

**NEW YORK STATE PSYCHIATRIC INSTITUTE - COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY
INSTITUTIONAL REVIEW BOARD**

PROTOCOL SUMMARY FORM

Date Received: _____

IRB # 5971

Version Date: **06/02/15**

Title of Proposed Study: OPTIMIZING TREATMENT OF COMPLICATED GRIEF

Name and Title of Principal Investigator M. Katherine Shear

Research Department Late Life Depression Telephone # 212-851-2176 Email ks2394@columbia.edu

List Co-Investigators: (or Sponsor if Principal Investigator is a research fellow or student):

A.) Naihua Duan B.) Charles Reynolds (University of Pittsburgh) C.) Naomi Simon (Massachusetts General Hospital)
D.) Sidney Zisook (University of California San Diego)

SITES AT WHICH STUDY/PROCEDURES WILL BE CONDUCTED: (check all that apply)

- P.I. Presbyterian Hospital Creedmoor
- Staten Island Research Clinic Westchester DES
- Community (specify)
- Other (specify)

FUNDING INFORMATION:

List grant name and grant number (if available): Optimizing Treatment of Complicated Grief (2R01MH060783-06A1)

Grant submitted on Nov. 5, 2008 to NIMH through CU grants office.
date (agency) (RFMH or CU: indicate which)

Grant currently funded through _____ grants office.
(RFMH or CU)

Grant supported by Pharmaceutical Company _____ through _____ grants office.
(name) (RFMH or CU)

PIRSG NARSD Private Foundation

No External Funding

NOTE: WRITE IN LAYMAN'S LANGUAGE, WITHOUT JARGON, TECHNICAL

TERMS OR UNDEFINED ABBREVIATIONS.

- I. ABSTRACT: Describe concisely objectives and methods of study.
DO NOT EXCEED 20 LINES

Complicated grief (CG) is a debilitating condition that is estimated to affect millions of people in the United States alone. We conducted the first RCT to address this condition (MH60783) and confirmed efficacy of a targeted

psychotherapy, complicated grief treatment (CGT). Participants in our prior study continued stable antidepressant medication while receiving CGT or Interpersonal Psychotherapy (IPT). Individuals taking antidepressants had better outcome in both treatments, though CGT was superior to IPT when administered with (60% responders v. 40%) or without (42% v.19%) antidepressants. Studies of antidepressant medication alone have shown mixed results with SSRIs appearing to be promising. However, there has been no randomized controlled study of SSRIs for CG. Determining the efficacy of SSRI treatment for CG, when administered with and without CGT, is of great public health importance. We assembled 4 groups of investigators with strong track records in bereavement research and extensive experience with intervention studies and multicenter projects, to conduct a study of citalopram (CIT) efficacy. We plan to enroll 1021 participants (106 at Columbia) with a primary diagnosis of Complicated Grief over 4.5 years, in order to randomly assign n=480 (n=50 at Columbia) to receive treatment with CIT with clinical management (CIT-CM), PBO-CM, CIT-CM + CGT or PBO-CM + CGT over a period of approximately 16 weeks. We want to determine whether citalopram shows a better response than placebo, when administered either with or without CGT. We will also address the question of whether CIT-CM performs as well when administered alone as it does when administered with CGT. The Columbia site will recruit 50 study participants and serve as the central coordinating site. We will maintain the database and oversee the biostatistical procedures of this study. Our role is to facilitate cross-site communication and ensure uniformity of accrual, consent, assessment, randomization, and treatment procedures.

II. Titles/names of persons designated to obtain consent.

M. Katherine Shear, M.D.

D.P. Devanand, M.D.

Shanthi Mogali, M.D.

Tino T. Huynh, M.D.

Steve Roose, MD

Bevin Campbell, PhD (training consent only)

Natalia Skritskaya, PhD (training consent only)

Greg Pelton, MD

III. RESEARCH PLAN

1. HYPOTHESES TO BE TESTED: If there are no specific hypotheses, describe study goals.

- A. CIT-CM will produce a significantly higher response rate than PBO-CM wherein CIT-CM will produce significantly greater improvement in complicated grief symptom severity, functional impairment, and associated symptoms.
- B. CGT + CIT-CM will produce a significantly higher response rate than CGT + PBO-CM wherein CGT + CIT-CM will produce significantly more improvement in complicated grief symptom scores, functional impairment, and associated symptoms.
- C. CGT + CIT-CM will produce a significantly higher response rate than CIT-CM wherein CGT + CIT-CM will produce significantly more improvement in complicated grief symptom scores, functional impairment, and associated symptoms.
- D. Exploratory Hypothesis:
 - a. Participants who meet criteria for MDD will show significantly greater difference between CIT-CM and PBO-CM than those without co-occurring MDD.
 - b. Treatment completion will partially mediate the effect for CIT-CM + CGT vs. PBO-CM + CGT.
 - c. Improvement in symptoms of depression will partially mediate the treatment effect for CIT-CM vs. PBO-CM and the treatment effects for CIT-CM + CGT vs. PBO-CM + CBT.

2. RECRUITMENT METHODS

- A. Recruitment Methods and Description of Approach to Research Subjects: Attach to this form any letters to be sent, texts of advertisements, etc., if available now. If not available now, they must be submitted to the IRB prior to the initiation of recruitment procedures.

Recruitment will be a major focus of this project. As the coordinating center, we will assist in educating and enlisting the cooperation of health and mental health providers at local institutions and in the community at large. We will advertise through the distribution of brochures and will respond to requests for media interviews. We will contact local and regional physicians, mental health professionals, community mental health and social service agencies, churches and other religious agencies and grief support organizations. We will encourage word-of-mouth referrals. On-site recruitment for this protocol will overlap in the first few years with our ongoing study of CGT in older adults (MH70741). We expect that this will create synergy for recruitment to both studies. Adults aged 18-59 are not eligible to participate in MH 70741 and we expect to easily recruit 10 younger patients per year.

Interested individuals will be screened over the telephone. We will administer the 5-item Brief Grief Questionnaire (BGQ) to identify potential study participants. Patients who are 18 years of age or older, bereaved for at least 6 months, and score 5 or above on the BGQ, will be invited to undergo an in-person assessment to establish eligibility and explain the study protocol. As the coordinating center, we will organize weekly communication among screeners across sites and prepare reports of screening visit outcomes.

We plan to follow recommendations made by bereaved parents who participated in a recently published longitudinal study [1]:

- Give us thorough, and written information before research participation
 - Listen respectfully to the mementos we find relevant to show, or tell you about
 - Give us enough time and quietness for the interview
 - Let us meet trained interviewers with knowledge of the bereavement process
 - Conduct the interview in an empathetic and cautious way
 - Give us the opportunity to reflect and ask questions during and after the interview
 - Some of us might need extra time and care before, during and after the interview
 - Discuss the result with some of us if possible
 - Send us the report, let us read it and give feed-back
- B. If subjects from other studies are to be asked to participate, list studies with their IRB #, principal investigator and title.

N/A

C. Subjects: Specify sample sizes, sex, ethnicity, age range, diagnostic group and other relevant characteristics. The composition of the proposed study population must be described (by number or percentage) in terms of (a) gender and (b) racial/ethnic group. If one gender and/or minorities are excluded or inadequately represented, a rationale should be provided.

Total N across the 4 sites = 1021 N to be recruited at NYSPI = 125 Age range: 18-95

Sample Description:

- i. We expect to screen n = 1952 (592 per major site, n = 176 at Columbia); we expect n = 1021 (n=125 at Columbia) of these to meet eligibility criteria and sign consent for a baseline assessment. Of the 1021 (125 at Columbia) individuals that undergo baseline assessment, we expect 480 (50 at Columbia), 47%, will meet eligibility criteria and agree to be randomized (n=143; n=50 at Columbia) to each of the treatments. Among these study participants we are committed to randomizing at least 40 suicide bereaved individuals across all sites and at least 10 at Columbia.
- ii. Participants will range in age from 18-95 years.
- iii. No minority group is excluded from research participation. We plan to enroll 25% racial and ethnic minorities and 10% English speaking Hispanic individuals. Specifically, we expect to enroll participants according to the following ethnic distributions: 5% Asian, 15% Black or African American, and 80% White.
- iv. We expect to enroll approximately 75% females.

3. STUDY INCLUSION AND EXCLUSION CRITERIA (list in outline form)

<u>INCLUSION CRITERIA</u>	<u>METHOD OF ASCERTAINMENT</u>
1. Males or females between the ages of 18 - 95 (inclusive)	Screening interview
2. A negative urine toxicology, i.e., a urine specimen that does not test positive for use of drugs of abuse	Urine toxicology at Screening
3. Diagnosed with Complicated Grief and this is the patient's most important (primary) problem	PI judgment based upon review with IE of SCID interview including a module for CG and direct question to the patient ^a
4. Have a score of ≥ 30 on the Inventory of Complicated Grief (ICG)	Self-report questionnaire (ICG)
5. Ability to give informed consent	Intake interview with investigator
6. Fluent in English	Intake interview and self-report
7. Willingness to have sessions audiotaped	Intake interview/ informed consent
8. Willingness to undergo random assignment	Intake interview/informed consent

<u>EXCLUSION CRITERION</u>	<u>METHOD OF ASCERTAINMENT</u>
1. Patients diagnosed with one or more of the following disorders: lifetime Schizophrenia or other psychotic disorder, current (past 6 months) substance abuse or dependence (except for nicotine), Lifetime Bipolar Disorder not regulated by mood stabilizing drug, Bipolar Disorder, current manic episode or Dementia.	SCID - IV, Clinical intake interview, Urine drug test, Montreal Cognitive Assessment (MOCA) < 21
2. Active suicidal or homicidal ideation, or judged to be at serious suicide risk.	Intake clinical interview; Columbia Suicide Scale
3. Pregnant or lactating women and women of childbearing potential not using medically accepted forms of contraception	Clinical interview, Urine pregnancy test
4. Acute, unstable or severe medical illness such as (but not limited to) stroke, epilepsy, or other neurodegenerative disorders, metastatic or active cancer, hepatic disease, or primary renal disease requiring dialysis.	Intake medical assessment (history, physical laboratory tests and/or review of medical records)
5. Patients with QTC > 460msec.	Baseline medical evaluation, including ECG and history of heart problems (i.e., syncope or family history of sudden death)
6. Current use of antidepressant medication or concurrent psychotherapy	Intake clinical interview. Antidepressant medication will be tapered when appropriate ^b
7. Prior intolerance of citalopram	Intake clinical interview
8. Prior failed treatment with citalopram or Lexapro, or current use of citalopram or Lexapro	Intake clinical interview
9. Pending or active disability claim or lawsuit related to the death	Screening and/or intake clinical interview

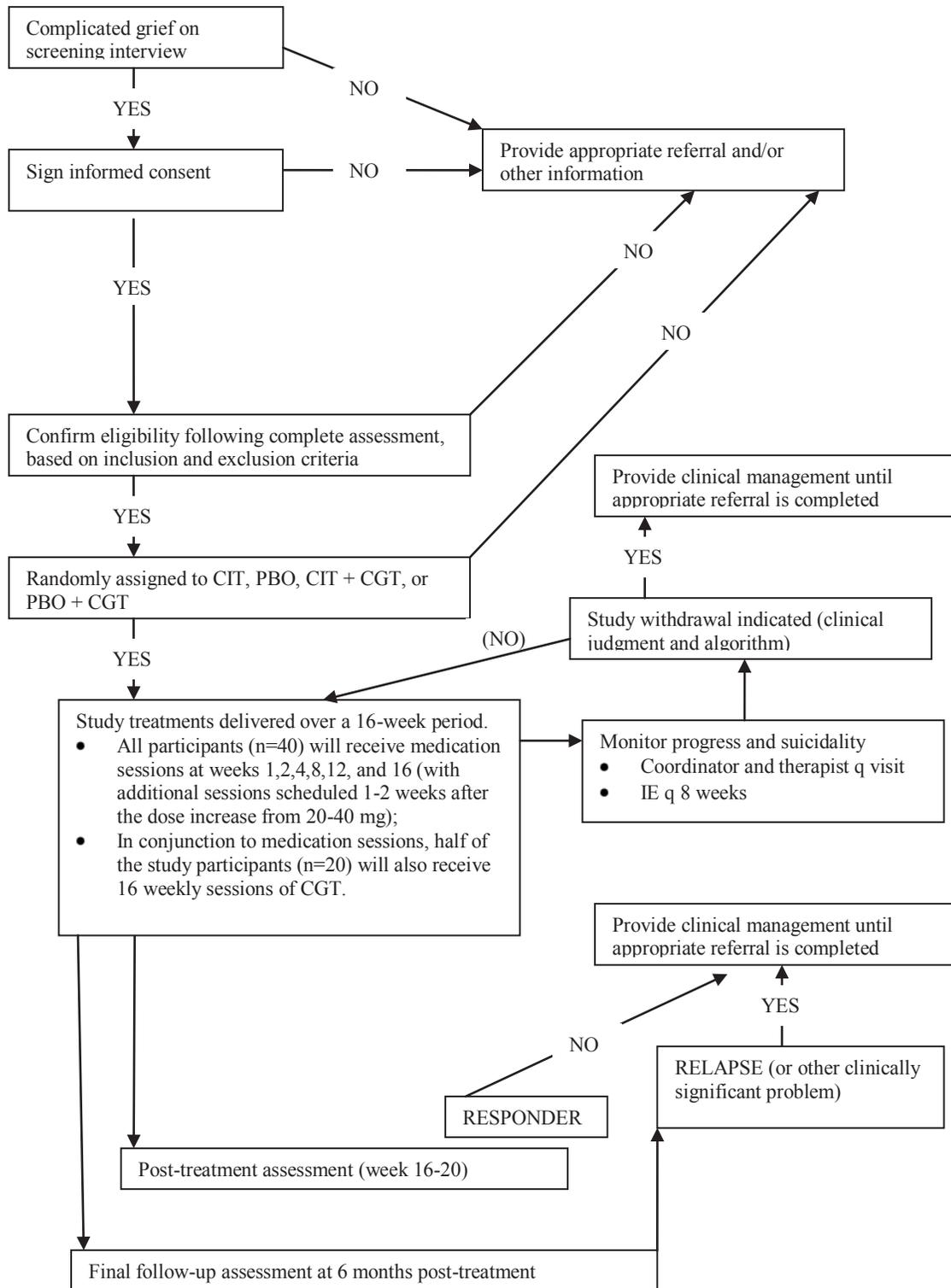
^a Trained evaluators conduct a SCID interview with an overview of current life problems and a module focused on a systematic review of CG symptoms and a question regarding whether grief is the patient's most important problem. This information is presented at an intake review with the PI and a decision is made whether grief is the primary problem. We have used this procedure in our other studies and have occasionally determined that a person who meets grief symptom inclusion criteria is more distressed by a different life problem or by other symptoms.

^b Antidepressant medication will be tapered according to procedures described on pages 6, 10, 16-17.

4. STUDY PROCEDURES: Please provide a flow-chart (diagram) of study procedures.

A. Provide details of all procedures including credentials (R.N., M.D.) of person(s) conducting each procedure including interviews. If medication is to be used, specify dose and dose schedule. For more complex designs, flow diagrams are helpful.

Figure 1: Study Flow Chart



STUDY PROCEDURES AND CLINICAL ASSESSMENTS

The following is an explanation of the procedures included in Figure 1.

SCREENING:

Potential study participants will be identified during a preliminary telephone screening. Screening will be performed by the research coordinator, other trained and supervised research staff, or supervised graduate students. Participants will provide verbal consent for screening. Demographic data and information related to the loved one's death (such as the relationship of the deceased to the potential participant and the date of the death) will be assessed at this time. In addition, the Brief Grief Questionnaire (BGQ; [2]) will be administered in order to determine initial eligibility of the potential subject. Individuals identified through the initial screen as having an BGQ score ≥ 5 , who are at least 6 months post loss, and are interested in participating in the research study will be scheduled for an assessment visit that includes a meeting with a study investigator who will obtain written informed consent prior to baseline assessment data collection. Individuals will sign consent to participate in a 3-step process: 1) Baseline assessment and determination of treatment study eligibility, 2) Randomization of eligible and willing participants to one of the four treatments, and 3) post-treatment assessment at week 16-18 followed by a final follow-up assessment at 6 months post-treatment (week 40).

STEP 1: Baseline assessment and determination of treatment study eligibility (see figure 1)

PRETREATMENT ASSESSMENT:

Screen-positive patients sign informed consent describing a 3-step procedure in which they will first undergo evaluation to determine eligibility for the treatment study. If they are not eligible, we will help them find an appropriate referral for treatment outside of the study. After consent is signed, patients will undergo a baseline assessment including instruments listed in table 1 below. A trained mental health professional will administer the following assessments: SCID, Structured Interview for Complicated Grief, Columbia Suicide Scale (CG-focused version), Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A), Clinical Global Impression Severity Scale – CG version, and Montreal Cognitive Assessment (MOCA). Study participants will be asked to complete the following self report measures: Inventory of Complicated Grief (ICG), Grief Related Avoidance Questionnaire (GRAQ), Loss-focused Impact of Events Scale (IES), Social Support Questionnaire, Pittsburgh Sleep Quality Index, Davidson Trauma Scale, Work and Social Adjustment Scale (WSAS) and the modified Yearning Questionnaire. Patients will be required to have a medical evaluation by their PCP within six months of entry into the study or a medical evaluation at the study site by a study physician. Patients receiving a medical examination at the study site will undergo a basic physical exam and blood draw (electrolytes, liver function tests, CBC with differential, thyroid function test). Medical Review Form and Treatment History Form will be completed. All patients will undergo a urine toxicology screen and will have their vital signs measured. A urine-pregnancy test will be performed on all female subjects of childbearing potential at baseline. Patients' medical information will be reviewed prior to determining eligibility for randomization, in particular to make sure that history of cardiac problems is evaluated and QT interval ≤ 460 msec.

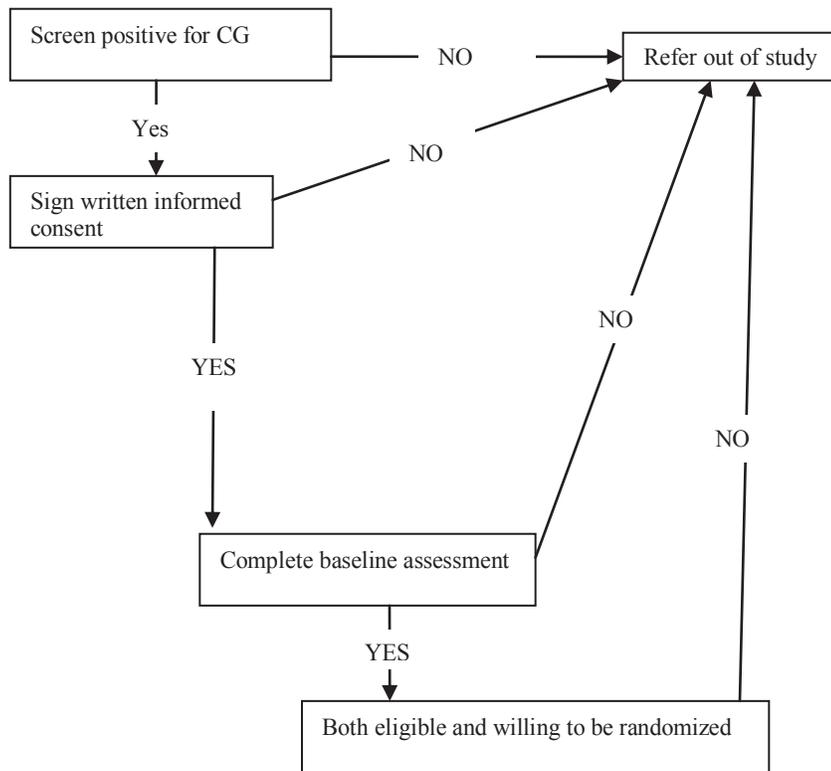
Patients will be required to taper and discontinue ineffective antidepressant medication when entering the protocol. Taper will be initiated following a preliminary assessment focused on inclusion and exclusion criteria to establish provisional study eligibility. Only those deemed eligible will be invited to discontinue medication. A study physician will monitor the taper procedure and will communicate with the prescribing physician in doing so. Participants taking an MAOI would need to discontinue the MAOI at least 14 days before starting treatment with citalopram. We will maintain close contact with the participant during the taper process, both in person (at least once weekly) **and** by phone to monitor clinical state. We will also communicate with a family member/close friend and with the original prescriber of the medication, with the subject's permission, to seek concurrence with protocol participation. Detailed procedures for deciding when to taper and for management of risks related to medication discontinuation are described in the study risk section on page 15-16 of the this proposal. The standard baseline assessment will be performed at approximately one week following completion of the taper.

If the patient meets protocol inclusion and no exclusion criteria, and is willing to be randomized, they will proceed to step 2. If the patient does not proceed to step 2 and meets inclusion and no exclusion criteria outlined below, he or she may be invited to participate as a training case. We expect to recruit up to 75 participants, male or female, who have complicated grief, and are not proceeding to step 2. They will be asked to sign a separate informed consent as training cases. The therapists who provide the treatment for this study are licensed mental health professionals naïve to CGT.

<u>INCLUSION CRITERIA FOR CGT TRAINING PARTICIPANTS</u>	<u>METHOD OF ASCERTAINMENT</u>
1. Males or females between the ages of 18 - 95 (inclusive)	Screening interview
2. Diagnosed with Complicated Grief and this is the patient's most important (primary) problem	PI judgment based upon review of the BGQ, ICG and IE SCID interview including a module for CG (SCI-CG)
3. Ability to give informed consent	Intake interview with investigator
4. Fluent in English	Intake interview and self-report
5. Willingness to have sessions audiotaped	Intake interview/ informed consent

<u>EXCLUSION CRITERIA FOR CGT TRAINING PARTICIPANTS</u>	<u>METHOD OF ASCERTAINMENT</u>
1. Patients diagnosed with one or more of the following disorders: lifetime Schizophrenia or other psychotic disorder, current (past 6 months) substance abuse or dependence (except for nicotine), Bipolar Disorder, current manic episode or Dementia.	SCID - IV, Clinical intake interview, Urine drug test, Montreal Cognitive Assessment (MOCA) < 21
2. Active suicidal or homicidal ideation, or judged to be at serious suicide risk.	Intake clinical interview; Columbia Suicide Scale
4. Acute, unstable or severe medical illness such as (but not limited to) stroke, epilepsy, or other neurodegenerative disorders, metastatic or active cancer, hepatic disease, or primary renal disease requiring dialysis.	Intake medical assessment (history, physical laboratory tests and/or review of medical records)
6. Concurrent psychotherapy treatment.	Intake clinical interview.
9. Pending or active disability claim or lawsuit related to the death	Screening and/or intake clinical interview

Figure 2: STEP 1: Screening and Assessment Procedures and Flow Chart



STEP 2: Randomization of eligible and willing participants to one of 4 study arms: CIT-CM, PBO-CM, CIT-CM + CGT, or PBO-CM + CGT.

Randomization:

Patients meeting entry criteria will be randomly assigned to one of 4 study arms with equal probabilities (25% to each arm), stratified by site and by the presence or absence of current MDD. Since citalopram is an antidepressant, and we expect a high rate (about 50 to 60%) of comorbid depression, we will stratify the randomization by presence of current MDD. Randomization will be performed using a user-ID/password protected web-based program at the central coordinating site, by the Division of Biostatistics and Data Coordination at the New York State Psychiatric Institute.

Study Treatments:

All study treatments will be delivered over approximately 16 weeks. CGT sessions will occur weekly, for a total of 16 sessions within a maximum of 20 weeks. Medication sessions will occur at weeks 1, 2, 4, 8, 12, and 16. Additional medication sessions will be scheduled for 1 week after the dose increase from 20 to 40 mg. Additional medication visits, by telephone or in-person, will be scheduled as clinically indicated. At the end of the 16-week treatment phase, participants randomized to CGT will discontinue psychotherapy. Medication will not be discontinued. Instead, all study participants will be treated by the study physician for a minimum of 3 months and then be referred back to their treating physician or an appropriate referral will be made to a physician otherwise uninvolved with the study for further medication management. The referral physician will receive information as needed for optimal clinical management, including information from the pharmacy regarding the participant's randomized assignment. The referral physician will tell patients their study medication assignment.

Complicated Grief Treatment (CGT): CGT is a targeted psychotherapy for complicated grief. The treatment integrates principles, strategies and techniques from interpersonal psychotherapy, trauma-focused cognitive behavioral treatment and motivational interviewing. It is guided by the idea that grief progresses naturally by oscillating attention to loss and restoration foci [3]. CBT strategies are used to address trauma-like symptoms.

Motivational interviewing strategies are used to enhance the restoration-focused work. Like IPT, the treatment is administered in 3 phases. The initial phase and the termination phase are very similar to IPT. In the middle phase, CGT integrates four enhancement techniques into the basic IPT framework: 1) imaginal “revisiting,” 2) imaginal conversation with the deceased, and 3) structured discussion of memories of the deceased, and 4) personal goals work. CGT utilizes more structured between-session plans than IPT. Imaginal revisiting exercises are audiotaped and the audio tapes are given to the patient who is asked to listen to the tape at home. This procedure is similar to that used in CBT treatment for PTSD.

Pharmacotherapy Procedures: Pharmacotherapy will be provided flexibly to optimize the likelihood of response. Participants will initiate double blind CIT or PBO at Session 1 with 20mg/day. However, participants aged 75 and over, and those deemed by the pharmacotherapist to have prior medication sensitivity, will initiate for the first week at CIT 10mg/day and then increase to 20mg/day flexibly starting at week 2 as tolerated. The 20 mg/day dose will be continued to week 4. If CG-CGI-I is ≤ 3 the same dose is continued. If CG-CGI-I > 3 and side effect burden based on the FIBSER is low, the dose may be increased to 40mg/day. For participants with a history of heart disease, another ECG will be conducted before a dose increase from 20mg to 40mg and then repeated 5 days after the dose increase to insure the QTc is below 500 msec. For patients age 60 and older, if the dose is to be increased above 20 mg, the absence of family history of sudden death and patient history of cardiac problems, including syncope, will be confirmed and a repeat ECG will be administered. The dose will be increased only if the QTc is < 480 msec. After the dose increase, another ECG will be administered two weeks later to determine that the QTc is not > 500 msec. Patients with a QTc interval > 500 msec following an increase will be removed from the study protocol, tapered off of the study medication, and transferred to the 3 month open follow-up care with a study psychiatrist in coordination with their PCP. A score of 5 to 7 on the FIBSER will trigger additional assessment of side effects and require justification for increasing the dose, while a score of >7 will signal no increase in dose. Participants will be seen at weeks 1, 2, 4, 8, 12, and 16 (6 visits) by a study physician. Additional sessions will be scheduled, following the dose escalation from 20 to 40 mg (usually at week 5 or 6). Pharmacotherapy will be prescribed in the context of clinical management focused on CG. CM includes psychoeducation about CG, rationale for medication use and sensitivities, and medication management response through systematic review of symptoms and side effects at each visit. CM includes support for medication, hope for improvement, and interest in the patient’s questions. Patients’ vital signs (blood pressure, heart rate, and weight) will be measured at weeks 4, 8, 12, and 16.

Medication adherence will be assessed by pill count and adherence rating scale [4]. Side effects will be assessed and recorded at each visit using the side effects assessment, the FIBSER, and at main assessment periods with the PRISE. Participants will also be encouraged to contact study staff immediately should any significant side effects, symptomatic worsening, or suicidal ideation or intent develop in between assessments. A study physician will be available for emergency page 24 hours a day, 7 days a week.

Medication will be continued beyond the post-treatment assessment. Responders will be continued for 3 months on double blind medication prescribed by the study physician. Nonresponders will be treated openly with an alternative medication for 3 months by the study physician. All patients will then be referred back to their personal physician or provided an appropriate referral by the study staff, as the patient prefers. Treatment non-responders will be told their study treatment assignment by the referral physician. The referral physician will receive information as needed for optimal clinical management, including information from the pharmacy regarding the patient’s randomized assignment. Patients who discontinue CIT/PBO during the study will be tapered and treated openly for 3 months by their study physician and then referred back to their personal physician or to a referral provided by the study staff.

Table 1: Assessment Instrument Timetable

Week	MA1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	20	MA2	Follow up
Treatment Visit ^c		C/P	C/P	C	C/P	C	C/P	C	C/P	C	C	C	C/P	C	C	C	C/P	C	C/P	C/P
Interview																				
SCID-IV	X																			
Struct. Clinical Interview for CG	X	X											X				X	X	X	X
CSS ^d	X				X				X				X				X	X	X	X
Clinician Suicide Assessment Checklist		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SIGH-A	X				X				X				X				X	X	X	X
CGI-I and S (Clinician Rated) ^e		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I & S (IE Rated) ^f	X				X				X				X				X	X	X	X
Acceptability Questionnaire (Clinician Rated)		X																		
Self Report																				
ICG	X				X				X				X				X	X	X	X
GRAQ	X								X				X				X	X	X	X
TBQ	X				X				X				X				X	X	X	X
QIDS-SR ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IES	X				X				X				X				X	X	X	X
CSQ									X										X	X
Davidson Trauma Scale	X												X				X	X	X	X
Social Support Inventory (ISEL short form)	X																		X	
Pittsburgh Sleep Quality Index (1 item)	X				X				X				X				X	X	X	X
WSAS	X				X				X				X				X	X	X	X
Expectancy Form			X						X											
Adherence Questionnaire			X		X				X				X				X	X	X	
FIBSER			X		X				X				X				X	X	X	X
PRISE		X	X		X				X				X				X	X	X	X
Difficult Times	X																			
Loss Summary	X																			
GIS*		X									X									
GSI*		X									X									
Grief PDSS-SR	X																			
Yearning Quest.	X																			
SAAM	X																X			X

^c Complicated Grief Treatment (C) sessions will occur on a weekly basis. Pharmacotherapy (P) sessions will occur at weeks 1, 2, 4, 8, 12, and 16 with an additional visit scheduled for 1 week after a dosage increase from 20 to 40mg and from 40 to 60 mg.

^d The Columbia Suicide Scale baseline assessment will be administered at MA1 while the Columbia Suicide follow-up assessment will be administered at all other times.

^e Instruments will be administered weekly for participants receiving CGT and monthly, at medication visits, for participants in the medication only arm of the study.

^f The CGI will be administered by the IE at major assessment points and during monthly telephone mini assessments.

*Instruments are administered to CGT participants only.

Study Assessments

Participants will be asked to complete study assessments during the treatment phase of the study. These assessments will be conducted at regular time intervals even if a participant misses a treatment session or discontinues treatment. Major assessments will be completed at baseline (Main Assessment: MA 1) and post-treatment (MA2). In addition, a small assessment battery consisting of the ICG, the IES, the QIDS-SR, the Work and Social Adjustment Scale (WSAS), and CGI-severity and improvement scales will be completed by the IE during a telephone assessment at 4-week intervals throughout the study. All participants will be asked to participate in a final follow-up assessment over the telephone at 6 months post-treatment. An interim treatment information form and an assessment battery, as indicated in table 1, will be completed at this time. In addition, a SCI-CG will be administered at week 1 by the pharmacotherapist.

Medication side effects will be measured by Likert scale ratings of Frequency, Intensity, and Burden of Side Effects Rating (FIBSER). This self report measure targets side effects attributable to the antidepressant treatment. The FIBSER will be used to guide evaluation of side effects, and to help guide decision to maintain or increase CIT. Patients will also be asked to complete the Patient Related Inventory of Side Effects (PRISE).

Study Personnel

Therapists will be experienced licensed clinicians with graduate degrees in social work, psychology or psychiatry. All therapists will be trained and certified in CGT. Throughout the study, CGT therapy sessions are audiotaped, reviewed by supervisors, and discussed with the therapists in ongoing weekly telephone meetings. All therapists will complete CIT-CMI training prior to treating study participants. Drs. Shear, Mogali and Huyhn will provide clinical backup in the event of emergent treatment issues. A study physician will be available at all times when study participants are being seen. Emergency back-up is available 24 hours a day through the late life depression clinic.

Pharmacotherapists will be experienced psychiatrists, trained and certified by the coordinating center in CG and in the procedures described in the pharmacotherapy manual. In order to standardize pharmacotherapy, all medication will be prescribed by physicians trained in the protocol. Pharmacotherapists will be provided with, and receive training, in use of a manual outlining principles of pharmacotherapy, psychoeducation and clinical management in this study. All new pharmacotherapists will receive supervision.

Other study personnel include a research coordinator, assessment raters, and research assistant. Trained clinicians or graduate students in mental health disciplines, trained to reliability, will serve as study assessment raters and will complete research assistant tasks. These individuals will work under the supervision of the project coordinator and the PI. All study personnel will complete CITI training prior to initiation of the study.

Clinical Management of Study Patients

Eligible participants who require medication taper will be assessed and managed as described on pages 16-17. Those who do not require medication taper will have their first treatment visit within 4 weeks of the baseline assessment. During the interval between assessment and first treatment visit, participants will receive weekly telephone calls from the study coordinator. The call will include a discussion of symptoms and suicidal thinking. If needed, the patient will be scheduled for a telephone or in-person visit with a study physician.

Prescribing physicians and CGT therapists will complete CG-CGI severity and improvement ratings and a Clinician Suicide Assessment Checklist modified from the CSS, and will review total QIDS-SR at each session. Weekly contact will be maintained with all patients throughout the study by the clinician either in person or over the phone. Any patient who endorses a suicide plan (3 or higher on the Clinician-Rated Suicide Assessment Checklist) will be followed by a clinician who will exercise judgment as to whether the patient needs to be seen. Patients receiving pills only (i.e. no CGT) who score 6 or 7 on the CGI will be dropped from the study and treated openly. Any patient who develops a new episode of major depression will be dropped from the study and treated openly.

If a patient exits the study treatment, he/she will be offered at least 3 months of medication treatment by a study physician who will stop the study medication and prescribe medication openly until an appropriate referral is made. All participants who choose to discontinue treatment will be asked to continue completing the remaining assessments at the scheduled times. In this way we will have a complete data set for the main study analyses.

At week 16, all subjects regardless of response will continue to be treated by a study physician for at least 3 months and treatment will continue until an appropriate referral is made. The study pharmacotherapist will continue to prescribe medication during this time. Treatment responders have clear evidence of improvement in complicated grief symptoms as determined by CGI = 1 (very much) or 2 (much improved) and will continue to receive double blind medication from the study physician during the 3-month transition period. They will then be referred back to their personal physician or provided a referral by the study staff. The referral physician will receive information as needed for optimal clinical management, including information from the pharmacy regarding the patient's randomized assignment. The referral physician will inform the patient of the study treatment and decide how to continue treatment. Non-responders will be prescribed at least 3 months of open label medication treatment and provided with supportive psychotherapy by a study pharmacotherapist who will stop their study medication and treat the patient openly for at least 3 months and until an appropriate treatment referral is made.

STEP 3: Post-treatment and Final follow-up assessments

We will conduct a post-treatment assessment within 2 weeks of the final treatment visit. This assessment will include instruments as described in Table 1. A final follow-up assessment (refer to study flow chart) over the telephone will be scheduled at week 40 post baseline for all study participants. This assessment will take 60 to 90 minutes. Following each of these assessments, patients will be judged responders or non-responders based on the CGI.

Audio Recording of Assessment, Psychotherapy and Pharmacotherapy Treatment Sessions

All assessment, psychotherapy and pharmacotherapy treatment sessions will be digitally audio recorded for purposes of establishing inter-rater reliability, providing ongoing treatment supervision, and evaluating treatment adherence and competence. Recordings will be transmitted electronically to supervisors or raters using a secure "http-safe" server system that is HIPAA compliant. Access to these recordings in all locations will be limited to authorized study personnel. Recordings will be kept for a maximum of 10 years from the beginning of the study. The participants name will not be revealed on recording labels. Audio recordings will be heard by the assessment or treatment supervisors, by other therapists administering this treatment and by raters who will judge how well the therapist or the independent evaluator is adhering to prescribed instructions. Others who will have access to these recordings include individuals working on training and research projects connected with this project. People who will listen to the audio recordings include supervisors, trainees and adherence raters. Our supervisors are off site and will be permitted to download files to their own computer. However, they will be asked to sign a statement indicating that they understand that they are permitted to listen to the tapes only and are not permitted to retain or duplicate recordings. We will require that they send an email to confirm receipt of each file and another one to confirm that they have deleted all copies from their computer. Adherence raters will use project computers to review recordings. Therapy trainees will be encouraged to use project computers but will also be permitted to download off site. When doing so, they will be required to send an email to confirm receipt and another to confirm that all copies have been deleted. Confidentiality will be protected by not utilizing the name of the participant and by keeping the recordings on an electronically secure, password protected hard drive in a locked room. There is no additional compensation for the audio recordings.

Participants will be asked to sign an optional consent form to videotape the therapy sessions in order to utilize the tapes for additional research and training purposes.

Data Management Plan

All project data will be entered into a web-based data collection system under the supervision of Dr. Howard Andrews. StudyTrax, an outside vendor, will be used as our data management system. Data entry screens will capture information from the assessment instrument table above (table 1). Secure Socket Layer (SSL) technology will encrypt and transmit the data to a central database, located on a physically and electronically secure server at StudyTrax as well as backed-up at Columbia University. The system is HIPAA complaint and has appropriate safeguards for data integrity and security. Additional information is included in appendix. Staff at each performance site will be able to view data on the subjects at their site, but not subjects at other sites. Furthermore, access to the web-based system is via a role-based user-ID/password system that allows each individual to view only data that he/she is authorized to see and to perform operations that are deemed appropriate for his/her role.

Data management staff will periodically download data into self-document SAS and SPSS files for analysis. We will periodically generate reports documenting subject accrual, data completeness, and data quality exceptions.

No explicit subject identifiers (name, medical record number, social security number, address) will be entered into the online system. Each subject will be identified by a sequential subject ID assigned by the web-based randomization system. It will be the responsibility of the performance sites to maintain and secure a table indicating the correspondence between the subject ID and the names and contact information of the participating subjects. This information will be held by the individual site and will not be transmitted to the data coordinating center.

Data Analysis Plan

Our primary analysis will follow the intention to treat principle [6-8] comparing participants' outcomes according to their initial treatment assignment, irrespective of their adherence to the assignment, to assess the impact of treatment assignment on the outcomes. In order to conduct ITT analysis appropriately, we will distinguish between protocol drop-out and assessment drop-out. To the extent feasible, we will follow patients who drop out of the assigned protocol (either voluntarily, or removed from the study due to adverse effects) and continue to collect their assessment data and include them in the ITT analysis according to their original assignment [9, 10]. In this way, protocol drop-out does not automatically lead to the termination of assessment. Therefore, the only missing data are assessment drop-outs among patients who could not be assessed despite our best efforts. We will emphasize to participants the importance of assessments even if they discontinue treatment. We expect to succeed in continuing to assess at least half of the treatment drop-outs, bringing our assessment response rate to 90% or higher.

Our primary analysis will be cross-sectional, comparing participant outcomes at the endpoint. We will also conduct longitudinal analysis as a sensitivity analysis to corroborate cross-sectional analysis at the endpoint. For missing data due to case non-response, such as assessment drop-out in cross-sectional analysis at the endpoint, we will use response propensity weighting [11, 12] to mitigate the potential for non-response bias that might result from assessment drop-out. For missing data due to wave non-response, we will use longitudinal analysis that implicitly extrapolates from observed to impute the unobserved waves. In particular, for participants with missing data at the endpoint who have completed at least two waves of assessment prior to the endpoint, the longitudinal model (through the implicit extrapolation) allows these participants to be included in the analysis for the treatment effect at the endpoint.

For analysis of covariance that includes covariates with missing data, we will use multiple imputation [13, 14] for the missing values to avoid information loss and potential non-response bias due to exclusion of cases with missing data.

The number of participating sites in the study is relatively small (n=4), therefore it is not feasible to attempt to generalize from these sites using random effects model. Instead we will specify site as a fixed effect, which limits the interpretation of the analysis results to the participating sites, without attempting to generalize beyond these sites.

B. What is maximum duration of delay due to research procedures before patient begins a treatment? (Include single blind placebo in this estimate.)

If the patient needs to discontinue excluded antidepressant medications, the maximum delay due to research procedures before beginning treatment would be 6 weeks. During this period the person would be receiving treatment from the study pharmacotherapist.

Aside from a delay because of concomitant medication, patients will be assessed and assigned to a pharmacotherapist and a CGT therapist (if in a psychotherapy study arm) with no delay, other than that due to scheduling. All efforts will be made to minimize any scheduling delay with a maximum treatment delay of up to 6 weeks.

C. What is maximum duration of delay before active treatment (medication or psychotherapy) of known efficacy is offered? (Include time period described in #1 above.)

The maximum duration of delay before receiving medication and/or psychotherapy is 6 weeks. There is no treatment of confirmed efficacy for CG, though CGT has been proven efficacious in a single prior study. There is a delay in efficacious treatment for major depression. However, we note that there has been no study of the treatment of MDD

among patients with CG, and there is some suggestion in the existing literature that depression responds less well to standard treatment in this population (see discussion in risk section pp 16-18).

Patients must enter treatment within 6 weeks of completing the baseline assessment. Every effort will be made to ensure that the period between the screen and assessment and between assessment and treatment are minimized.

D. Describe treatment to be provided (if any, including duration) at the end of the study.

The study pharmacotherapist will continue to prescribe medication for at least 3 months and until an appropriate referral is obtained. Responders will continue double blind medication prescribed by their study doctor. Non-responders will be offered at least 3 months of open medication treatment and supportive psychotherapy by a study pharmacotherapist who will stop their study medication and treat the patient openly.

Patients who discontinue CIT/PBO during the study will be tapered in consultation with their study physician and offered at least 3 months of open treatment until an appropriate referral is made.

E. If an experimental treatment will be used, describe other accepted methods of treatment available, if any.

There are no established proven efficacious treatments for CG.

5. BLOOD SAMPLES: State quantities to be drawn over what period and for what purpose.

Approximately 20 cc's of blood will be draw at baseline from patients that have not had a recent medical examination by their PCP and require a medical examination at the study site.

6. INSTRUMENTS: List measures to be used, including tests and interviews and time required for the completion of each. Attach copies unless standard instruments are used.

Subject Self-report Measures:

Inventory of Complicated Grief (ICG) [15]: The 19-item ICG assesses symptoms of CG. This scale has been utilized previously in treatment studies of CG. This measure will be used to establish eligibility and as an outcome measure in this study.

Grief-Related Avoidance Questionnaire (GRAQ): This questionnaire was developed by the study investigators to elicit information related to avoidance of common situations and activities following the death. This scale has good psychometric properties and CG patients endorse a range of scores on the scale. This scale will be used to assess avoidance as a possible moderator predicting better outcome with CGT.

Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR): This 16-item patient self-report measure assesses the 9 DSM symptom criteria for a major depressive episode. This measure has been utilized as the principal instrument driving the critical decision points for measurement-based care of several depression trials, and will be used to examine change in depressive symptoms over time.

Work and Social Adjustment Scale (WSAS) The WSAS is a modification of a scale introduced by Hafner and Marks [16], consisting of 0-8 point ratings of the extent to which symptoms interfere with five areas of daily functioning: work, home management, private leisure, social leisure, and family relationships. It is a well-validated, widely used measure [17]. It will be administered at major assessment points as a secondary outcome measure.

Inventory of Social Support: Social support is an important predictor of both health and psychological outcomes [18, 19], and has been found to be particularly important in buffering the effects of stressful life events such as health problems, bereavement, and natural disasters [20]. Based on their demonstrated importance in the literature, four domains of social support will be measured: 1) received support (3 items); 2) satisfaction with support (3 items); 3) social networks (2 items), and 4) negative interactions (4 items).

Client Satisfaction Questionnaire (CSQ) [21]: The Client Satisfaction Questionnaire is a self-report questionnaire designed to measure satisfaction with services received by individuals or families. It will be used to assess satisfaction with each treatment.

Impact of Events Scale (IES): The IES is a 15-item scale measuring current stress related to a specific event. The scale consists of two subscales: intrusion and avoidance. The internal consistency of the scale is adequate (alphas =

.80 to .93 for intrusion; alphas = .73 to .84 for avoidance), and the test-retest reliability is high ($r = .93$). The scale also shows sensitivity to change over time, particularly over the course of treatment for PTSD. This scale will be used to assess intrusive images, a putative mediator of improvement in grief intensity with CGT.

Pittsburgh Sleep Quality Index (PSQI) [22]: The PSQI was developed to measure the quality of sleep over the past month. The PSQI contains 19 self-report questions. The scale shows good psychometric properties, including high internal consistency ($\alpha = .83$), good test-retest reliability ($r = .85$) and discrimination between sleep disordered and others. This scale will be used to assess differential effects of medication and placebo on sleep disturbance.

Davidson Trauma Scale [23]: The Davidson Trauma Scale is a 17-item, patient administered scale that asks patients to evaluate the frequency and severity of certain trauma related symptoms over the past week.

Typical Beliefs Questionnaire (TBO): This 34 item questionnaire evaluated how strongly subjects endorse certain beliefs that are common during bereavement related to self, the relationship, and perceptions of the world. The questionnaire is included in the appendix.

Difficult Times Questionnaire (DT): A brief questionnaire that asks people to identify which days are especially difficult for them with respect to grief, and to rate how difficult they expect these days to be.

Grief Intensity Scale (GIS): This 7-item questionnaire that assesses severity of grief symptoms.

Grief Support Questionnaire (GSI): A 2-item questionnaire explores social support for grieving individuals.

Expectancy Form: A brief questionnaire asks participants what they expect to get out of their treatment.

Loss Summary: Provides an overview of losses the participant may have experienced. It allows researchers to assess whether complicated grief is present for another loss.

Grief Panic Disorder Severity Scale – Self-Report (Grief PDSS-SR): PDSS-SR [31] is a brief validated self-report assessment of panic attack symptoms. It was shortened and modified to assess panic symptoms related to grief.

Yearning Questionnaire: is a patient self-report instrument to further assess core grief symptoms of yearning for their loved-one, thought to be central to the new syndrome. It consists of 21 items and another 12-item addendum. It is based on the Yearning in Situations of Loss Scale [32].

State Adult Attachment Measure (SAAM) [33]: is a 21-item self-report measure of adult attachment that has good reliability and validity and allows capturing fluctuations in the sense of attachment security and insecurity.

Interview:

Montreal Cognitive Assessment (MoCA) [24]: The MoCA is a brief cognitive screening tool with high sensitivity and specificity for detecting mild cognitive impairment. We will use a MOCA score ≥ 21 to establish eligibility for randomization as we have found scores in this range among healthy young adults, in our pilot/feasibility work.

Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A)[25]: a structured interview form of Hamilton Anxiety Scale. It provides additional guidance in administration and anchor points.

Medical Review Form and Psychiatric Treatment History Form: two demographics form designed to be systematic about collecting medical and psychiatric history information. Medical Review Form includes Cumulative Illness Rating Scale (CIRS). The forms are included in the appendix.

Clinical Global Impression Severity and Improvement Scales (CGI-S and CGI-I): Brief rating scales [26] frequently used in clinical trials. For this study, versions modified for complicated grief will be used. The scales are included in the appendix.

Clinician-Rated Suicide Assessment Checklist (adapted from Columbia Suicide Scale): The treating CGT Therapist or Pharmacotheapist will select the most appropriate answer from a 0 to 5 suicide assessment, including 0=Patient has no wish to be dead; 1=Patient has a wish to be dead, or not alive anymore, or to fall asleep and not wake up but does not have thoughts of ending her or his life; 2=Patient has non-specific thoughts of wanting to end her or his life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to do this and without plans to carry it out; 3=Patient has thoughts of suicide and has thought of at least one method to do so but has not worked out any specific plans or details (e.g. "I thought about taking an overdose but I don't have a specific plan as to when, where or how I would actually do it....and I would never go through with it"); 4=Patient has active suicidal thoughts without specific plans but with some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them"; 5=Patient has thoughts of suicide with details of plan fully or partially worked out and some intent to carry it out.

Acceptability Questionnaire: is a brief clinician self-rated questionnaire to assess the pharmacotherapist's view of the usefulness and ease of administration of the Structured Clinical Interview for Complicated Grief (SCI-CG).

Measures of Medication Side Effects:

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER): This self report provides 3 global ratings each on a Likert-type scale rated 0-6. One rates frequency, another intensity, and the third estimates the overall burden or degree of interference in day-to-day activities and function due to the side effects attributable specifically to the antidepressant treatment. The FIBSER will be used to guide evaluation of side effects, and at week 8 to help guide decision to maintain or increase CIT to 40mg/day.

Patient Rated Inventory of Side Effects (PRISE): This is an easy to use, 7 item self report that asks patients to qualify medication side effects by identifying and evaluating the tolerability of each symptom. Side effects are broken down into 9 symptom domains and under each domain, multiple symptoms are listed in which the patient can endorse. The items include the most commonly reported side effects with antidepressant medications and should take the patient less than 5 minutes to complete. This measure will be used to descriptively examine side effects associated with protocol treatment.

Adherence Questionnaire [4]: This is a two-question inventory that asks patients how many days of medication they have missed and whether they took the medication exactly as prescribed.

IV. ADDITIONAL INFORMATION

1. Will subjects receive any compensation: YES X NO _____
If yes, how much? _____ (See Consent Form Guidelines re: payment procedures)

Participants will be reimbursed \$20 for the baseline and \$10 per study treatment session for up to a total of \$180.

2. Will procedures involve imaging studies and radiolabelled compounds?

YES ___ NO X

If yes, what radiotracers? _____

Approval is required from the CPMC Radiation Safety Committee.

3. If investigational drugs are involved, complete the following:

1. Generic or chemical name
2. Other name
3. Manufacturer
4. IND #

4. If an investigational device is involved, complete the following:

1. Name
2. Manufacturer
3. IDE #

5. Describe risks to subjects and procedures for minimizing risks.

This study is designed to provide information on the relative efficacy of citalopram alone, pill placebo alone, CGT plus pill placebo, and CGT plus citalopram for the treatment of complicated grief. Citalopram is an available, safe and well-tolerated SSRI antidepressant that is FDA approved for the treatment of Major Depressive Disorder and Generalized Anxiety Disorder. There are no prior randomized trials of any pharmacotherapy specifically for CG, but preliminary data suggests potential efficacy of escitalopram, a related compound. All pharmacotherapists will provide psychoeducation and supportive clinical management as guided by the Pharmacotherapy Manual (see Appendix).

CGT is a CG specific psychotherapy we have previously demonstrated efficacy for compared to a standard grief-focused, interpersonal therapy [27].

Main Study Risks:

The most important risks of this study are related to discontinuation of antidepressant medication for the purpose of study eligibility and to the use of placebo medication. We first discuss the rationale for these procedures and their risk and risk management. We then discuss other study risks and their management.

- Rationale for discontinuing antidepressant medication and the risk in doing so

Rationale: We are permitting participants to discontinue medication because we believe it is important to include patients currently taking antidepressant medication because in our prior studies there were many people on antidepressant medication who met eligibility criteria and wished to participate in a CG-focused study. Our results suggest that many people may be treated with medication that is inadequate to control their CG symptoms. It would be clinically questionable to exclude these patients, and doing so would limit the generalizability of our study. At the same time, if we permitted concurrent use of antidepressant medication, we would not be able to achieve our specific aims to test the efficacy of citalopram. We therefore plan to permit participants to discontinue antidepressants when this is deemed appropriate.

Risk: Patients who meet inclusion criteria for this study while taking antidepressant medication will need to discontinue this medication. There are both clinical and ethical issues pertinent to discontinuation of medication in order to enter a research study. Discontinuation of medication may result in symptom worsening or even the onset of new symptoms. We describe below procedures for decision making about medication discontinuation and for monitoring clinical status.

- Rationale for use of placebo medication and attendant risk

Rationale: Complicated grief is a debilitating condition that has proven relatively refractory to standard psychotherapy for depression. Pilot studies of medication treatment show SSRIs to be associated with statistically significant improvement in CG symptoms with about half the rate of improvement in grief than in depression and average post-treatment CG symptom scores in the range that is still considered clinically significant. It is very important to determine whether SSRIs are efficacious for people with CG, and this is our primary study aim. Placebo medication is necessary for this determination.

Risk: We will randomize participants to medication and placebo both with and without accompanying CG-targeted psychotherapy (CGT). A majority of participants in this study are expected to meet criteria for a current mood or anxiety disorder. Medication has been proven efficacious for these disorders, and studies suggest that depression responds similarly to medication in the context of bereavement [28, 29]. We note, however, that medication efficacy has not been demonstrated for depression among bereaved individuals with CG. In our prior study, many individuals on antidepressant medication still met criteria for MDD with elevated Hamilton Depression scores, raising the possibility that depression responds less well to medication among patients with CG than among bereaved without CG.

CGT was significantly more effective than Interpersonal Psychotherapy in reducing depression as well as CG symptoms. Although there has been no head to head comparison, CGT appears to be more effective than medication. Therefore, while we will carefully monitor all patients in this study, we believe the risk of non-response and worsening with placebo is greater among those participants receiving medication only. Since pilot studies suggest that SSRI medication may not be as effective for CG as for other mood and anxiety disorders [28, 30], medication will be administered in a double blind fashion, and since participants will be seen less frequently than those in the combination treatment, we plan to pay careful attention to monitoring depression and CG symptom status among individuals receiving medication only (i.e. citalopram or pill placebo).

- Procedures to manage risk of antidepressant discontinuation

Individuals with CG who present on antidepressant medication and who wish to participate will undergo a thorough assessment that includes a focused review of factors that could influence the decision about whether to discontinue medication: a list of current medication(s) with start date, current dose and side effects, a brief summary of the course of CG and co-occurring symptoms, before and after antidepressant use, a brief medication treatment history with information about medication type and effectiveness, reasons for discontinuing antidepressants in the past, and method and consequences of any prior experience with antidepressant discontinuation, a summary of current and past suicidal ideation and any past attempts, and information about where these occurred in relation to starting or stopping antidepressant medication. We will note any current psychosocial stressors that might lead to worsening depression upon antidepressant discontinuation and provide a brief summary of pros and cons of discontinuation. Subjects experiencing a robust response to medication (i.e., clinically significant improvement as judged based upon reports by the patient and prescribing doctor) in their current episode will not be tapered off medication for study participation.

We will obtain written permission to consult with the patient's prescribing physician. The medication summary will be sent to the prescribing physician. We will proceed with antidepressant taper after discussions among the prescribing clinician, patient, and study PI in which it is determined that antidepressant taper is clinically appropriate. We will not pressure patients to taper medication if they do not wish to do so. While each case will be evaluated individually using clinical judgment that takes into account clinical and psychosocial circumstances, the following are examples where discontinuation would not be considered appropriate: 1) Prior discontinuation attempt resulting in clinically significant worsening or relapse of mood or anxiety disorders or clinically significant worsening of CG symptoms; 2) History of recent MDD with clinically significant antidepressant response; 3) Clinically significant suicidality prior to starting medication that is no longer present.

Antidepressants will be tapered during weekly visits that include symptom and safety monitoring as described in the risk management section above. Midweek telephone calls will be scheduled when indicated and 24 hr access to a physician will be available at all times. CGI severity and improvement will be assessed by the study pharmacotherapist, either in person or by phone, on a weekly basis during the taper period. Taper will be discontinued if a participant has

- a. TWO weeks of CG-CGI-I ≥ 5 (minimally worse) and CG-CGI Severity > 5 (more than marked), OR ONE week of CG-CGI-I > 5 (more than minimally worse) and CG-CGI Severity ≥ 5 (marked or more).
- b. Greater than or equal to 30% increase in QIDS-SR from baseline and total QIDS-SR greater than 17 for two consecutive weeks.
- c. Clinician Suicide Assessment Checklist score increased from baseline to level 4 or 5.

Patients who do not complete the antidepressant taper are considered screen failures and will not be randomized. However, these individuals will still be offered our usual 3 months free clinical follow-up visits with a pharmacotherapist to help stabilize them. If indicated, antidepressant medication will be restarted immediately. We will also offer up to 3 months of open-label active medication treatment to the participants who are deemed ineligible after the medication taper. Antidepressant medication taper will be stopped at the patient's request, if there is clinically significant worsening of symptoms, as assessed using clinical global impression scores for grief, depression and anxiety, if there is emergence of clinically significant suicidality, if there is emergence of significant physical side effects, or at any time judged appropriate by the study physician.

Optimal antidepressant discontinuation is managed differently for different medications. For example, while SSRI discontinuation may be reasonable over a 2 week period for those on average doses (e.g. sertraline 100/day), those on an SNRI may require a slower taper with small dose reductions and associated clinical assessment once a week. However, if tapering is not completed within a 6 week period we will consider this a screen failure and work to stabilize the patient clinically and then refer to appropriate follow up care. Participants who successfully discontinue medication will remain medication free for a 1 week period prior to randomization. Clinically significant worsening of symptoms during this period will result in withdrawal from the study protocol and the patient will be offered 3 months of open treatment with a study physician.

- Procedures for managing placebo risk

We will monitor and review participant symptoms during each study visit. However, pharmacotherapy visits occur biweekly after the first month and then monthly (at weeks 1, 2, 4, 8, 12 and 16). A session will be scheduled for the week after any citalopram dose increase. For the reasons outlined above we will pay special attention to participants in the medication only arms of the study. Prescribing physicians will complete CGI improvement ratings for complicated grief at each study visit.

- a. If CG-CGI-I ≥ 5 (minimally worse), or QIDS-SR $\geq 30\%$ increase from baseline and total QIDS-SR ≥ 17 , or Clinician Suicide Assessment Checklist ≥ 4 at any time during the study, the study physician will schedule weekly contact, in person or by phone, until criteria are no longer met or participant meets exit criterion.
- b. If CG-CGI-I = 4 at any time after treatment week 4, the study coordinator or physician will schedule at least biweekly phone contact. The call will focus on whether there has been any change in symptoms or suicidal thinking. If there is any further worsening the patient will be scheduled for an in-person visit with the pharmacotherapist.

Exit criteria: A decision to discontinue study treatment will be made by the PI and will be triggered by any of the following:

- a. CG-CGI-I > 5 (more than minimally worse) for two consecutive weeks;
- b. Greater than or equal to 30% increase in QIDS-SR from baseline and total QIDS-SR greater than 17 for two consecutive weeks;
- c. CG-CGI Improvement ≥ 4 (no change or worse) and CG-CGI Severity > 2 (mildly ill) after week 12;
- d. Patient endorses level 5 on the Clinician Suicide Assessment Checklist;
- e. Patient develops a new episode of major depression;
- f. Participant is receiving pill only and CG-CGI-I = 6 or 7 for two consecutive weeks;
- g. Judgment by a study clinician that termination should be considered.

We note that there is always a risk associated with the management of patients with suicidal thinking on an outpatient basis. This risk will be considerably mitigated by the systematic and careful assessment of suicidality throughout the protocol. See Procedures to Monitor and Manage Suicidality below.

In summary, we will monitor patients closely in this study and we will provide treatment for those who are judged non-responders at the time of study treatment discontinuation, whether before or after completion of the study protocol. Most study participants will receive active treatment that is expected to relieve symptoms of CG, depression and anxiety. Those who do not will be offered active treatment upon study treatment termination. Overall, we believe the risks of this study are reasonable with respect to the potential benefits on an individual level as well as with respect to knowledge obtained.

Other risks of this study:

Adverse reactions to citalopram: The risks and discomforts associated with citalopram are as follows: dry mouth, nausea, diarrhea, sweating, drowsiness, trouble sleeping, problems with sex, allergic reaction (itching or hives, swelling in face or hands, swelling or tingling in the mouth or throat, tightness in chest, trouble breathing), confusion, or weakness. There is also a risk of QTc interval prolongation (abnormal heart rhythm) when prescribed at a dose above 40 mg/day. In addition, there is a risk of increased suicidality with initiation of SSRI antidepressants in individuals with depression age 24 and under: All individuals in this protocol will receive close monitoring for the development of suicidality (see Procedures to Minimize Risk below), and children under the age of 18 are excluded.

- Discomfort from blood draw, bruising and/or bleeding at the needle site. Occasionally, a person feels faint when blood is drawn. Rarely, an infection, which can be treated, may develop at the injection site.
- Discomfort or anxiety from discussion of personal information. In particular, participants might find discussion of grief symptoms distressing. The IE raters will be alert to this possibility and trained to handle it. The study staff will regularly discuss experience and management of patient emotional distress. A study doctor-on-call will be available 24 hours.
- Uncomfortable about having treatment session's audio and/or videotaped and reviewed by others (necessary for treatment adherence checks).
- Interference with daily activities due to scheduling of assessment sessions, treatment sessions and

treatment-related activities.

- There is a risk of intense emotional reactions during the CGT imaginal and situational re-visiting and imaginal conversation exercises, as well as grief monitoring. Treatment procedures, especially the revisiting therapy components, are specifically designed to provoke intense emotion. Therapists are trained in skills to help manage intense emotions and instructions for reducing high levels of emotion are provided in the treatment manual. Therapists participate in weekly supervision session. Because of the special vulnerability of bereaved individuals, we will take extra care, as described above, to provide very sensitive and respectful care.

Procedures to minimize risks:

All risks will be reviewed in the consent form, and subjects will be informed of their right to refuse any procedure or withdraw from the study at any time. All assessment and treatment procedures will be conducted by trained and experienced staff. All treatment sessions will be audio and/or videotaped, and therapists will be closely supervised. Subjects will be assessed regularly and may be withdrawn from the study if their clinical condition deteriorates substantially.

All participants will be medically cleared for enrollment in the study (see methods) and will meet regularly with clinicians experienced in the assessment and treatment of patients with CG. The study exclusion criteria include unstable medical illness that may complicate the treatment process. The protocol formalizes assessment and monitoring of symptoms and adverse effects. If a patient experiences any adverse reactions to the study medication, citalopram, the study doctor will assess these and provide appropriate treatment or referral as indicated. Additionally, at present there is insufficient information regarding the safety of citalopram during pregnancy or breast-feeding. For reasons of safety, all women of childbearing potential will be required to use a reliable form of birth control throughout the study: (e.g.: oral contraceptives, surgical sterilization (of the subject or of her male partner), IUD (intrauterine device), condom and spermicide or diaphragm and spermicide).

We will ensure that all patients and their family members have 24 hour access to a physician providing coverage for our protocol at each of the enrolling sites. Participants and their family members will be instructed to call at any time if there is any concern about suicidality and will be encouraged to call us for any questions or concerns. Patients are provided with cards with twenty-four hour emergency contact numbers. In the event of an emergency the physician will determine the necessary clinical intervention and provide and coordinate appropriate care. The clinicians and study coordinators maintain close contact with participants and reschedule appointments as needed. Subjects who leave the study prematurely or who fail to respond to treatment will be offered referral for alternative therapy.

Procedures to Monitor and Manage Suicidality

In our prior study we documented suicidal behaviors, including suicide attempts, plans and indirect suicidality that comprise recklessness and/or neglect of medical care for subjects with this condition. Therefore, the following risk assessment procedures will be utilized: Patients will be assessed at baseline using a structured clinical interview for lifetime suicidality that focuses on the period of time since the death, using the Columbia Suicide Scale (CSS). This instrument provides information about past history of suicidal ideation and attempts as well as information about suicidal thinking, plans and attempts since the death. There are subscales pertaining to reckless or neglectful behavior and assessing reasons for living. Information from this assessment will be provided to all therapists. Those with a past history of attempt(s) and/or current serious ideation will be flagged for the therapist, on-site supervisor and site PI. Additionally, study participants will be assessed for suicidality at each study visit by their clinician who will complete the Clinician-Rated Suicide Assessment Checklist. Depending upon assessed risk, treating physicians will follow the safety procedures outlined in the table below. In addition, subjects who call to report an increase in suicidal ideation at any time, will be further evaluated by a study clinician and if necessary, a study psychiatrist.

LEVEL OF SUICIDE RISK	CLINICIAN ACTION PLAN	DOCUMENTATION
None	Nothing	No suicidal ideation, plan, intent, or attempt. No psychotic symptoms. No high-risk behaviors.
Mild Risk (Pt. Feels he/she would be better off dead; passive SI)	Make sure the patient does not have suicide plan and/or suicide intent. Obtain agreement to contact the clinician and/or to refer to the closest ER if the suicidal ideation worsens.	Content of passive SI as well as no intent, no plan. Patient agreement to contact clinician Steps to take if suicide risk increases
Moderate Risk: active suicidal ideation or desire to harm self, has thoughts about how to do this, but not currently intending to carry it out.	Confirm that there is no current intent to act on suicidal plans. If the suicide plan, or desire to harm self, is seriously considered, follow the directions below (Intermediate risk). If the patient clearly states that he or she would never act on this plan, ask for the reasons, develop a safety plan, including steps to be taken if the SI increases in severity, and obtain agreement; document the conversation.	Identify the plan or how the patient has thought of completing suicide Estimated level of risk, including reasons for living Detailed description of any safety plan including patient agreement, or reason why this was not considered necessary. Steps to take if suicide risk increases.
Intermediate Risk (seriously considered plan, or very strong desire to harm self)	Review in detail suicide plan, including details of where, when and how the patient would carry this out and assess level of intent. Verify reasons for living and ensure that these currently outweigh reasons for dying and/or that the patient is not intending to carry out a plan to harm her/himself in the immediate future. Discuss triggers for suicidal thinking and develop a management plan. If significant other is included in plan, call or speak directly to this person and obtain agreement for management plan. Notify project coordinator and PI of the occurrence of intermediate risk SI.	Suicide plan, intent and reasons for living Safety plan, including patient agreement, and agreement of significant other, if included in the plan Reason(s) why sending the patient to the ER was deemed not necessary Plan for follow up, including Steps to take if risk increases.
High/Urgent Risk (immediate intent to harm self)	The patient is referred to the ER. The patient is usually accompanied by physician, other clinical professional or significant other. Under rare circumstances, the treating physician may decide it is safe to permit the patient to go to the ER unaccompanied. If the patient is not in the clinic (phone contact) ask to talk to a relative who might accompany pt. to ER. If necessary call police, to initiate involuntary admission to the ER Contact ER as soon as patient is referred there and transfer necessary assessment information Notify the PI immediately.	Details of assessment of suicidality Reason for referral to the ER Plan for follow up, including contact with ER physician, significant other Plan for termination from study and post-study clinical management

6. Describe benefits to subjects, if any.

Participants may benefit from the close monitoring provided in this study. In addition, they may receive treatment by skilled therapists and/or treatment with a medication with proven safety and efficacy for major depressive disorder

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