Statistical Analysis Plan:

Comparative Mechanisms (Moderators, Mediators) of Psychosocial Treatments of Chronic Pain

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Study Aim 1: Examine the comparative efficacy of three psychosocial treatments. We will test whether the three psychological therapies (CBT, ACT, and EAET) are effective by comparing each to TAU at the primary endpoint of post-treatment. We will also test whether any of three therapies is superior to the other therapies. We will determine regions of significant difference by testing at which week(s) of treatment the differences between therapies and TAU, and among the therapies, emerge. We will examine these treatment differences on the two primary outcomes (pain intensity and pain interference), specifically testing ACT's efficacy on pain interference, EAET's efficacy on pain intensity, and CBT's efficacy on both outcomes. The four conditions will also be compared on secondary outcomes that stem from IMMPACT recommendations (physical functioning, depression, sleep, global impression of change). Tertiary or exploratory outcomes include those measured weekly during therapy (anxiety, anger, positive affect, fatigue, PTSD symptoms, opioid use, patient satisfaction, adverse events) and those measured only at baseline, post-treatment, and follow-up (interpersonal problems, emotional awareness, psychological flexibility, fibromyalgia diagnostic criteria, health care use, and substance use). Conditions will be compared at the 6-month follow-up to determine whether differences in outcomes identified at the primary endpoint (post-treatment) are maintained, enhanced, or attenuated over time.

Analyses for Aim 1: Linear mixed models will compare the four treatment conditions to detect differential slopes of change from baseline to post-treatment on the two primary outcomes and again on the secondary and tertiary outcomes. Significant omnibus (4-arm) tests will be followed by post-hoc comparisons of each treatment with TAU as well as each treatment with each other. Similar analyses will compare treatment conditions from post-treatment to 6-month follow-up and from baseline to 6-month follow-up. The magnitude of between- and within-condition effects will be calculated for all comparisons, based on change scores corrected for test-retest reliability of the measure.

Study Aim 2: Identify specific and shared mediators. Test whether there are specific mediators for each treatment or shared mediators across treatments. If mediators are treatment-specific: (1) the putative specific mediator will change primarily in the relevant treatment; (2) show in lagged analyses that mediator changes precede improvements in outcomes primarily in the relevant treatment; and (3) outcome improvements will be accounted for by changes in treatment-specific mediators. Evidence for shared mediators would emerge for mediators that change with treatment and that precede and predict subsequent changes in outcomes across multiple treatments. In the event that shared mediators are identified, analyses will determine which mediators are critical and strongest across the treatments. The therapies and their primary and secondary treatment-specific mediators are as follows: CBT (primary: behavioral activation, pain control beliefs; secondary: pain self-efficacy); ACT (primary: pain acceptance,

self-compassion; secondary: chronic pain values); EAET (primary: emotional approach coping, attributions of pain to brain and stress; secondary: psychological insight, emotional breakthrough). Secondary mediators that are hypothesized to be general rather than treatment-specific are stages of change, pain anxiety, therapeutic alliance, treatment credibility, and treatment engagement.

Analyses for Aim 2. Mixed models will initially test whether changes in mediators occur differentially across treatment groups. Linear mixed-effects models will explore putative mediators across program timepoints examining treatment condition, time, and Time x Treatment condition interactions as fixed effects. Next, we will examine whether between-session changes in mediators predict subsequent changes in outcome variables, but not vice versa, as well as whether such changes occur differentially across treatment conditions. Variance in putative mediators will be decomposed into within-subject and between-subject components, which will be used as predictors of outcomes in separate linear mixed models. Additionally, cross-lagged models reversing this procedure and predicting mediator scores with person mean-centered lagged deviations in outcomes will establish temporality of the association between mediators and outcomes.

Study Aim 3: Identify moderators and moderated mediators. We will test hypotheses based on the Limit, Activate and Enhance (LA&E) model, which describes potential baseline moderators of different treatments. We expect that people: (1) high in pain catastrophizing will respond best to CBT; (2) high in experiential avoidance will respond best to ACT; (3) low in alexithymia and/or with a trauma history will respond best to EAET. Further, we expect moderators to exert effects on outcomes via hypothesized mediators (e.g., high pain catastrophizers will respond to CBT via increases in behavioral activation). In addition, there are other potential baseline moderators for which we do not have treatment-specific hypotheses (Big 5 personality traits, chronic overlapping pain conditions, perceived social support, psychological flexibility, interpersonal problems).

Analyses for Aim 3. Baseline characteristics hypothesized to serve as moderators of the relationship between treatment condition and outcomes (e.g., trauma history) will be examined using Treatment x Moderator x Time interactions. Significance of these interaction terms would indicate that differences in outcome time trends across treatment conditions exist based on these moderating factors. Such moderation effects would also be further tested by examining estimates via separate linear mixed models for treatment groups, exploring moderator x time simple effects to determine uniqueness of moderation to specific treatment conditions, as well as pairwise comparison linear mixed models when appropriate. In addition, we will examine whether associations between lagged mediator changes and outcome changes over the course of treatment depend on hypothesized moderators (moderated mediation effects). We will include a moderating factor as a moderator of the relationship between lagged mediator changes and outcomes via the addition of lagged Mediator x Moderator x Time interaction terms in linear mixed models. Such linear mixed models will be explored separately by treatment condition to reduce model complexity.