*[USE THIS BIOMEDICAL PROTOCOL TEMPLATE IF YOUR PROJECT INVOLVES **ANY** PHYSICAL CONTACT OR MEDICAL INTERVENTIONS WITH PARTICIPANTS]*

INSTRUCTIONS:

- Depending on the nature of your research, some sections may not be applicable to your research. These sections can be removed as needed.
- When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.

PROTOCOL TITLE:

Treatment of Stress-Related Psychopathology: Targeting Maladaptive and Adaptive Event Processing

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If the principal investigator's primary role at UH is resident, fellow or student, identify a faculty advisor.

☒ N/A

OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):

☒ N/A

VERSION NUMBER:

Include the version number of this protocol if assigned by an outside entity.

N/A

DATE:

12/14/2021

Objectives

Directions: Describe the purpose, specific aims or objectives. Be sure to also include the hypothesis being tested

Positive Processes and Transition to Health (PATH) includes six, 90-min sessions that target maladaptive event processing (unproductive processing, avoidance, and impaired reward sensitivity), while also promoting parallel adaptive event processing (constructive processing, approach, and reward seeking) for destabilizing life events and for positive events. PATH uses a platform of narrative revisiting of destabilizing life events, as well as positive life event reminiscence. Patients will be selected for having experienced a destabilizing life stressor and related psychopathology. The R61 trial ($N = 45$) will examine whether PATH engages the therapeutic targets, with clear Go/No Go rules. In the R33, patients ($N = 135$) will be randomized to PATH or progressive muscle relaxation (PMR) and assessed over a 3-month follow-up.

The Specific Aims are:
Specific Aim 1: Engage Therapeutic Targets (R61): In an open trial ($N = 45$), we will examine whether PATH changes therapeutic targets (unproductive processing, avoidance, impaired reward processing) from pre- to 3-month follow-up, with at least medium effects ($d = 0.60$) on two of three primary target measures and at least ($d = 0.50$) on one secondary target measure. We will examine dosing and timing of effects.
Specific Aim 2: Replication of Target Engagement (R33): In a randomized control trial ($N = 135$), we will examine whether PATH alters therapeutic targets from pre- to 3-month follow-up in comparison to PMR.
Specific Aim 3: Link Changes in Targets to Changes in Stressor-related Outcomes (R33): We will examine whether changes in therapeutic targets (pre- to post-) predict improvement in PTSD and depression symptoms (pre- to 3-month follow-up).
Specific Aim 4: Feasibility and Dropout/Acceptability of PATH (R61/R33): We will examine whether patients perceive PATH as helpful and complete/adhere to treatment, and therapist fidelity.

There is an urgent need to develop novel treatments, given the prevalence, impact, and cost of PTSD and MDD (e.g., Hoge & Chard, 2018). PATH is an innovative intervention that targets three interrelated, transdiagnostic processes that maintain stressor-related psychopathology. PATH's unique early and sustained focus on positive emotions could improve adherence and outcome, particularly in those with the reward deficits commonly seen in PTSD and MDD. Further, PATH's focus on positive emotions and "stuck" processing targets unique processes largely absent in current PTSD therapeutics. PATH is novel in in applying exposure principles to depression, not just PTSD. This brief, positive, mechanistically precise, transdiagnostic treatment has the potential to improve treatment engagement and outcomes, identify clear therapeutic targets that predict better outcomes, and ultimately reduce the costly burden of stressor-related psychopathology.

We hypothesize that (1) those in PATH will have significant changes in the therapeutic targets, (2) those in PATH will show a greater change in therapeutic targets than those receiving Progressive Muscle Relaxation (PMR), (3) changes in therapeutic targets predict improvement in PTSD and depression symptoms, and (4) those in PATH will perceive the intervention as helpful and adhere to treatment.

Background

Directions: Describe the relevant prior experience and gaps in current knowledge describing how it will add to existing knowledge. Include any relevant preliminary data.

Novel, more effective, efficient, tolerable, transdiagnostic interventions are needed. Posttraumatic stress disorder (PTSD) and depression (MDD) frequently co-occur (more than 60%; Rytwinski, Scur, Feeny, & Youngstrom, 2013), with shared distress-related symptoms and substantial impairment and disease burden (Post, Zoellner, et al., 2011; WHO, 2004). State-of-the-art psychotherapies for PTSD and MDD show clinically meaningful gains (Cuijpers et al., 2014; Watts et al., 2013). Yet, there is substantial room for improvement, given considerable dropout rates, time-intensive and emotionally taxing interventions, and a significant minority left with debilitating symptoms and risk for relapse. Emerging models of psychopathology (e.g., Hayes et al., 2015; McNally, 2016) propose that negative and positive feedback loops create vicious cycles that increase the risk of getting "stuck" in pathological states (e.g., Holtzheimer & Mayberg, 2011; van de Leemput et al., 2014). Accordingly, next-wave psychotherapies must target key maladaptive processes and facilitate transition to more adaptive ones (Hofmann & Hayes, 2019). Therapies following stressful life events focus almost exclusively on negative emotion, which may contribute to dropout. Capitalizing on positive emotions early may make treatment less daunting and harness the power of the positive affect system.

Exposure to destabilizing life events (e.g., sudden loss of loved one, sexual assault, job loss) ranges from 50-89.5% in the U.S. population (Kessler, 1995; Kilpatrick et al., 2013). There is compelling support for the etiological role of such stressful life events for a range of psychopathology (Harkness & Monroe, 2016), including persistent problems in the negative and positive valence systems related to PTSD and MDD. Decades of research have isolated central maladaptive and adaptive processes linked to psychopathology and resilience following destabilizing life events (Aldao et al., 2010; Hayes et al., 2015; Waugh & Koster, 2015). These therapeutic targets include: **unproductive/constructive event processing** (e.g., rumination vs. updating with corrective information, meaning-making); **avoidance/approach** (e.g., disengagement vs. engagement); and **impaired reward sensitivity/positive emotion engagement** (e.g., impaired reward processing vs. reward seeking). Together, these maladaptive processes are hypothesized to form a "stuck" system that prolongs negative mood, interferes with adaptive event processing, and increases reactivity to future stressful events, whereas their adaptive counterparts disrupt this system and promote resilience.

Positive Processing and Transition to Health (PATH)

PATH targets three transdiagnostic maladaptive processes and facilitates their more adaptive counterparts: 1) unproductive and constructive processing, 2) avoidance and approach, and 3) impaired reward sensitivity and positive emotional engagement and reward seeking. PATH is designed for individuals who have stressor-related psychopathology and can treat symptoms of PTSD or depression or the combination.

Inclusion and Exclusion Criteria

Describe how individuals will be screened for eligibility. Using the tables below, describe the inclusion and exclusion criteria that will define who will be included and excluded in your final study sample.

Inclusion Criteria

1. *Destabilizing life event involving profound loss or threat, with a minimum duration of 12 weeks since the event.*
2. *Between the ages of 18 and 65.*
3. *Elevated target: Scores of at least moderate (1 or higher) on at least 2 of the 3 target mechanisms: re-experiencing or ruminative processing of the destabilizing event (PSS-I items: 1, 2, 3, 4 or QIDS-C item 11), avoidance (PSS-I items 6, 7, 8), or reward deficits (PSS-I items 12, 13, or QIDS-C item 13)*
4. *Elevated symptoms on either the PSS-I or QIDS-C (at least moderate): 18 on PSS-I (Foa et al., 2016) and/or 11 on QIDS (moderate depression severity; Rush et al., 2003), with symptoms persisting for 1 month or longer.*

Exclusion Criteria

1. *Current diagnosis of psychotic, bipolar, or substance use disorder.*
2. *Severe self-injurious behavior or suicide attempt within the prior 3 months.*
3. *Unwilling or unable to discontinue current CBT or unstable dose of psychotropic mediations within prior 3 months.*
4. *Ongoing intimate relationship with the perpetrator (in assault-related event).*
5. *No clear memory of event or occurred more than 5 years ago.*
6. *Residence outside of the states of Ohio, Delaware, or Washington*

Number of Research Participants

Directions: Indicate the maximum number of research participants to be accrued locally, and, if this is a multi-site study, indicate the maximum number of research participants to be accrued across all sites.

This study is being conducted in collaboration with the University of Washington and the University of Delaware. In total, for the R61, 45 participants will be evenly accrued across all sites, and for the R33, 135 participants will be evenly accrued across all sites.

Recruitment Methods

Describe how subjects will be identified (the source of potential research participants), and also how, when, and where they will be recruited. Describe all methods of contact / communication.

We will emphasize online advertising (e.g., Craigslist and study website, pathway2help.com). We will increase our visibility in the community by boosting awareness of our programs and ongoing research. This includes routine postings on free advertising websites (e.g., Craigslist and study website). We expect that the bulk of our study participants will come from online advertisement.

In addition to online advertising, we will also send letters describing the study to healthcare providers who can bring this study to the attention to their patients who may be eligible. We will also send these providers brochures that they can distribute to interested patients. These brochures contain a site-specific phone number and a link to the study website so that interested participants can contact the study team to learn more about this project. Finally, we will also post paper flyers for the study throughout the

community, such as on college campuses, churches, grocery stores, libraries, etc.

Setting

Directions: Make sure to describe:
1) The sites and locations where your research team will conduct the research.
2) Where your research team will identify and recruit potential research participants, and
3) Include the physical location where research procedures will be performed.

Adults will be recruited from the Cleveland, OH area. Interviewers will collect demographic data and complete an eligibility screening form (type of destabilizing event, inclusion/exclusion criteria) via phone screens. Potentially eligible individuals will be scheduled for an intake and complete informed consent in-person before doing an assessment; those excluded will be given referrals. All assessments and intervention sessions will take place in the Mather Memorial building at Case Western Reserve University, in Room 137. (However, see below for COVID-19 changes to the study setting.) Adults will also be recruited from Wilmington/Newark, DE (University of Delaware) and Seattle, WA (University of Washington).

COVID-19 Changes

For the foreseeable future, due to the COVID-19 pandemic and current restrictions on in-person research across all three sites, all study procedures will take place remotely and online, rather than in-person. Specifically, the different procedures are as follows:
-Participants will be recruited from across states instead of across cities. That means adults can reside anywhere in Ohio, Delaware, and Washington, instead of just the Cleveland, Wilmington/Newark, and Seattle areas.
-Intakes will occur via the secure videoconferencing platform Zoom.us (HIPAA compliant and currently used by the University Counseling Center), rather than in-person. Participants will review and sign informed consent forms via REDCap, while the assessor is on Zoom with them.
-The participants will receive the PATH intervention through Zoom rather than in-person.
-For participants without technology to complete the measures, a member of the study team will drop or mail the Kindles off at their home in sealed envelope and receive them after subjects complete all study procedures.

There is a potential we will go back to in-person procedures in the future (i.e., when restrictions are lifted), should we reach that point, we will modify the protocol to reflect this change.

Consent Process

Describe if the study will be obtaining consent, or if the study will be applying for a waiver of consent.

Potentially eligible individuals will complete their informed consent in-person before starting intake (see below for COVID-19 changes). Participants will be informed that participation is optional and that they may discontinue participation at any time. Participants will be provided with the contact information for study staff and the Human Subjects division.

COVID-19 CHANGES

Potentially eligible individuals will complete their informed consent via REDCap, while an assessor is on Zoom with them. Assessors will provide participants with the same information as above. Consent forms have been uploaded that reflect changes to an online and remote intervention and assessments. Assessors will also ask about collecting emergency contact information, in case it's ever needed.

Sharing of Results with Research Participants

Directions: Describe whether results (study results or individual subject results such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with the research participants or others (e.g. the subject's primary care physicians) and if so, describe how the results will be shared.

☒ Results will **not** be shared with research participants

☒ Results will **not** be shared with research participants' doctors

Study Design

Directions: Describe and explain the overall study design. (eg: single visit, single-blind, double-blind, non-randomized, randomized, blood draw, investigational drug, device etc.)

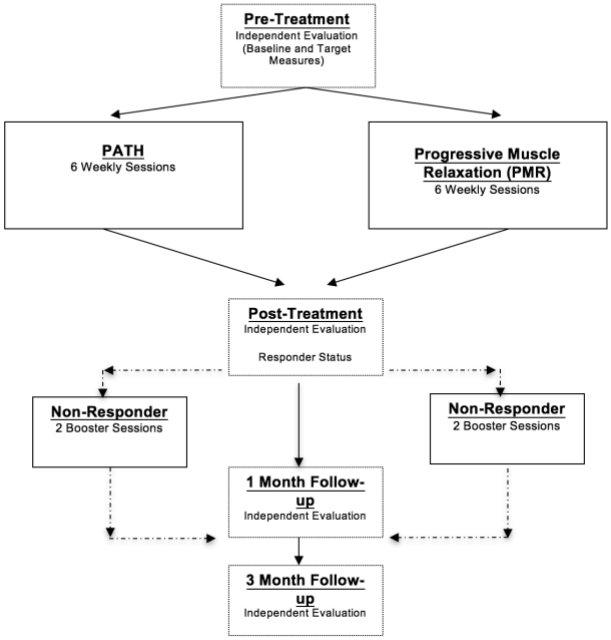
Open Trial of PATH: Engage the Targets (R61)

The R61 will be an open trial to determine if Positive Processes and Transition to Health (PATH) engages the proposed targets: unproductive processing, avoidance, and reward deficits in a *sample of 45 adults* who have experienced a destabilizing life event involving profound loss or threat, report persistent stressor-related symptoms of PTSD and/or depression, and are elevated on symptoms related to 2 of the 3 therapeutic targets. Patients will receive six 90 minute sessions of PATH (with 2 boosters, if partial responders). Primary targets will be assessed at pre-treatment, week 3, post-treatment, and at 1- and 3-month follow-up; secondary targets at pre-treatment, weekly during treatment, post-treatment, and at 1- and 3-month follow-ups. If GO criteria are achieved (Table 3), we will proceed to the R33.

RCT of PATH: Target Engagement and Link to Clinical Outcomes (R33)

The R33 will examine target engagement (unproductive processing, avoidance, and reward deficits) and whether change in PATH targets predict functional outcomes (PTSD, depression). The sample will be 135 adults who have experienced a destabilizing life event and report persistent stressor-related symptoms (Table 1). Patients will be randomized to PATH or progressive muscle relaxation (PMR; six 90 minute sessions) and assessed on the same schedule as in the R61. See Figure 2 for study design.

Figure 2. Study Design R33



Study Procedures

Directions: 1) Provide a description of all study-related research procedures being performed 2) include procedures being performed to monitor research participants for safety or minimize risks 3) include all drugs and/or devices used in the research and the purpose of their use and their regulatory approval status 4) describe the source records including medical or educational records, which will be used to collect data about subjects.

Session 1 (Overview) provides the PATH rationale and a review of life events (PATH of life: negative and positive). Therapists explain that unproductive processing, avoidance, and reward deficits work together to prolong distress and will be the targets of PATH. Therapists describe parallel processes of constructive processing, approach, and positive emotional engagement that help one to move forward and make meaning. In line with this, a rationale for an explicit focus on positive events/emotions will be provided.

Sessions 2-4 focus on a verbal narrative of the destabilizing life event (revisiting negative event and processing as is done in imaginal exposure), reminiscence and processing of a major positive life event, and real-life practice to enact what was taught. In positive reminiscence, clients vividly remember the positive event providing details and focus on positive emotions. Therapists will encourage savoring of the experience and encourage facial expression of the positive emotions, so that clients do not dampen, avoid, or minimize the experience. This is particularly relevant with depression.

In **Session 2 (Unproductive Processing)**, therapists will describe in more depth the unproductive processing loop that can keep people locked in recurrent thinking and worrying as they try to make meaning of difficult life events. The therapist will describe how one can repetitively try to make sense of the event without updating meaning and overgeneralize across situations and beliefs about the self, others, and future, which can be overwhelming. In **Session 3 (Avoidance)**, avoidance will be described as the tendency to push away feelings, thoughts, memories, people, and situations to attempt to reduce distress.

Clients are taught that avoidance often backfires and is associated with intrusions, re-experiencing, and rumination. In **Session 4 (Reward Deficits)**, therapists will describe in depth how reward deficits can perpetuate distress and interfere with the benefits of positive emotion and reward processing.

Sessions 5 (Integration) focuses on constructive processing and provides opportunity for integration and consolidation of learning. **Session 6 (Future Events)** focuses on future negative and positive events to promote application of new learning and resilience. Booster sessions focus on positive and negative life events since the last session and adaptive processes (constructive processing, approach, and reward). All sessions will include cultivation and elaboration of positive emotions to promote engagement and to build on the benefits of positive emotion.

***Progressive Muscle Relaxation (PMR*).** PMR is for the R33 as one of the randomization conditions and will be adapted from Berstein, Borkoveck, and Hazlett-Stevens (2000). PMR will be conducted in six, 60-90 min individual weekly sessions with a study therapist, helping control for non-specific effects of contact time, treatment expectancy, and general support. This intervention is likely to be credible because of the focus on stress management, and it does not focus directly on the PATH targets. Muscle groups are tightened and then relaxed with the attention of the patient focused on the contrast between tension and relaxation. Through regular practice, the person becomes more aware of tension in the body and can induce relaxation as needed (Field, 2009). During the six sessions of training, patients will be encouraged to practice PMR and learn how to deliberately induce physical relaxation to reduce stress and mental tension. Sessions will move from relaxation of 16-muscle groups to 7 muscle groups, 4 muscle groups, and finally to relaxation by recall. Patients will be instructed to practice daily, if possible, but at least two or three times a week, and to integrate the practice into their daily life. Every session, patients will be provided with audio recordings of the PMR conducted that session with their therapists, as well as homework reporting forms to assist their home PMR exercises.

Study Timeline

Directions: State approximately how long each visit will take, how long total study enrollment will last.

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
PATH Pilot Study (Study 1)												
Procedures Finalized and Staff Trained	X											
Final IRB Approval and Material Prep	X											
Assessor and Therapist Training	X		X		X							
Recruit Participants	X	X	X	X	X	X	X					
Patient Treatment		X	X	X	X	X	X	X				
Assessment			X	X	X	X	X	X				
DSMB Annual Report/Meeting				X								
25% Recruitment Target (*n* = 12)			X									
50% Recruitment Target (*n* = 22)				X								
75% Recruitment Target (*n* = 34)					X							
100% Recruitment Target (*n* = 45)						X						
Analyzing and Interpreting Results							X	X				
Evaluation of Go/No-Go Rules								X				
Manuscript Preparation and Submission									X	X		
General Grant Procedures												
Research Performance Progress Reports				X				X				
Data Sharing NDCT			X		X		X		X			

	Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
PATH RCT (Study 2)												
Refine PATH	X											
Procedures Finalized and Staff Trained	X											
Final IRB Approval and Material Prep	X											
Assessor and Therapist Training	X				X				X			
Recruit Participants		X	X	X	X	X	X	X	X			

Patient Treatment	X	X	X	X	X	X	X	X	X		
Assessment	X	X	X	X	X	X	X	X	X	X	
25% Recruitment Target (*n* = 34)		X									
50% Recruitment Target (*n* = 67)				X							
75% Recruitment Target (*n* = 101)						X					
100% Recruitment Target (*n* = 135)								X			
Analyzing and Interpreting Results									X	X	X
Manuscript Preparation and Submission									X	X	X
General Grant Procedures											
Research Performance Progress Reports			X				X				X
Data Sharing NDCT		X		X		X		X		X	X

Phone Screening. Members of the study team will collect demographic data and complete an eligibility screening form (type of destabilizing event, inclusion/exclusion criteria). Brief versions of the PSS-I and QIDS-C will be used. Potentially eligible individuals will be scheduled for an intake; those excluded will be given referrals and we will retain their demographic information and reason for exclusion for the creation of consort diagrams. All clinical data will not be utilized and ultimately deleted.

Pre-treatment Assessment. After informed consent, a study team member (licensed therapist or under the supervision of someone licensed) will administer measures of PTSD (PSS-I), depression (QIDS-C), and suicidality (C-SSRS)**.** Assessors will be blind to treatment assignment (in R33). Patients will complete baseline self-reports and laboratory paradigms. See Figure 2.

Active Treatment. Someone on the study team (licensed or under the supervision of someone licensed) will administer the treatment sessions. In the R61, all patients will receive PATH. In the R33, patients will be randomized to PATH or PMR, using a computerized algorithm accounting for initial symptom severity.

Post-Treatment Assessment. A study team member, either someone licensed or under the supervision of a licensed therapist, will re-administer PSS-I, QIDS-C, and C-SSRS; patients will complete self-reports and tasks of target engagement. Treatment dropouts will be immediately assessed and will stay in the assessment portion of the study.

Booster Sessions. Partial responders (less than 20% reduction on PTSD or MDD symptoms; Graham et al., 2017) to the 6 sessions of PATH or PMR will receive 2 booster sessions from members of the study team (licensed or under the supervision of someone licensed). All others will enter follow-up. This will provide **dosing and timing** information by examining how many participants respond to 6 sessions, and how many become responders with the booster sessions.

1- and 3-Month Follow-up Assessments. Patients will be re-evaluated 1 and 3 months after treatment by a member of the study team (licensed or under the supervision of someone licensed). The PSS-I, QIDS-C, and C-SSRS will be re-administered, and all self-reports and tasks of targets engagement will be completed. Additional treatment will be documented and referrals provided as needed.

Data to be Collected for your study (AFTER consent and HIPAA Authorization have been obtained)

List all data to be collected for the research study or attach a data collection sheet (e.g. laboratory values, physician notes, length of stay, etc.)

At the beginning of the intake, participants will complete the informed consent process prior to the collection of study data. After the informed consent process, information for the NIMH Data Archive GUID (full name, sex, date of birth, and city of birth) will be collected at baseline. More information about the GUID can be found in section 9 of the supplemental protocol. During intake, also after the informed consent process, a participant information and history interview, a destabilizing life event history interview, and a brief goal assessment interview will be conducted.

All of the following measures (either given by a study team member or self-report), except for the Working Alliance Questionnaire, treatment acceptability and feasibility measures, and the Hassles and Uplifts Scale, are assessed at every time point: pre-treatment, after session 3 of the intervention, post-treatment, and at the 1- and 3-month follow-ups. The Treatment Credibility scale is administered at session 1 of the intervention and post-treatment, the Utility of Techniques Inventory at session two through six, the Perceived Stress Scale at pre-treatment, mid-treatment (after session 3), and post-treatment, and the Client Satisfaction Questionnaire at post-treatment assessment, and the 1- and 3-month follow-ups. The Working Alliance Questionnaire will be administered after sessions one through six. The Posttraumatic Cognitions Inventory, Behavioral Activation for Depression Scale, and Snaith-Hamilton Pleasure Scale will be administered at pre-treatment, every treatment session, post-treatment intervention, and at the 1- and 3-month follow-ups. The Hassles and Uplifts Scale is a very brief ecological momentary assessment (EMA) that will be administered daily for one week pre-treatment (i.e., after the intake and before the first session of PATH), one week mid-treatment (i.e., one week after third session of PATH), and one week post-treatment (i.e., after the sixth and final session of PATH and before the post-treatment assessment). The phone screen will be done over the phone and entered into REDCap. However, see below for specific COVID-19 changes.

COVID-19 CHANGES

Independent evaluator assessments, dependent on the sites' rules and regulations on in-person research at the time, will be administered over Zoom, with any paper copies being stored in double-locked cabinets. All self-report measures will be answered by participants on REDCap. Either participants will use their own technology, or we will provide them Kindles to complete the measures. For the foreseeable future, however, all data will be collected online and remotely as a consequence of the COVID-19 pandemic.

Target Engagement for R66 and R31

Each target will be assessed in two ways: laboratory task and self-report. The laboratory tasks are objective assessments of the targets. The complementary self-report measures are well-validated, sensitive to treatment change, and reliably associated with psychopathology (PTSD, MDD).

Target: Unproductive Processing.

Affective Updating (Primary Measure; Pe et al., 2013; Pe, Raes, et al., 2013). The Affective Updating task will be administered online through Inquisit Lab on Millisecond. The Affective 2-back task will measure updating of affective information in working memory. The task requires participants to continuously monitor and modify relevant affective information in working memory. Performance is inhibited by rumination. At each trial, participants must remove previously relevant affective information from working memory, which has now become irrelevant (trial n-3), encode and identify newer, relevant affective information in working memory (trial n), and match the valence of this new information with relevant but old affective information (trial n-2). Forty-seven positive and 49 negative words are included. Under high levels of stress, deficits in affective updating predict more depressive symptoms over one year (Pe et al., 2016) and efficiency of reappraisal (Pe et al., 2013). Effective updating in contrast, predicts subjective well-being (Pe et al., 2013).

Posttraumatic Cognitions Inventory (Secondary Measure; PTCI; Foa et al., 1999). The PTCI is a 36-item self-report of negative, overgeneralized stressor-related thoughts. Each item (e.g., "The world is a dangerous place", "I am inadequate") is rated from 1 (totally disagree) to 7 (totally agree); higher scores reflect more rigid negative cognitions. The PTCI has excellent convergent and discriminant validity, internal reliability, and good test-retest reliability (Foa et al., 1999). Total scores will be used. In 6-sessions of PE, the PTCI was sensitive to change from pre- to post-treatment (d = 0.80; Zoellner et al., 2017).

Target: Avoidance.

Idiographic Behavioral Approach Task (Primary Measure; BAT). Each BAT is unique to each participant, so a file of the measure has not been uploaded to the IRB. An idiographic BAT (e.g., Mori & Aermendariz, 2001; Haynes, 2001) will use in vivo confrontation with feared or avoided stimuli (e.g., news/videos of similar events, pictures of loved one, related objects), measuring avoidance behavior. BATs have consistently demonstrated treatment sensitivity, often showing large effects (e.g., $\eta^2 = .35$, Wolitzky & Telch, 2009). A general list of idiographic stimuli will be developed and reviewed with participants at pre-treatment, and up to 3 situations will be selected. Each BAT will last approximately 5 min, with a 2-min baseline and 3-min task. There will be a 5-min baseline prior to the first task and a resting period between tasks.

Behavioral Activation for Depression Scale (Secondary Measure; BADS; Kanter et al., 2006) is a 25-item self-report of approach and avoidance in cognitive and behavioral domains not specific to depression. Items are rated from 0 = Not at all to 6 = Completely. Total scores will be used. The BADS has good factor structure, internal consistency, construct, and predictive validity (Kanter et al., 2009; Manos et al, 2011) and sensitivity to change (d =.86; CBT for depression, O'Mahen et al., 2017).

Target: Reward Deficits.
Probabilistic Reward Task (Primary Measure; PRT; Pizzagalli et al., 2005). The PRT assesses reward responsivity (e.g., Der-Avakian et al. 2013; Pizzagalli et al., 2005, 2008, 2008). In each trial, participants choose which of 2 difficult-to-differentiate stimuli was presented. Stimuli are cats and dogs in ratios of 6:10. At the start of the task, a fixation cross appears on the screen. After a delay of 500ms, a constellation of dog and cat faces appear, with one of the animal faces appearing more frequently than the other. Participants decide whether more cats or dogs were presented. Unknown to them, correct identification of the "rich stimulus" is rewarded 3 times more frequently ("Correct! You won 5 cents"). Reward propensity is calculated by increase in response bias during the final block relative to the first. Degree of response bias toward the frequently reinforced alternative is a robust measure of reward sensitivity (Pizzagalli et al., 2005, 2008; Vrieze et al., 2013). Performance has been found to be modulated by dopaminergic compounds (d = 1.45; Pizzagalli et al., 2008) and to improve with treatment (Burkhouse et al., 2018). The PRT will be administered online through GitHub on www.cognition.run.
Snaith-Hamilton Pleasure Scale (Secondary Measure; SHAPS; Snaith et al., 1995). The SHAPS is a 14-item self-report measuring the capacity to experience pleasure. On a four-point scale (1 = Strongly Agree to 4 = Strongly Disagree), varying statements are rated (e.g., "I would find pleasure in small things"; "I would find pleasure in a telephone call from a friend"). The measure has good convergent and discriminant validity and reflects a unidimensional construct of anhedonia (Leventhal et al., 2006; Nakonezny et al., 2010).

Additional Assessment Instruments for the R61 and R33

The Everyday Discrimination Scale – Revised (EDS-R; Williams et al., 1997) is a 9-item self-report measure of subjective experiences of discrimination, with a follow-up question querying what they believe to be the main reason for those experiences. Items are rated on a Likert scale ranging from 1 (*never*) to 6 (*almost every day)*. Total scores range from 9 to 54, with higher scores indicating higher perceived everyday discrimination.

The Pandemic Emotional Impact Scale (PEIS; Palsson et al., 2020) is a 16-item self-report measure assessing the effects of COVID-19 on the lives and emotional wellbeing on participants. For each item on the PEIS, respondents are asked how much their wellbeing and functioning has been different recently, compared to how it was before the beginning of the pandemic. The response options are "Not at all (0)", "A little bit (1)", "Moderately (2)", "A lot" and "Extremely (3)". The index score is the sum number of all PEIS items given a "Moderate" or greater rating by each respondent.

The Hassles and Uplifts Scale (DeLongis et al., 1988) can be adapted to be a brief, self-report, EMA that assesses daily positive and negative experiences. Specifically, participants are asked to rate on each day whether 8 domains (i.e., relationships; work/education; finances; health; social, political, and environmental issues; recreational activities; home and lifestyle management; and other) were a "Hassle," "Uplift," "Both," or "None." For the domains that participants rate as a "Hassle," "Uplift," or "Both," they are further asked to rate how much of a hassle or uplift the events were by selecting from the following result options: "None or not applicable (0)", "Somewhat (1)", "Quite a bit (2)", "A great deal (3)." Furthermore, participants are asked to rate how they coped with the hassles and uplifts they endorsed with the following response options: "Not at all (0)", "A little bit (1)", Some (2)", and "A lot (3)". Lastly, participants are asked to what extend they have generally felt positive emotions or negative emotions throughout the day of the assessment with the following response options: "Not at all (0)", "A little bit (1)", Some (2)", "A lot (3)".

Because the number of items a participant completes depends on how many domains they endorse as a "Hassle," "Uplift," or "Both," the number of items completed each day ranges from a minimum of 10 (if participants report that all domains are "None" a hassle nor an uplift) to a maximum (if participants report all domains were "Both" a hassle and an uplift) of 34 items.

The Perceived Stress Scale (PSS; Cohen, Kamarck & Mermelstein, 1983) is a 10-item self-report measure that assesses participants' self-perception of stress in their lives. More specifically, the PSS measures the extent to which participants think their lives are unpredictable, uncontrollable, and overloaded. Items are rated on a Likert scale ranging from 0 *(never)* to 4 (*very often)*. Total scores range from 0 to 40, with higher scores indicating higher levels of perceived stress.

The Working Alliance Questionnaire (WAQ; Falkenström, 2015) is a 6-item self-report measure assessing the participants' thoughts and feelings about the relationship with their therapist. Items are rated on a 6-point Likert scale from 0 (not at all) to 5 (completely). Total scores range from 0 to 30 with higher score indicating higher working alliance.

The EDS-R and PEIS will be given at the pre- and post-treatment assessments. The PSS will be given at pre-treatment, mid-treatment, and post-treatment. As noted, the Hassles and Uplifts Scale will be given daily for one week pre-treatment, one week mid-treatment, and one week post-treatment.

Psychopathology Symptom Measures

Both PTSD and depression will be assessed with state-of-the-art, psychometrically-validated interview and self-report measures (PTSD Symptom Scale-Interview, PSS-I-5; PTSD Diagnostic Scale, PDS-5; Foa et al., 2015; Quick Inventory of Depressive Symptomatology-C, QIDS-C; Quick Inventory of Depressive Symptomatology-SR, QIDS-SR; Rush et al., 2003). The Structured Clinical Interview for DSM-5 (SCID-5-RV; First et al., 2015) and the Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2009) will be administered by members of the study team (licensed or under the supervision of a licensed therapist) used to assess inclusion/exclusion criteria and monitor suicidality.

Positive and Negative Affect Scale (PANAS; Watson et al., 1988) will be used to assess state affect across assessments and sessions, particularly for examining dose and timing of PATH in Specific Aim 1.

Response to Positive Affect – Dampening Subscale (RPA-D, Feldman et al., 2008) is an 8-item self-report measure assessing dampening responses to positive affect states. Respondents rate the items on a 4-point Likert scale, ranging from 1 (almost never) to 4 (almost always).

All self-report psychopathology symptom measures will be given at each assessment point and at each session.

Treatment Engagement, Acceptability, and Feasibility

Treatment dropout, defined as completing fewer than 4 sessions. Homework adherence between sessions will be assessed using a modified version of the Utility of Techniques Inventory (UTI, Foa et al., 1999). As is standard in many cognitive and behavioral treatment approaches, therapists will also complete an in-session record of client engagement/adherence; specifically, therapists will complete the Negative Event Revisiting Recording Form, on which they record clients' subjective units of distress (SUDs) every 5 minutes while clients engage in the negative event revisiting exercise during sessions 2 through 6. Similarly, therapists will complete the Positive Event Reminiscence Recording Form, on which they record clients' subjective units of pleasure (SUPs) every 5 minutes while clients engage in the negative event revisiting exercise during sessions 2 through 6. Treatment credibility (Treatment Credibility Scale, CS, Addis & Carpenter, 1999) and client satisfaction (Client Satisfaction Questionnaire, CSQ-8; Attkisson & Greenfield, 1994; 2004) will also be assessed. Finally, therapist adherence will be rated via independent rater using a to-be-developed checklist based on a random subset of 10% session recordings.

Milestones (Go/No Go Criteria)

Go/No Go Criteria. For "Go" to be achieved and to proceed to the R33, two criteria must be met. See Table 3. The first is that at least 2 of the 3 primary targets must change. A moderate effect size (d = 0.60) was chosen to reflect evidence of clinically meaningful target engagement (see Gold et al., 2017), in line with NIMH guidelines for a preliminary signal of target engagement/efficacy in intervention trials.

Table 3. Target Mechanism Engagement

Phase	Target Mechanism/Outcome	Primary Indicator	Secondary (self-report) Indicator	Go/No Go[1] Pre-Post Effect Size (Cohen's d)
R61	Unproductive Processing	Affective Updating Task		d ≥ 0.60
			Posttraumatic Cognitions Inventory	d ≥ 0.50
	Avoidance	Idiographic Behavioral Approach Task		d ≥ 0.60
			Behavioral Activation for Depression Scale	d ≥ 0.50
	Reward Deficit	Probabilistic Reward Task		d ≥ 0.60
			Snaith-Hamilton Pleasure Scale	d ≥ 0.50
R33	Posttraumatic Stress Severity	PTSD Symptom Scale-Interview		d ≥ 0.80
	Depression Severity	Quick Inventory of Depressive Symptomatology-Interview		d ≥ 0.80

Note. [1]For Go to R33, at least 2 of the 3 primary mechanism indicators must change and at least one of the secondary indicators must change. For

Second, at least one of the secondary measures must show a moderate effect (d = 0.50) from pre- to post-treatment. We included measures of each of the targets, as they are conceptualized as interrelated parts of a "stuck" system. For "Go" to an R01 after the R33, in addition to target engagement, primary outcomes of PTSD and depression must show clinically meaningful gains (e.g., Barth et al., 2016; Cusak et al., 2016).

R33 PATH Refinement. Beyond examining outcome data from the R61, we will: 1) conduct interviews with standardized questions with 20% of patients, selecting those with small and large gains on therapeutic targets; 2) conduct a feedback session with therapists to identify aspects of the manual that need refinement; and 3) examine booster session data regarding whether additional sessions are needed for the R33. The interview guides will be submitted as through a modification before they are conducted.

Data Analysis Plan

Directions: Describe the data analysis plan, including any statistical procedures. If applicable, provide a power analysis, describe primary and secondary study endpoints including safety endpoints.

General Analytic Strategy

For Specific Aims 1–3, we will use random effects models, a specific application of general linear mixed models (GLMMs) that helps to address common issues with longitudinal clinical treatment data, including missingness, serial correlation, and time-varying covariates (e.g., Gallop & Tasca, 2009). These models allow for person-specific deviations from overall mean time effects and are robust to missing data, using maximum likelihood estimation in cases of ignorable non-response. This analytic approach allows for initial modeling of different covariance structures, as well as non-linear time transformations that are especially useful when between-assessment intervals are not consistent across time. For Aim 3, mediation will be tested using the product of coefficients method with bootstrapped standard errors (MacKinnon, 2009) and based on a lagged mediation design (e.g., Hofmann, 2006). This approach addresses the need for temporal precedence of predictor to outcome and accounts for change between time points of a target DV. Analyses involving secondary metrics (i.e., PTCI, BADS, SHAPS) will shift to a more conservative GLM framework.

Data will be screened for accuracy, missing values, and fit with the assumptions of GLMM (e.g., linearity, multivariate normality; Tabachnick & Fidell, 2007). Data transformations or model re-specifications will be performed, if needed. Outcome data will be plotted against time to guide selection of applicable time variables; similarly, covariance matrices will be examined to inform selection of the best covariance structure. Best fitting models will be evaluated based on these plots and model fit information (e.g., AIC, BIC). We will use pattern-mixture models to examine whether missingness can be considered ignorable. For non-ignorable missing data, values will be multiply imputed and data recombined (Rubin, 1987) in the mixed model program or comparable model-supported approaches. We will examine associations between primary dependent variables with factors such as gender and time since event and make appropriate adjustments (e.g., covarying predictors). In analyses nesting subjects within treatments (Aim 2), dummy codes will be used (Snijders, 2005).

Power Analysis

Our approach to power analyses aims to balance pragmatic factors with analytic considerations. We focus primarily on Specific Aim 1 (R61) and Specific Aim 2 (R33). Primary analyses for both aims will involve random effects models; however, because it is difficult to accurately estimate covariance structures of such models, *a priori* power or sample size estimations have limited value. Fang (2006) has shown that ideal sample sizes often far exceed clinical resources for conventional trials, whereas other studies have shown that small sample sizes do not bias estimates of fixed effects (e.g., Bell et al., 2008). Accordingly, we frame our power calculations in line with GLM models that mirror the primary tests and hypotheses of our more complex random effects/GLMM models. In general, estimates were calculated based on $\alpha = .05$ and power $(1 - b) = .80$, using intent-to-treat, repeated-measures designs (e.g., paired t-tests). Power calculations were completed using G*Power (Faul et al., 2007). For Aim 1, with an estimated pre-post effect size of $d = 0.60$ (one-tailed tests), we are well-powered with a sample of 45. In fact, for a sample size of 45, an alpha of .05, and power of .80, we will be able to detect a small to moderate effect size of .38. For Aim 2, we based power estimates on a primary comparison of time by treatment interaction in an RMANOVA model. For a five time points, two groups, RMANOVA with a correlation of $r = .70$

between measures, we are well powered to detect treatment X time small effect size of .07 with 67 patients per treatment. For Specific Aim 3, using Monte Carlo simulations in MPlus 6.0 (Muthen & Muthen, 2002) with the same alpha, power, and sample size of at least 67 per condition, we are adequately powered to detect an indirect effect size as small as $d = .50$.

Specific Aim 1: Engage Targets (R61)

We will examine whether PATH engages targets with at least medium-size effects ($d = 0.60$) on 2 of 3 of primary targets from pre- to post-intervention. Primary target dependent variables are: Affective Updating, BAT, and PRT. We will conduct a planned contrast of pre- and follow-up time points within each separate model. This test is analogous to a contrast in ANOVA or a paired t-test, but superior in terms of estimation of missing data and modeling of covariates. The resulting test yields an effect size that can be converted to a d (Feingold, 2013) and compared to our target threshold of $d = 0.60$ for all three models as part of our Go/No-Go rules. For secondary measures of PTCI, BADS, and SHAPS, we will use the GLM approach described above and compare to our target threshold of $d = 0.50$ as part of our Go/No-Go rules.

Dosing and timing of treatment effects. Dosing will be assessed by graphing individual symptom trajectories to identify groups of individuals who may need more treatment, including specifically the shift of positive and negative affect over time (PANAS). To understand timing of effects, primary analyses will be augmented with tests focused on brief, critical change intervals, yoked to the introduction of new target-related content (session k). We will compare residualized change in target (primary measures: Affective Updating, BATs, PRT) in the pre-introduction phase (session k-1 to session k) to change in the post introduction phase (session k+1 to session k+2). These windows will differ for each target, as they are introduced sequentially (e.g., reward deficits, pre-introduction = session 1 and 2, post-introduction = session 3 and 4). Change scores will be compared using t-tests. Similar analyses will be utilized with the PANAS.

Specific Aim 2: Replication of Target Engagement (R33)

We will examine whether PATH alters therapeutic targets in comparison to PMR. Primary dependent variables are Affective Updating, BATs, PRT. Secondary dependent variables are PTCI, BADS, and SHAPS. We will compare the main effect of treatment (PATH or PMR) over time separately in each of three models. These models will estimate the effects of treatment on both the level of the target at 3-month follow-up and change over time (slope). Random intercepts and random coefficients for time-varying covariates (e.g., time) will be specified, if the model fit is better than a fixed effects model. For example, $y_{ik} = \beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Treatment} + \beta_3 (\text{Treatment}_i \text{ x Time}_{ik}) + v_{0i} + v_{1I} \text{Time}_{ik} + \varepsilon_{ik}$ where Treatment represents a dummy-coded effect (Group = 0 for PATH, 1 for PMR), i=subject, k=time, and y = DV of interest. We hypothesize that differences will emerge between PATH and PMR specifically for Affect Updating, BAT, and PRT. For secondary measures, we will use the GLM approach above in an ANCOVA-like design to test the interaction of treatment and time.

Specific Aim 3: Linking Changes in Targets to Changes in Stressor-related Symptoms (R33):

We will examine whether changes in target mechanisms (pre- to post-) predict improvement in PTSD (PSS-I) and depression (QIDS-C) at pre-, mid, post-, 1-, 3-month follow-up. In GLMs, we will evaluate targets from pre- to post-treatment and at 3-month follow-up, with corresponding metrics to assess change in symptoms (PSS-I, QIDS-C). In the GLMs, treatment will predict changes in symptoms from pre- to post-treatment (controlling for baseline levels) and pre- to follow-up. GLMMs will be conducted as above, and treatment will be used to predict levels and change in symptoms. Next, in GLMs, we will

predict pre-post change in target mediators (unproductive processing, avoidance, reward deficits) from treatment (A path) and follow-up outcomes from the mediator (B path), controlling for treatment and baseline symptoms. GLMM will test for mediation by predicting the mediator at all time points from treatment, and the outcome at all time points from the mediator, controlling for treatment. Similar analyses will be used for secondary measures.

Specific Aim 4: Feasibility and Dropout/Acceptability of PATH Intervention (R61/R33):

We will examine feasibility and acceptability of PATH. Dependent variables are treatment helpfulness (CS, CSQ), adherence (UTI), completion, and therapist fidelity. For the R61, we will use benchmarks from our PTSD RCT (Zoellner et al., 2019) for CS ($M = 37.26$, $SD = 7.33$) and CSQ scores ($M = 11.70$, $SD = 4.76$). We hypothesize PATH scores will not significantly differ from benchmarks, based on a sign test. Adherence (UTI) is expected to exceed 50% in PATH, dropout to be below 20%, and therapist fidelity to exceed 80%. In the R33, PATH and PMR will be compared via *t* test and chi-square analyses across these indices.

Risks to Research Participants

List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.

Risks associated with PATH are mild to moderate discomfort when exposed to distressing memories. All event processing will be carried out with the full knowledge and consent of the patient. Exposure-based therapies for both PTSD and depression have produced considerable benefit to patients (e.g., Cusack et al., 2016; Hayes et al., 2005; 2007; Grosse-Holforth et al., 2012; 2017). Although some patients do not benefit from these treatments, there are only a handful of reports of negative side effects, such as an increase in PTSD symptoms in five combat veterans (Pitman et al., 1991). None of the patients in our past or current treatment studies sustained prolonged negative reactions to exposure (e.g., Foa, Zoellner, Feeny, Hembree, & Alvarez Conrad, 2002; Jayawickreme et al., 2014).

There is the possibility that participants will not exhibit significant symptom reduction to the PATH program or PMR. Further, there is the possibility of a return of clinically significant symptoms during the follow-up phase (i.e., relapse).

Provisions to Protect the Privacy Interests of Research Participants

Directions: Describe the steps that will be taken to protect research participants' privacy interests. (Consider issues such as physical space, proximity to other, and participant preferences)

Participants will be instructed that information shared in sessions is confidential. Participants will be instructed about the limitations and obligations in regard to reporting of elder abuse, child abuse, suicidality and homicidality. We will follow state laws and professional ethics in handling these issues. Participants will be reminded at each appointment that they do not need to disclose any information that they are not comfortable with sharing. Participants will be given the phone number for Case Western staff and will be given the Cuyahoga County 24-hour crisis hotline (216) 623-6888.

Potential Benefit to Research Participants

Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. If there is no direct benefit, state the potential benefit to society.

We anticipate that receiving PATH will lead to improvements in functioning for participants, including reduced symptoms of PTSD, depression, and functioning. However, this cannot be guaranteed.

Withdrawal of Research Participants

Directions: Describe the anticipated circumstances under which research participants will be withdrawn from the research without their consent. Also include the procedures that will be followed when a research participant withdraws or are withdrawn from the research, including partial withdrawal from procedures with continued data collection.

At every session, patients will be clinically monitored for suicidal risk or serious depression, and withdrawn from the study if these conditions are present and preclude participation. If research participants choose to withdraw from the study, they will do so by contacting the local investigator (Dr. Feeny).

Alternatives to Participation

Directions: List other available clinical treatments, what would be included if a subject continued on standard of care therapy. If this is not a clinical trial, you may select the box indicating that the alternative is not to participate. If there is a viable alternative you must list it in the consent.

Individuals are free not to participate in this study, free to not answer questions, and free to stop being in the study at any time. As an alternative to this study, individuals may choose to receive counseling or therapy from another community provider. If individuals choose to do this, we will provide them with contact information for other counselors who work with survivors of trauma. This therapy will be at the individual's own cost.

Costs to Research Participants

Describe what costs research participants will be responsible for as a result of their participation in the research, including but not limited to: clinical services required by the protocol deemed billable to insurance, transportation to study visits, parking, costs of drugs, cost of therapy, lost broken or stolen devices, etc. Explain who will be responsible for payment of provided services in the event of insurance denials. List what procedures, drugs, devices, supplies will be paid by the study sponsor or covered by other funding. List the other funding source.

N/A There will be no cost to research participants.

Research Participant Compensation

Describe the schedule, payment method, and payment total of any incentives or compensation that research participants will receive for participation in the research (e.g., gift cards or cash with amount, t-shirts, devices, bags, swag, etc.)
Describe the schedule, payment method, and payment total of any reimbursement that research participants will receive for participation in the research (e.g., gift cards or cash with amount, etc.)

During the intervention, there is no monetary compensation for participation. Participants will be compensated $50 per assessment after treatment (post-treatment, 1- and 3-month follow up assessments) and up to $7 per Probabilistic Reward Task assessment (assessed up to 5 timepoints). Participants can earn up to $185 total for completing all assessments.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol. Indicate if there will be a Data and Safety Monitoring Board or Committee. Provide information about the DSMB/C including the contact information of the committee member(s) (as applicable); whether it is independent from the study sponsor; how often it meets; the type of data that will be used; written reports, etc.

We will create a Data Safety and Monitoring Board (DSMB). We will include experts in statistics, PTSD and depression psychotherapy and clinical trials. These individuals will be experts in their fields and not associated with the trial in any manner. The DSMB will review the research protocol and plans for data safety and monitoring. They will be responsible for evaluating the progress of the RCT including recruitment, retention, and ongoing risk benefit ratio. The DSMB will receive an annual report that reviews recruitment, randomization, preliminary results for intervention, and safety data. Masked data will be presented to the DSMB, with the PI and investigational team remaining blind to the ongoing trial results. Only members of the DSMB will see interim data. The DSMB will also consider factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. The DSMB will convene annually to review this report and provide written feedback for the PI on questions or concerns related to the trial that need to be addressed. The PI will respond within 24 hours to any serious concerns raised by the DSMB. Each year the DSMB will recommend continuation or stoppage of the trial.

Drs. Zoellner, Hayes and Feeny will be responsible for data and safety monitoring and will provide continuous, close data monitoring at each site. Dr. Zoellner will follow UW's SAE reporting policy in promptly reporting serious adverse events to the UW Institutional Review Board (IRB) and to NIMH. Dr. Feeny will follow CWRU/UHC SAE reporting policy in promptly reporting serious adverse events to the CWRU/UHC Institutional Review Board (IRB) and to NIMH. Dr. Hayes will follow UD's SAE reporting policy in promptly reporting serious adverse advents to the UD Institutional Review Board (IRB) and to NIMH. Drs. Feeny, Hayes and Zoellner will report all SAEs to their respective IRBs within 24 hours. A report of all non-serious adverse events will be provided to the IRB yearly. NIMH will be informed of all actions taken by the IRB as part of its continuing review.

Oversight of the data and safety monitoring will be the responsibility of the CWRU IRB, the UW IRB, the UD IRB, and the DSMB. The investigators will ensure that procedures are reviewed and approved by the IRB before beginning any new study procedures. A report will be provided to the IRB and DSMB following each annual meeting that will include recommendation for continuation or conclusion of the study.

Drugs or Devices

N/A

Additional Information

Directions: If you have any additional information regarding your study not covered in the template, please include it here.

All patients in the PATH program will be assigned a therapist throughout the study, who will carefully monitor clinical state and therapy effects. Patient symptoms will be assessed at each visit. Moreover, to minimize risk, actively suicidal patients or those deemed to be at high risk (i.e., severe self-injurious behavior or suicide within the previous three months) will not be eligible for this study. We will conduct a

thorough assessment of current suicidality and suicide history at the intake (Columbia-Suicide Severity Rating Scale; C-SSRS; Posner et al., 2009). If an individual reports thoughts about harming themselves or others during the phone screen, the phone screen assessor will conduct a thorough assessment of suicidal and/or homicidal ideation and contact their supervisor, who will make a determination about whether the individual is at high risk and needs to be referred for immediate crisis services, such as going to the ER or calling the mobile crisis unit. Individuals who are deemed to be at lower risk (i.e., suicidal ideation without current method, plan, or intent) will complete a safety plan with the supervisor and agree to contact crisis services or go to the ER if their suicidal ideation worsens. Referrals for treatment will also be provided. Suicide risk will be discussed for each participant in our weekly team meeting prior to entry into the trial, and to reiterate, patients at high risk will not be eligible but will be provided with referrals for immediate treatment. During active treatment, suicidal ideation will be clinically monitored by study clinicians. The QIDS-SR will be used specifically to monitor suicide risk. At follow-up assessments, suicidal ideation will be routinely assessed by independent evaluators. Using these procedures in our most recent clinical trial, in which over 60% of patients have current MDD, has allowed us to safely manage risk.

Potential side effects from PATH (i.e., temporary emotional reactions) will be addressed by reassuring patients that these reactions are common for a subset of individuals and unrelated to whether they have long-term improvement. The therapist will also be trained to help titrate emotional responding during life event exposure. In the first exposure session, the patient will be given control over the level of detail in recounting the traumatic memory. During subsequent sessions, the therapist will use procedures to promote increased detail, vividness, and emotionality when the client seems uninvolved. When the patient is too emotional, reassurance and distancing techniques will be used (e.g., allowing the patient's eyes to remain open).

Non-response and relapse of responders are possibilities. Throughout the course of the study, patients' current symptoms, including suicidality, will be carefully assessed. Before every treatment session and at every assessment, patients will complete self-report ratings of their PTSD (PDS-5) and depression (QIDS-SR). The treatment provider (PATH or PMR) at the start of the session will review symptom ratings. For those with suicidal risk or serious depression, patients will be withdrawn from the study if these conditions are present and preclude participation. If a clinician is concerned about the level of a client's suicide risk based on client verbalization or QIDS-SR, the session will focus on risk assessment and management. If necessary, procedures are in place for imminent at risk patients to be escorted to local emergency rooms. If a patient calls their treatment provider or the research coordinator in crisis, an emergency session will be scheduled immediately. All concerns about suicide risk will be brought to the attention of the PIs (licensed clinical psychologists) immediately. All patients will be given 24-hour suicide prevention hotline numbers at the beginning of the trial and reminded of this on as needed basis. In addition, patients will have access to the emergency rooms at University Hospital of Cleveland (UHC, CASE's affiliate), Wilmington Hospital and Christiana Care Hospital in Delaware, and at UW Medical Center, and to study clinicians within 24 hours. Finally, built into the protocol is the provision of up to two Adjunctive Services and Attrition Prevention (ASAP) sessions to address emergent clinical issues. In our prior trials, we have not needed to exceed the provision of two ASAP sessions. Taken together, we have used these procedures successfully for the past decade in our previous trials to manage risk successfully. Non-responders will be offered continued treatment, as outlined in Approach Section, free of charge or various referral options. Relapsed patients in the follow-up phase will be offered additional treatment sessions or various referral options. The referral options include treatment through outpatient psychiatry at CASE, UD (Wilmington Hospital, Christiana Care Hospital), or UW.

Community-Based Participatory Research

Describe the involvement of the community in the design and conduct of the research.

Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

N/A

International information

If you will be conducting international research, address the following issues:

- Sites/locations
- Data sharing

N/A

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