“Relief”: A Behavioral Intervention for Depression and Chronic Pain

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3c. STATISTICAL ANALYSIS PLAN: We will examine the distribution and outliers for each variable, and use transformations or bootstrapping if needed. We will test whether baseline demographic and clinical variables are balanced between groups and practices, and adjust in analyses (based on intention to treat principle).

Aim 3: *Reach, Feasibility, Acceptability of Relief and RMH***:** We will calculate estimates and 95% CI of the following measures for all subjects and for each sex separately: 1) Reach: Proportions screened, and met study criteria for both conditions. 2) Feasibility: Proportions of patients who initiate Relief and proportion of RMH patients who contact mental health care services; research procedures (timely referrals, assessments) in both conditions; Relief session completion rates and smartphone use. 3) Acceptability to patients: CSQ at baseline, 6, 9, and 12 weeks will be analyzed as in Aim 4. *Relief Benchmark tests*: >75% session attendance rate, >70% smartphone ratings, and CSQ score ≥ 3 (out of 4)] will be performed using one-sample z-tests of proportions. We will evaluate clinician and practice staff satisfaction every 6 months.

Aim 4: *Preliminary Effectiveness:* We will use separate linear mixed models for primary and secondary outcomes measured at baseline, 6, 9 and 12 weeks with a subject-specific random intercept and slope and fixed effects for time, treatment, practice, therapist, treatment x time interaction. We will use model building and fitting strategies.[60] In the final model, we will also estimate end of treatment improvements in outcome (from baseline) within each treatment group. As this is an underpowered developmental study, we will control false discovery rate using the Benjamini-Hochberg approach,[61] and not the Family-Wise Error Rate, to adjust for multiple comparisons. Our primary goal will be to estimate effect sizes (or percentage reductions from baseline) with 95% CI and assess clinical significance. Using approaches of Initiative 2.1 (Methods Core), we will conduct exploratory joint analysis of primary and secondary longitudinal outcomes. We will also test between group differences in use of mobile technology measures described in 3b8 above and employing the time series approach of Initiative 2.1 (Methods Core). ***Aim 5****: Mediation:* For each mediator (MAIA, PANAS, secondary measures) we will use the cross-lagged panel model method[62] to estimate the time-specific and treatment effect on outcomes related to the mediator.[63] In exploratory analysis, we will estimate the indirect effect of longitudinal mediators (Initiative 2.1, Methods Core).

Exploratory Aim: We will repeat analyses of Aims 4 and 5 separately for each sex and provide sex-specific estimates of effectiveness and target engagement. We will compare the effect of Relief vs. RMH on quality of life (WHOQL-BREF),[32,33] on opioid and benzodiazepine use (generalized linear mixed models), and suicidal ideation (MADRS item 10) as in Aim 4. To evaluate cost and potential savings, we will: a) compare the reimbursable and non-billable cost of the interventions, i.e. hours of administrative time, therapists' training, supervision vs. change in use of health care services (assessed by the CSI) by participants in Relief vs. RMH.

Power: Consistent with the R34 mechanism, we did not perform power analysis. Instead, we calculated the width of the confidence interval (CI) for estimated effectiveness. We simulated 1000 datasets following a 2-level cluster randomized longitudinal design (N=40 in Relief vs 20 in RMH in 4 practices), a range of intra-class correlations (ICC) and estimated the width of CI for treatment difference (Cohen's d) at week 12 using linear mixed effects regression model. For 80% confidence of the CI, the estimated CI width will be 0.66-0.75. The range of CI width is based on a range of ICCs for level 1 (0.25-0.45) and 2 level (0.05-0.10) clusters. The estimated CI width is consistent with reported CI widths of effectiveness estimates obtained in meta-analyses of RCTs comparing CBT with control conditions in depression.[64]