Accelerated Resolution Therapy for Treatment of Complicated Grief in Senior Adults
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BACKGROUND AND RATIONALE

An estimated 10 million Americans suffer from prolonged, complicated grief (PCG)[1], a serious health concern that significantly impairs the health of older adults. Trauma, depression, anxiety, diminished cognitive functioning and substance abuse issues are all more common among individuals who experience complicated grief.[2-4] These mental health issues contribute to neglect of physical health, leading to exacerbation of chronic illness, development of new illness, and declines in physical functioning, as well as longer hospital stays.[5]

Prolonged, complicated grief (PCG) disproportionately affects older adults, with more than 25% of older adults experiencing grief, compared to 5-7% of the general population.[6,7] PCG is associated with numerous psychological problems including loneliness, social isolation, anxiety, clinical depression, cognitive impairment, and post-traumatic stress syndrome[8,9]. Compounded losses of multiple close family and friends, increased likelihood that the deceased will be a spouse or partner, and financial burden associated with the loss, may lead to a higher incidence of complicated grief among older adults.[6,9]

Individuals presenting for care with a primary diagnosis of PCG exhibit elevated rates of post-traumatic stress disorder (PTSD) (48% current, 52% lifetime).[10] In non-treatment settings, approximately 15% of bereaved individuals also meet the diagnostic criteria for PTSD[11]. High rates of comorbid PCG have been documented in individuals with a primary diagnosis of major depressive disorder. [12,13]Consistent with this relationship, a history of prior trauma or loss and a history of mood and anxiety disorders also predict greater likelihood of developing PCG.[14]Whether PCG is primary or secondary to PTSD, there is significant symptom overlap, yet unique differentiating features.[11,15]

Whereas PTSD is characterized typically by fear, horror, anger, guilt, or shame, combined with an anxious hyperarousal state and exaggerated reactivity, the experience of PCG is marked primarily by yearning, loss, or emptiness.[16] This includes an intense longing for the deceased and distress over the loss of the relationship, which is not a central component of PTSD.[15] To further differentiate, with PTSD after a loss, intrusive thoughts are fixated on the death event itself, leading individuals to avoid internal and external reminders of the death event in and of itself. On the other hand, in PCG, individuals may experience intrusive and involuntary thoughts about diverse aspects of the relationship with the deceased, including positive content that the bereaved longs for, and avoidance is mostly limited to those stimuli that serve as reminders of the reality or permanence of the loss.[16] However, the cardinal symptom of emotional numbing since the time of the loss is shared by both PCG and PTSD.[16]

ART is an evidence-based therapy for the treatment of depressive symptoms and trauma and stress-related disorders[17-21] that includes the core components of trauma-focused therapy including imaging rescripting, voluntary image replacement, guided visualization with use of eye movements, desensitization and processing of distressing memories, and in-vitro exposure to future feared triggers.[22] Mental health professionals are delivering ART in clinical practice to assist with grief; however, there is a need for formal research evaluation of the effects of ART on complicated grief and psychological distress. Preliminary results in other populations suggest co-occurring reductions in distress as well as improved emotional health and better sleep quality. However, we have not investigated the effects of ART in the setting of complicated grief in older adults, a logical application for this emerging trauma-focused therapy because of the high correlation and significant overlap in symptoms between CG and PTSD.[4]

The scientific premise for the proposed project consists of the: (i) substantial treatment challenge and burden of PCG among older adults; and (ii) theoretical rationale as to why adaptation of the current ART protocol (used to treat PTSD) may be a promising approach in the treatment of PCG. In brief, ART is a novel non-pharmacologic intervention that can be delivered in just 1-5 sessions. It is a federally-recognized as an evidence-based treatment for PTSD in civilians and veterans. [18,19,23] At present, it is unknown whether ART can be used to improve complicated grief and psychological trauma in persons with PCG. However, the

similarities and significant overlap between PTSD and PCG provide a theoretical rationale that this promising PTSD intervention can offer similar benefits for individuals with PCG, especially those who also suffer from concomitant psychological trauma. This is augmented with anecdotal reports of successful treatment of PCG by use of ART among mental health practitioners trained and proficient in the ART protocol.

PURPOSE AND SPECIFIC AIMS

The purpose of our proposal is to examine whether ART is effective for the treatment of prolonged and complicated grief and associated psychological trauma among older adult hospice caregivers who have experienced the death of an immediate family member at least 12 months ago. We propose to measure outcomes of ART in the treatment of PCG by studying a series of 50 participants treated with four weekly sessions of ART delivered by licensed mental health providers, twenty-five who will receive ART immediately upon enrollment and 25 who will receive ART four weeks after enrollment to allow for comparison between groups. The primary outcomes of PCG symptoms, psychological trauma, and depressive symptoms will be evaluated following each session.

The ***specific aims*** of this *wait list controlled* prospective pilot trial are to:

1) Compare pre-to-post ART symptom changes in magnitude and rate of change of PCG, psychological trauma, and depressive symptoms, comparing results between a post-ART group and a group who have not yet received ART.
2) Investigate variation in treatment response by baseline symptom levels of PCG and PTSD, and depressive symptoms.

A **secondary aim** will be to compare within and between session changes in the stress biomarkers, salivary alpha amylase and salivary interleukin-6, to evaluate objective changes in the stress response in relation to treatment with ART. Results of this study will provide information about the short-term outcomes of treatment with ART in the setting of prolonged complicated grief. This, in turn, will inform optimal dosing and participant selection criteria for treatment with the ART protocol for use in a future randomized controlled clinical trial.

DESIGN AND METHODS

Experimental design. This is a randomized *wait list controlled* treatment study (*n*=50) whereby primary caregivers (age >60 years) of an immediate family member who died after enrollment in hospice, and who indicate significant symptoms of PCG and psychological trauma, will receive 4 weekly sessions of ART (described below). *Participants will be randomly assigned to receive ART either a) during the first four weeks after enrollment, or b) beginning four weeks after enrollment (Figure 2). This 4-week delay in treatment will serve as a formal control condition to compare acute response. The presumption is that is the waitlist period is unlikely to result in either significant improvement or worsening of PCG, given that all participants will have been grieving for at least a year and have few available resources to help them process the loss beyond one year. On the other hand, the waitlist condition will theoretically help to remove any expectation effects from anticipated receipt of therapy. Participants in both groups will be provided with information about how to obtain help in the event of an emotional crisis. Assessments will occur upon enrollment, weekly during ART for both groups, at the end of the waitlist period or after treatment completion, and at 8-week follow-up (Table 1), and will include reliable and valid self-report measures. After the 4-week waitlist period, control subjects will receive the ART intervention.*

Sample. We will recruit older adult (>60 years) immediate family members of an individual who received hospice care prior to death. The study will take place at the University of South Florida (USF). Participants will be recruited from Suncoast Hospice, a subsidiary of Empath Health. Suncoast Hospice has 6,000 deaths/year with 1-4 family members per patient, resulting in 6,000

– 24,000 bereavement contacts per year. Estimating conservatively that 5% of the bereaved will experience PCG, and half of those would also suffer from psychological trauma, this would provide a potential pool of participants of 150-600 per year, more than enough to meet our recruitment goals. It has been reported that females experience PCG more frequently than males, which may be due to the longer life expectancy of females,[24] and because of that we expect to have more females in the study.[25] We will attempt to recruit males in equal numbers and will also evaluate gender as a predictor of response to ART. Sample size is based on power analysis.

Rationale for Intended Dose and follow-up timing. Previous studies of ART conducted by our group for treatment of PTSD consisted of an average of approximately 3.5 sessions delivered to study participants.[18,19,23] Because there are no data yet regarding optimal dose in PCG, we propose to deliver the standard dose of 4 sessions of ART in the setting of PCG. However, we will purposely re-assess symptoms of PCG following each session, to help determine optimal intervention length for a future full-scale randomized controlled trial. After treatment completion (both groups), the 8-week post-ART assessment is meant to shed light on whether improvements in symptoms are sustainable, in preparation for a larger, more definitive study.

Recruitment. Participants will be recruited from Suncoast Hospice, a member of Empath Health. Grief counselors there will identify persons who meet criteria for PCG as they near the end of the 13 months of grief support provided through the hospice program. They will provide a brief summary of the study either verbally or by showing them a recruitment video, or both. Dr. Cindy Tofthagen (co-I) or a study staff member will attend monthly meetings with the grief counselors to provide information on eligibility criteria and encourage appropriate referrals. Grief counselors, with verbal permission from the potential participant for referral, will contact the study team by either phone or email and provide contact information. A study coordinator will call or email, depending on preference, and provide details about the study. If the individual expresses continued interest, an appointment for face to face screening and enrollment, if eligible, will be made. As described, this hospice center has 6,000 enrolled persons per year who die, leaving 1-4 bereaved persons who are eligible for services. We anticipate minimal difficulty in recruiting 50 participants proposed in this study; however, if recruitment lags, and another site is needed, a second site in the same county as USF, where Dr. Tofthagen (co-PI) has conducted multiple studies, will be added.

Inclusion criteria. To enroll in the study, individuals must meet the following criteria: (i) Adult age 60 years of age or older; (ii) previous primary caregiver of immediate family member who died after enrollment in hospice with the death occurring at least 12 months prior to enrollment (iii) current symptoms indicative of proposed diagnostic criteria for complicated grief disorder, as proposed by Shear et al. (2011); (iv) current score of $\geq$25 on the 19-item Inventory of Complicated Grief; (v) current symptoms indicative of significant psychological trauma, as documented by score $\geq$33 on the 20-item DSM-5 PTSD checklist (PCL-5)[26] or score of $\geq$4 on the PDSQ PTSD subscale; and (vi) denial of suicidal ideation or intent, with no evidence of psychotic behavior.

Exclusion criteria. Individuals will be **excluded** from the study who meet the following criteria: (i) engaged in another psychotherapy regimen that could also influence symptoms of PCG (ii) have a major psychiatric disorder (e.g. bipolar disorder) deemed likely to interfere with treatment delivery; (iii) have current substance abuse dependence (alcohol and/or drug) treatment anticipated to interfere with treatment delivery. All persons recruited for potential study participation will undergo a clinical intake assessment, with completion of ART intake form, by Dr. Diego Hernandez, a licensed clinical psychologist, to determine study eligibility.

Study intervention. All participants will receive ART on a weekly basis for 4 sessions.[18,21,23] The dose of 4 sessions has been selected to insure what is believed to be an effective dose based on previous studies of ART for treatment of PTSD. As background, within each treatment

session, the ART protocol (Appendix A) first uses the technique of imaginal exposure to elicit physiological reactions associated with patient recall from beginning to end (verbally or non-verbally) of a traumatic/distressing experience (i.e. death of an immediate family member in our case). As physiological reactions emerge, the participant is directed to focus their attention on the specific body-centric reactions while laterally performing smooth pursuit eye movements[27] which are achieved by tracking the clinician's hand which oscillates from left-to-right at a short distance from the participant's eyes. This process is employed to substantially reduce the magnitude of the physiological reaction(s). After two full courses of processing (reducing) all physiological reactions that are induced by imaginal exposure of the distressing experience, the technique of imagery rescripting[28] is used. Imagery rescripting is broadly defined as working directly with imagery in order to change meanings and ameliorate distress.[28] Thus, in this phase, the participant is directed to imagine a positive way in which they prefer to recall their experience(s), including emphasis on "replacing" negative images in the brain with positive images. This technique is based on the process of memory reconsolidation, which allows for "adding" of positive material to the recall of negative, highly emotional past experiences.[29] The ART intervention for this study will focus specifically on modification of the traumatic memories/images associated with the death of the loved one. These memories will be selected for use with imaginal exposure and imagery rescripting, and based on the conventional ART protocol as described. In addition, Gestalt therapy may be used in which the participant can imagine interacting with the lost family member, such as "going back" and saying goodbye or making amends for unfinished business or regrets. **Intervention fidelity** will be achieved by having the ART clinicians complete an ART Fidelity Checklist which has been used in the previous studies of ART, and will be adapted specifically for treatment of PCG. Dr. Kip (co-PI), will randomly select and review 10% of all fidelity checklists, stratified by ART clinician, to verify compliance or identify potential deviations or omissions from the standardized ART protocol. If needed, refresher training in the ART protocol will be provided to study clinicians.

Data Collection. Data collection will occur at screening/enrollment, at the end of the 4-week waitlist period (control subjects), weekly during the 4-week intervention period, and at 8-week post treatment follow-up. Thus, time on study per participant will be 12 or 16 weeks depending on random assignment. *To minimize participant burden, we have parsimoniously selected instruments to evaluate our three primary outcomes: PCG, psychological trauma, and depressive symptoms. Co-morbidity information, grief counseling history, and demographic information will be collected. Outside of the initial informed consent, screening, and clinical evaluation, which will take 1.5-2 hours, completion of outcome measures will take less than 20 minutes.*

Instruments (Table 1)

The Short-Portable Mental Status Questionnaire (SPMSQ)[30,31]is a 10-item test measuring the presence and the degree of intellectual impairment, including dementia versus being cognitively intact. The concepts measured include orientation, memory function related to capacity for self-care, remote memory, and capacity to perform several mental operations. Test-retest correlation has been reported as 0.82, and validity has been demonstrated between the SPMSQ and a clinical diagnosis of intellectual impairment. The SPMSQ will be used to screen for cognitive impairment prior to enrollment.

The Charlson Comorbidity Index (CCI) assesses comorbidity levels by taking into account both the number and severity of 19 pre-defined comorbid conditions.[32] It provides a weighted score of comorbidities which can be used to predict function and mortality. Comorbidity assessment will be conducted and number of hospitalizations and visits to healthcare providers over the past year will also be collected at enrollment.

PCG will be evaluated by mean treatment response on the 19-item Inventory of Complicated Grief (ICF)[33] over the course of the 4-week intervention period for the PCG regimen. Scores range from 0-76 with a score $\geq$24 indicating presence of complicated grief.

Cronbach's alphas were 0.92-0.94 and 6-month test-retest reliability was 0.8; concurrent validity ranged from 0.67-0.87 when compared to existing grief measures.[33]

The PCL-5 (PTSD Patient Checklist)[26] is a 20-item self-report instrument that will be used to assess the 20 DSM-5 symptoms of PTSD (psychological trauma)(corresponding to criteria B-E). The total symptom severity score ranges from 0 to 80. A diagnostic cut-point for PTSD of 33 has been recommended.[26] In addition, it is generally accepted that a reduction of 10 points or more on the PCL-5 is indicative of statistical and clinically meaningful improvement. The PCL–M has been shown to have excellent concurrent validity (r=.93)[34]and evidence of test–retest reliability (r=.96).[35] The PCL-5 will also be used during screening to ensure that all participants meet criteria for psychological trauma.

The Prolonged Grief Disorder-13[36] (PGD-13) is a diagnostic tool to assist mental health professionals in diagnosis of complicated grief by evaluating 13 items. The PGD-13 will be used during screening to ensure that all participants meet diagnostic criteria for PCG.

The Center for Epidemiologic Studies Depression Scale(CES-D)[37]is a widely used 20-item scale that has proven useful both as a screening instrument to detect individuals at risk for depression, and to measure the symptoms of depression. The CES-D has demonstrated reliability, validity, sensitivity, and specificity and[38,39] will be used for assessment of depressive symptoms.

The CDC HRQOL–14 "Healthy Days Measure" is a 14 item health related quality of life measure consisting of three core modules; the 4 item healthy days module, 5 item activity limitations module, and 5 item symptom module (https://www.cdc.gov/hrqol/hrqol14_measure.htm). Scores are computed by adding a respondent's physically and mentally unhealthy days, with a maximum of 30 for one person. The CDC HRQOL-14 is in the public domain, has been validated in a wide range of community dwelling adults, and will be used to assess changes in health related quality of life in response to treatment[40].

For the biomarkers of sAA and IL-6, measurement will occur using the protocols listed in the Salimetrics® α-Amylase Kinetic Enzyme Assay Kit for kinetic measurement of sAA activity (Appendix B) and Salimetrics® Salivary Interleukin-6 Elisa Kit KIT (Appendix C). The unstimulated passive drool method will be used. Participants will be asked to tilt head forward, allowing the saliva to pool on the floor of the mouth, and then pass the saliva through the SalivaBio Collection Aid (SCA) into a polypropylene vial. Participants will be advised to avoid eating, brushing teeth, or smoking for an hour prior to collection, and to avoid alcohol intake for at least 12 hours before each salivary collection. Participants will be provided with water and will rinse their mouth with water 10 minutes prior to salivary collection, in order to avoid specimen compromise from sugar or acidic foods that lower sample pH or stimulate bacterial growth. Each specimen will be labeled with the patient's study ID number, date, and time of collection. To avoid bacterial growth, all salivary samples will be immediately put on ice and transported to the USF College of Nursing Biobehavioral Laboratory where they will be frozen at or below -20ºC within 8 hours of collection, where samples can be stored up to 6 months. At time of assay, the samples will be thawed, centrifuged at 1500 x g (@3000 rpm) for 15 minutes.

In addition to the above instruments, a brief demographic, clinical history, and use of medications form will be completed at screening/baseline. The use of medications will also be documented over the course of treatment with ART and follow-up.

Table 1. Data Collection Instruments and Schedule

No.	Instrument	Minutes to complete	Screening	Base-line	End Waitlist	During ART	8-wks Post ART
1	Consent form	30	I / C				
2	Inventory of Complicated Grief	5	I / C		C	I / C weekly	I / C

3	Prolonged Grief Disorder form	3	I / C				
4	PCL-5 (psychological trauma symptoms)	5	I / C		C	I / C weekly	I / C
5	Short-Portable Mental Status Questionnaire (administered by clinician)	-----	I / C				
6	Psychiatric Diagnostic Screening Questionnaire (PDSQ) (PTSD subscale only-completed by clinician)	15	I / C		C	End of treatment I/C	
7	Inclusion/exclusion form (completed by study staff)	-----	I / C				
8	ART CG Intake Checklist (completed by clinician)	-----	I / C				
9	Demographic form	5		I / C			
10	Medical History form	5		I / C			
11	Medication Use	5		I / C	C	I/ C weekly	I / C
12	CES-D (depressive symptoms)	5		I / C	C	I/ C weekly	I / C
13	CDC HRQL-14 (health related QOL)	5		I / C	C	I/ C weekly	I / C
14	ART Fidelity form (completed by clinician)	-----				After each ART session	
15	Adverse Event form (competed by study staff)	-----		As occurring during the study			
16	Serious Adverse Event form (competed by study staff)	-----		As occurring during the study			
17	Biospecimen Tracking form (completed by study staff)	-----				I / C weekly	
18	Salivary alpha amylase & salivary interleukin-6 (collected by study staff)	-----		I	C	I / C pre and post ART	

*Assessment of prior hospice counseling sessions, how majority of sessions were delivered (individual, group, or phone), time since counseling. I: Intervention group (ART). C: Control group (waitlist).

Data analysis plan. Continuous variables will be expressed as mean ± standard deviation (SD); categorical variables will be expressed as percentages. For **Specific Aim #1**, the primary outcome will be change on the19-item Inventory of Complicated Grief (ICG). Secondary outcome measures will include change on the 20-item PCL-5 (PTSD) and 20-item CES-D (see Table 2). Initially, baseline characteristics will be compared by random assignment by use of student *t*-tests or Wilcoxon tests (based on distributional properties) for continuous variables and Fisher's exact test for categorical variables. This will inform potential need for statistical adjustment for any unanticipated imbalances in presenting characteristics. Analysis of covariance (ANCOVA) will be used to compare pre/post differences on outcome measures by random assignment, adjusting for baseline value of the outcome of interest. Standardized effect sizes for outcome measures will be calculated[41] along with corresponding 95% confidence intervals. The analysis will be conducted by the intention to treat (ITT) principle among subjects with 4-week pre- and post- assessments (i.e. "completers"). However, a second ITT analysis will be conducted that takes into account participants who withdraw from the study or do not provide complete pre- and post-assessment data. To be conservative, missing values on the primary and secondary outcomes, all of which are continuous variables, will be imputed as difference values of zero (i.e. no treatment effect). Whereas this approach is generally expected to reduce the overall effect size, there may be a corresponding increase in statistical power due to a larger sample size and smaller standard of error (i.e. by imputing pre/post difference values of zero to represent no treatment effect). To "correct" for the reduced standard errors, a third analysis will be conducted using the ITT principle and original standard errors derived from the subjects who received and completed their assigned regimen. For all 50 subjects who receive ART (i.e. after the control period for waitlist subjects), the full set of pre-ART, weekly ART sessions, and 8-week follow-up assessments will be evaluated. This will include within-subject changes on the ICG, PCL-5, and CES-D that are graphically plotted and formally tested by repeated measures analysis of variance specifying an exchangeable correlation structure. These analyses are designed to gain insight into the rate of change in symptoms over the 4 weeks of ART (i.e. minimum required dose), as well as sustainability of response at 8-weeks. To examine

relationships between absolute scores and change scores on the ICG, PCL-5, and CES-D, Pearson correlation coefficients will be calculated. Given expected correlation among these measures, mediational models will then be fit by random assignment. For these models, scores on the ICG at 4 weeks will serve as the outcome of interest, random assignment (ART or waitlist) as the direct effect, and change score on the PCL-5 or CES-D as a potential mediator (indirect effect). These analyses will provide insight into the magnitude of direct effect that the ART intervention has on change in ICG scores, along with the extent to which such changes appear to be mediated through corresponding changes in symptoms of PTSD and depression. For within session assessments of sAA and IL-6 (beginning and end of sessions 1 and 4), changes will be evaluated by use of repeated measures analysis of variance. For **Specific Aim #2**, linear mixed models will be used to examine variation in ICG, PCL-5, and CES-D scores over time in relation to baseline covariates, assuming an autoregressive correlation structure. This analysis is designed to identify presenting baseline characteristics that appear to be most associated with favorable treatment response over time.

Statistical power.

For Aim #1 comparison by random assignment for the primary outcome of ICG, we assume all 50 subjects in the analysis, including imputation (as described above) for minimal dropout expected in the 4-week intervention or control period. The sample will provide 80% power (2-sided type I error rate of 0.05) to detect a "large" effect size of 0.81.[42] Thus, consistent with the R21 mechanism, the analysis is not meant to be confirmatory, but rather an estimate of likely effect size associated with the ART intervention. For within-subject analyses of sustained ART response at 8 weeks among all 50 subjects, we conservatively assume up to 20% loss to follow-up and within-subject correlation of 0.5. Thus, with an effective analytic sample size of 40 subjects (50 x 0.80) and the assumptions defined above, the study will provide 80% power to detect a "medium" effect size of 0.51.[42] Of note, in previous studies of ART (within-subject and between group designs) for treatment of psychological trauma, large effect sizes have been observed.

Potential Problems and Alternative Strategies. Given the inclusion criterion of at least 12 months time since death of the family member, some subjects may be disappointed if initially assigned to the 4-week waitlist control condition. Whereas this period of time is purposely brief, multiple contacts will be made during the 4-weeks to confirm the data collection schedule and future scheduled receipt of ART after the waitlist period. In addition, the sample size in this exploratory study is modest, and will therefore place a premium on minimizing loss to follow-up during the intervention period and at the 8-week assessment. Again, consistent contact will be maintained with study subjects to maximum study retention.

HUMAN SUBJECTS PROTECTION

Risk of the Intervention to Human Subjects.

Potential risks to research subjects fall into 2 categories: (i) participation in the study and (ii) receipt of treatment with ART. Regarding item (i), there is the theoretical possibility of an unanticipated breach of confidentiality, as well as potential emotional distress experienced by completion of self-report questionnaires.

Potential Risks of the Intervention

Although small, there is some risk that receipt of psychological therapy, particularly exposure based therapies (such as ART), can potentially worsen psychological symptoms. In addition, there could be a temporary increase in distress to the subject as a result of treatment. However, in earlier studies of ART, no such reactions occurred. Never-the-less, it is possible that distressing and unresolved memories may emerge. Some subjects may experience reactions during a treatment session that neither they nor the clinician may have anticipated, including a high level of emotion or physical sensation. Subsequent to the treatment session, the processing

of incidents and memories may continue, and other dreams, memories, and feelings, may emerge.

Adequacy of Protection against Risks from the Intervention.

For all participants, those who show any unexpected evidence of psychological symptoms or distress through the completion of the study instruments or treatment with ART will receive appropriate intervention, including counseling and treatment by Dr. Diego Hernandez.

For the proposed study, we will be recruiting and enrolling adults with prolonged, complicated grief. While PCG is a debilitating condition in and of itself, it is not known to confer heightened risk of adverse events upon participation in clinical studies. Study subjects will be symptomatic (i.e. the rationale for the study and treatment to be provided), and thus, potentially vulnerable to an expectation of treatment success which may or may not be ultimately experienced. Drs. Kip and Tofthagen will review cases and provide clinical support and supervision to the ART therapists to ensure participant safety and the use of best clinical practices in delivering the ART protocol with fidelity.

Prior experience with ART demonstrates an excellent safety profile, including working with many cases of complex PTSD. For our randomized controlled trial of ART published in Military Medicine in 2013, a total of 57 U.S. service members and veterans were enrolled. Of these, 50 were treated with Accelerated Resolution Therapy (ART) that encompassed a total of 183 treatment sessions. In this high risk population, there were only 4 adverse events that were attributed as possibly or probably related to receipt of ART. Of these, only one was considered serious and required external treatment. With the proposed population of participants with prolonged, complicated grief, we anticipate some adverse reactions to occur during treatment sessions with ART and have licensed mental health providers on the research team, who have substantial experience with administering ART, and will intervene to ensure the safety and well-being of all participants. Any adverse events will be reported to IRB within 24 hours of occurrence.

It is anticipated that a significant percentage of subjects will be taking medications, including but not limited to anti-depressants, anti-anxiolytics, and sleep medications. Subjects will be instructed to continue with their current medication regimen as instructed by their primary care physician. When medications are prescribed as “Pro re nata” (“prn”), and also have the potential to significantly interfere with cognitive ability (i.e. required for the ART protocol and imagery rescripting), such as Xanax, subjects will be asked not to take these specific medications immediately prior to an ART session. However, they will be permitted to bring these medications with them to their ART session to be available for use, if needed.

Participants will be provided with contact information for the co-PIs (Drs. Kip and Tofthagen). It will be made explicitly clear to the subjects that they should seek out Drs. Kip or Tofthagen at any time should they experience significant distress. Should a participant report significant distress related to ART or their grief condition that is indicative of an adverse event, they will be provided counseling with a licensed mental health counselor and/or advised to contact their healthcare provider immediately, at their own expense. During treatment sessions, the ART clinician will carefully monitor subject response to the therapy and intervention protocol. If there is evidence of significantly heightened anxiety or distress, the therapist will temporarily stop the session and intervene through the use of counseling and possibly methods of relaxation to restore the subject to a calm state. Should a participant, or potential participant, exhibit suicidal ideations or evidence of severe emotional instability during screening or at any time during the study, they will be treated immediately or referred for higher level care, such as in-patient psychological treatment.

Saliva Specimen Collection and Handling

Saliva will be collected for evaluation of acute and chronic stress response, using sAA and IL-6. Saliva is considered biohazardous, requiring caution during collection, handling, and storage. The research team member will wash hands prior to collection and don gloves during

salivary collection. Coolers used to transport specimens will be labeled as biohazardous waste. Each specimen will be labeled with the participant's study ID number, date, and time of collection. To avoid bacterial growth, all salivary samples will be immediately put on ice and transported to the USF College of Nursing Biobehavioral Laboratory where they will be frozen at or below -20ºC within 4 hours of collection, where samples can be stored up to 6 months. At time of assay, the samples will be thawed, centrifuged at 1500 x g (@3000 rpm) for 15 minutes. Following completion of the study, all specimens will be disposed of, by placing in an appropriate biohazardous waste disposal container.

Potential Non-Clinical Risks from Study Participation.

Potential non-clinical risks to study subjects include the collection of health information and inadvertent disclosure of such information, including lack of confidentiality. Specifically, a large battery of self-report data on psychological and physical health will be collected from study subjects at baseline and during the course of the study intervention and follow-up. The investigative team will require access to identifiable private information about human subjects in order to carry out enrollment, intervention, and data collection. This will include contact information necessary for scheduling all study-related visits and data collection.

Adequacy of Protection against Non-Clinical Risks.

Each study subject will be assigned an arbitrary, de-identified code number to ensure anonymity of the research data, and no identifiable private information will be associated with any of the research data files except a list containing the participant name, ID number, and contact information, to contact participants regarding follow-up appointments and upcoming data collection. All research data will be initially collected, by the Research Coordinator/Data Manager, on hard copy forms and stored in locked file cabinets behind a locked closed office door, as will the and the written list linking participants name and contact info with their study ID,. Data from the hard copy forms will be entered into an SPSS database that is accessed from desktop computers located in locking offices and with a secure password login and maintained on a secure network. Possession of all study materials will be stored in a locked cabinet in a locked research office at all times, and all study-related files will be password protected. Study information obtained will be kept strictly confidential, and it will not be possible to identify any participant from reports that may emanate from this research. The USF Institutional Review Board (IRB) will review and approve the study prior to involvement of any human subjects. The research team will enroll subjects recruited from hospice. Participants will be provided with a verbal explanation of the nature of the study in a private area. After participant questions are answered, informed consent for participation will be obtained from the subject and a study information packet, including information about the study, study withdrawal, and contact numbers of investigators will be provided to all participants.

Potential Benefits of the Proposed Research to Human Subjects.

Benefits to participation include potential significant reduction in prolonged, complicated grief and related comorbidities, including but not limited to symptoms of depression, anxiety, sleep dysfunction, and psychological trauma. Broader knowledge to be gained from the effects of the ART intervention may be the development and future validation of an alternative, effective non-pharmacological approach to management and treatment of prolonged, complicated grief. The risks for participation in this study are reasonable because prolonged, complicated grief is physically and emotionally burdensome, and current treatment options are suboptimal.

Importance of the Knowledge to be Gained.

We expect to obtain support for our central hypothesis that adaptation of the ART intervention yields empirical evidence as a particularly promising mind-body approach for substantial reduction in symptoms of prolonged, complicated grief and related comorbidities. Confirmation of this evidence would be pursued through the conduct of a subsequently proposed full-scale clinical trial. Ultimately, this may lead to better management of prolonged, complicated grief, by use of a non-pharmacological intervention.

DATA SAFETY AND MONITORING PLAN

A safety and data monitoring committee, consisting of 3-4 senior scientists with a mix of clinical, basic research, and behavioral expertise will be constructed. These will be scientists not involved in the proposed research project. The PMRC will review all cases of serious adverse events within 48 hours of occurrence to determine probability of association with the study intervention.

In addition, the Principal Investigators, Drs. Tofthagen and Kip, will be responsible for monitoring the safety and efficacy of the study, executing the DSM plan, and complying with all reporting requirements to PMRC and IRB. They will meet weekly with the other investigators to review the data structure, data processing and security of the system. The investigators will review the study logs monthly for enrollment responses and attrition rates of participants, plus review notes regarding any adverse reactions to participating in the study. Monitoring will include expected versus actual recruitment rates, any attrition during the period of the study, and any adverse events.

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