced

by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*
Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).
Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/compliance/human-subjects-research/institutional-review-board/human-research-compliance/immediate

13.1.5 Reporting Events to Participants

See above procedures for reporting incidental MRI findings to participants

13.1.6 Events of Special Interest

The strategy for reporting adverse events is as follows:

1. Clinical or study personnel will immediately notify the PI.
2. The PI will consult with a senior clinician at the Institute to discuss potential risks and decide on a plan of action.
3. The PI will notify the Weill Cornell IRB about adverse events (AEs).
4. If the adverse event is serious (SAE), the NIMH will be informed.

13.1.7 Reporting of Pregnancy

Not Applicable

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. *(Modify as necessary)*

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

https://research.weill.cornell.edu/compliance/human-subjects-research/institutional-review-board/human-research-compliance/immediate

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

Not Applicable

13.2.3 Reporting of SAE to <*Insert Pharmaceutical Company Name*>

Not Applicable

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

Reporting of UPIRTSOs will follow the guidelines of the study sponsor, the NIMH, which are described here: https://www.nimh.nih.gov/funding/clinical-research/nimh-reportable-events-policy.shtml
The reporting of UPIRTSOs applies to non-exempt human subjects research conducted or supported by NIMH. An incident, experience, or outcome that meets the definition of an UPIRTSO generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Examples of corrective actions or changes that might need to be considered in response to an UPIRTSO include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

The NIMH and Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The PI, Dr. Solomonov, will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Safety and Monitoring Board (DSMB), and the NIMH Program Officer. All reports will be in writing, prepared and signed by the PI. These reports should indicate that the monitoring entities (i.e., the PI and IRB, ISM and/or DSMB) and appropriate regulatory entities (e.g., OHRP, FDA) have been notified in accordance with the approved monitoring plan and federal regulations.
The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 10 business days of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within 10 business days of the IRB's receipt of the report of the problem from the investigator.

A timeline and flowchart for the reporting of all reportable events can be found here: https://www.nimh.nih.gov/funding/clinical-research/nimh-reportable-events-policy.shtml

15. Data and Safety Monitoring Plan (DSMP)

In consultation with NIMH program officers, we will establish a Data Safety Monitoring Board (DSMB) that oversees our study activities to ensure the safety of participants, the validity of our findings, and assesses the need for further data collection. The DSMB responsibilities will include:

1. The review of protocols, informed consent procedures, and safety plans.
2. The monitoring of study progress as reflected in the rate of participant recruitment, adherence to timetables, and the quality of collected data.
3. The evaluation of the study's risk-benefit ratio as new evidence-based treatments become available.
4. The determination of whether the study should be continued, modified, or terminated in light of adverse events.

5. The analysis of interim findings and the confidentiality with which they are being maintained.
6. Consultations with the investigators regarding protocol measures that impose undue burden on study participants or that pose possible ethical concerns or conflicts of interest.

We will also provide the DSMB copies of all reports submitted to NIMH and manuscripts submitted for publication in professional journals.

We will use the adverse event grading guidelines provided by the Office of Research Integrity and Assurance at Weill Cornell Medicine. We will report all adverse events to the IRB in the timeline indicated by Weill Cornell's Human Research Protections Program Immediate Reporting Policy. As required, we will report in writing serious adverse events to the IRB within 5 days from the time that we become aware of their occurrence. We will report all other adverse events to the IRB monthly. We will submit individual adverse events, as well as summary tables every six months to the DSMB, but we will respond to the DSMB recommendation if a higher frequency of reporting is desirable.

If there is a suicide attempt or if a participant has increased suicidal ideation while in the study, and after the PI takes the appropriate clinical steps for the participant's safety,we will report to the IRB and DSMB according to guidelines. We will provide the DSMB summaries of adverse events over specified time periods and report all adverse events to the Weill Cornell IRB within the timeframe specified by IRB regulations. The PI will disclose to the NIMH reportable events in time frame consistent with NIH's Reportable Events Policy.

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Appendix A