Reducing the Transition from Acute to Chronic Musculoskeletal Pain among Older Adults (BETTER from Pain)

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(BETTER from Pain Study)

Statistical Analysis Plan

Version 1.1

This statistical analysis plan is an expanded version of the summary analysis plan included in the study protocol and supersedes the summary plan included in the study protocol. Any significant changes made to this analysis plan after study initiation will be documented herein.

1. Study Objectives

The objectives of this 3-arm randomized trial are as follows:

Objective 1: To evaluate the effects of two Shared Decision Making based interventions (full and video-only intervention) relative to Usual Care on musculoskeletal pain (MSP), as measured by the combined pain severity and interference scores from the Brief Pain Inventory Short Form (BPI-SF), through 6 months following the initial visit.

Sub-Objective 1a: To evaluate the intervention effects separately on the two components of the BPI-SF, pain severity and interference, evaluating both longitudinal change through 12 months and differences at discrete time points of 1, 3, 6, and 12 months.

Sub-Objective 1b: To evaluate the intervention effects over time on other key secondary outcomes, including opioid use, analgesic-related side effect frequency and severity, physical function, overall health, sleep quality, and healthcare utilization.

Objective 2: To assess the mechanisms by which the interventions (full and video-only) influence outcomes.

Objective 3: To estimate the incremental cost per case of persistent pain (defined as pain ≥4 on 0-10 scale present at one year) prevented by either the full or video-only intervention compared with usual care.

This document describes the analyses planned for Objectives 1 and 2, and other supporting quantitative analyses. The cost-effectiveness analysis to be applied for Objective 3 will be described elsewhere.

2. Study Design Overview

Four hundred patients presenting with acute MSP recruited from four sites (3 emergency departments (EDs) and one Urgent Care) will be randomized to one of three arms:

1. **Full Intervention** (video + telecare + primary care provided (PCP) communication)
2. **Video-only Intervention** (video but no telecare or PCP communication)
3. **Usual Care**

Enrolled participants will complete a baseline assessment in the ED/Urgent Care or remotely by phone[1], a phone call at 1 week to assess processes that might mediate recovery, and phone calls at 1, 3, 6, and 12 months to assess outcomes.

ClinicalTrials.gov Identifier: NCT04118595

[1] Due to the COVID-19 pandemic, all study operations were successfully converted to remote operations between March 12th and April 8th, which received IRB approval on April 8, 2020. On April 13th, screening and enrollment by phone re-started and has continued without interruption. Since April, all study activities including recruitment, enrollment, intervention delivery, and follow-up calls have been conducted by study personnel remotely.

3. Analysis Populations

Two analysis populations will be defined for this study:

- *Intention-to-Treat (ITT) Population:* This population will include all participants who were randomized, analyzed according to the group to which they were randomized. Nobody will be excluded, regardless of treatment actually received.
- *Per-Protocol Population:* This population will be a subset of the ITT population and will exclude all participants who were found to meet exclusionary criteria after enrolling in the study, specifically patients who are admitted to the hospital and patients who are found to have pain that is not musculoskeletal in origin. The Per-Protocol population will also exclude participants who did not receive their intended treatment (i.e., participants in Groups 1 or 2 who viewed less than 50% of the video or watched the video more than 24 hours after visit, and participants in Group 1 who were not reached for the telecare call).

4. Unblinding Plan

As an open-label study, participants, providers, and many study staff will know to which group individual participants have been randomized (the Research Assistants who conducted the follow-up interviews were blinded to treatment arm assignment). However, efforts will be made to keep the principal study statistician blinded to randomization group during the course of the trial. Any key decisions regarding study outcomes, the appropriateness of test statistics or model assumptions, changes to this analysis plan, or any other statistical issues will be made in a blinded review of the data (i.e., blinded to the true randomization groups). The generated allocation sequence has been generated by the Lead Data Manager and uploaded to the secure REDCap randomization module. Datasets provided to the principal statistician prior to unblinding will not include randomized treatment assignment. Primary ITT analyses will be initially programmed using dummy (computer generated) treatment assignments. Unblinding with respect to the true randomization groups will only be done for the final interpretation of the results. Membership in the Per-Protocol Population cannot be adjudicated without knowing actual group assignment.

5. Scoring of Outcome Variables and Certain Baseline Control Variables

Many outcome variables and some baseline control variables will be measured using validated scales or indices. The scoring to be used for each of these scales/indices, including handling of missing scale items, is described in this section.

a. The Brief Pain Inventory Short Form (BPI-SF)

The BPI-SF is composed of two sub-scales, one for pain severity and the other for interference. Pain severity is measured using four items to assess pain at its "worst in the past week", "least in the past week", "average in the past week", and "right now". Each of these is scored on a 0 to 10 scale, with 0 indicating "none" and 10 indicating "worst". A Pain Severity Score will be obtained using the mean of these four items. If at most one of the four items is missing, we will use item-mean imputation and take the mean of the 3 non-missing items.

Interference is measured using seven items assessing how much the pain interferes with seven daily activities or conditions. Each item is scored on a 0 to 10 scale, with 0 indicating "does not interfere" and 10 indicating "completely interferes". A Pain Interference Score will be obtained as the mean of the non-missing items as long as at least 4 of the 7 items is non-missing (i.e., using item-mean imputation).

The primary outcome is the Combined Pain Severity and Interference Score, which will be obtained by averaging the Pain Severity and Pain Interference scores, assuming that neither is missing.

See https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf

b. Overall health measured by the PROMIS Global Health-Physical 2a

This scale consists of two items, each scored from 1 to 5 with higher scores indicating better global health. In the follow-up survey, these are the variables PHYHLTH and PHYACT. These items will both have to be reverse-scored prior to summing. Missing items will not be imputed. A total score is computed by summing these two items, and is then converted to a t-score for analysis using the table below.[2]

PROMIS Global Health v1.2 - Physical 2a		
Short Form Conversion Table		
Raw Summed Score	T-Score	SE*
2	23.4	5.5
3	29	5.1
4	33.4	4.9
5	37.3	4.8
6	41.1	4.8
7	45	5.1
8	50	5.4
9	56	5.9
10	63.3	7.1
*SE = Standard Error on T-score metric		

From: http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Global_Scoring_Manual.pdf

c. Physical Function measured by the PROMIS-Physical Function 4

This scale consists of four items, each scored from 1 to 5 with higher scores indicating better physical function. In the follow-up survey, these are the variables CHORES, STAIRS, WALK15M, and SHOP. These items will all have to be reverse-scored prior to summing. Missing items will not be imputed. A total score is computed by summing these four items, and is then converted to a t-score for analysis using the table below.[3]

[2] Updated 7/24/2022 – Rather than using the table values, we will have the PROMIS scales scored by the website https://www.assessmentcenter.net/ac_scoringservice, which will allow for some missing items. On this website, select "Existing short form or profile", PROMIS, adult respondents, and global health domain, then search. Select "PROMIS scale v 1.2 – Global Health", and select the default calibration sample.

[3] Updated 7/24/2022 – Rather than using the table values, we will have the PROMIS scales scored by the website https://www.assessmentcenter.net/ac_scoringservice, which will allow for some missing items. On this website, select "Existing short form or profile", PROMIS, adult respondents, and physical function domain, then search. Select "PROMIS SF v2.0 – Physical Function 4a", and select the default calibration sample.

Adult v2.0 - Physical Function 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	22.5	4.0
5	26.6	2.8
6	28.9	2.5
7	30.5	2.4
8	31.9	2.3
9	33.2	2.3
10	34.4	2.3
11	35.6	2.3
12	36.7	2.3
13	37.9	2.3
14	39.2	2.4
15	40.5	2.4
16	41.9	2.5
17	43.5	2.6
18	45.5	2.8
19	48.3	3.3
20	57.0	6.6
*SE = Standard Error on T-score metric		

From:

https://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Physical_Function_Scoring_Manual.pdf

d. Analgesic-Related Side Effects Frequency and Severity

A modified Opioid-Related Symptom Distress Scale (OR-SDS) will be used to assess subject-reported levels of frequency and severity concerning 10 symptoms known to be associated with opioid medication usage, such as drowsiness, dizziness, and constipation. Added to this measure are 5 other symptoms (including shortness of breath, falls, abdominal pain, bloody stool, and 'other'), reflecting side effects for patients taking NSAIDs or acetaminophen. Symptom frequency will be rated as: 1=rarely, 2=occasionally, 3=frequently, or 4=almost constantly, with higher ratings indicating more frequent symptoms. Symptom severity will be rated as: 1=slightly, 2-moderate, 3=severe, or 4=very severe, with higher ratings indicating more severe symptoms. Patients who deny a symptom or those who report not taking any pain medications will be given a score of zero for frequency and severity. A mean symptom distress score will be calculated based on patient reported scores for frequency and severity. Responses of "I don't know" will be coded as missing for this calculation.

e. Sleep Quality using Items from Pittsburgh Insomnia Rating Scale

Two items, each on a scale from 1 to 4, will be used to assess sleep problems, with higher scores indicating more problems with sleep. The two items will be added together to calculate a single sleep quality score, with no imputation for missing items.

f. Gagne Comorbidity Score

The Gagne Comorbidity Score will be calculated based on baseline data. The weights indicated below will be applied to each item, as detailed here: https://scholar.harvard.edu/gagne/software/combined-comorbidity-score .

```
if disease = 'metastatic_romano'            then weight = 5;
if disease = 'chf_romano'                   then weight = 2;
if disease = 'dementia_romano'              then weight = 2;
if disease = 'renal_elixhauser'             then weight = 2;
if disease = 'wtloss_elixhauser'            then weight = 2;
if disease = 'hemiplegia_romano'            then weight = 1;
if disease = 'alcohol_elixhauser'           then weight = 1;
if disease = 'tumor_romano'                 then weight = 1;
if disease = 'arrhythmia_elixhauser'        then weight = 1;
if disease = 'pulmonarydz_romano'           then weight = 1;
```

```
if disease = 'coagulopathy_elixhauser'        then weight = 1;
if disease = 'compdiabetes_elixhauser'        then weight = 1;
if disease = 'anemia_elixhauser'              then weight = 1;
if disease = 'electrolytes_elixhauser'        then weight = 1;
if disease = 'liver_elixhauser'               then weight = 1;
if disease = 'pvd_elixhauser'                 then weight = 1;
if disease = 'psychosis_elixhauser'           then weight = 1;
if disease = 'pulmcirc_elixhauser'            then weight = 1;
if disease = 'hivaids_romano'                 then weight = -1;
if disease = 'hypertension_elixhauser'        then weight = -1;
```

6. Missing Outcome Data, Out of Window Visits, and Sensitivity Analyses

Missing data for the primary outcome will be ignored (treated as missing at random) in the primary ITT analysis. For the 1-, 3-, and 6-month visits, outcomes for any visits that fall outside the ±7 day window will be set to missing for the primary analysis (with time computed as follow-up call date minus enrollment date). However, as a first sensitivity analysis, we will repeat the primary analysis using all observed data even if the visits fall outside the visit window. This analysis will repeat the same comparison of mean BPI-SF scores at 30, 90, and 180 days, but time will be treated continuously in this model and actual visit dates will be used. As a second sensitivity analysis, we will repeat the primary analysis using multiple imputation to account for any missing BPI-SF scores. The multivariate normal multiple imputation method will be used, and imputations will be based on all of the control variables included in the primary model.

For each outcome measured using a scale, missing scale items will be imputed as described in Section 5 above. Data missing by design (e.g., due to a skip pattern in the data collection form) will be filled in logically where appropriate.

7. Analysis of Participant Follow-Up

We will present an account of the final disposition (completed, withdrew, lost, or died) for each participant in the ITT Population, including any admission violations and group assignment. The number and proportion of participants in the ITT population who provided information for the analyses of the study objectives will be summarized by randomization group. Frequencies of participants with missing primary outcome data will be summarized by randomization group and study visit. We will provide a CONSORT diagram showing the flow of participants through the trial, indicating withdrawals by treatment arm with reasons, when provided.

8. Analysis of Baseline Data

We will summarize baseline data (i.e., pre-randomization data) for the ITT Population, by randomization group, site type (ED vs. Urgent Care), and overall. Measures of central tendency and dispersion for continuous and certain discrete variables will include means, standard deviations, medians, minima, and maxima. Categorical data will be summarized with frequencies and percentages. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. No inferential statistics (i.e., p-values and/or confidence intervals) for comparing data between groups will be presented.

9. Primary Analysis of Primary Outcome (Objective 1)

The primary analysis of BPI-SF will use the ITT Population, and will be repeated secondarily using the Per-Protocol Population. We will use a linear mixed model to conduct an analysis of covariance (ANCOVA), controlling for site type (ED vs. Urgent Care), baseline pain severity, age, gender, race,

comorbidity score, baseline intermittent opioid use, a history of chronic pain, and access to a PCP (access to a PCP was used to stratify the randomization and, as such, it is important to control for it in all models). These control variables were selected a priori based on prior evidence of prognostic value and will not be subjected to significance testing. This model will include all pain severity scores (1, 3, 6, and 12 months) as outcomes; will include fixed effects for group, visit, and group-by-visit; and will use an unstructured covariance matrix for the error terms. We will first test a 6 degrees of freedom (df) linear contrast of the overall null hypothesis of no mean difference in the primary outcome at any of the 1-, 3-, and 6-month follow-up assessments across the 3 groups at the 5% significance level. If the overall null hypothesis is rejected, we will then conduct two separate 3 df contrasts to compare each of the intervention groups with the control group using a Bonferroni-adjusted 2.5% significance level. We will secondarily estimate mean pairwise differences along with 95% confidence intervals at each time point, including data collected at the 12-month follow-up time point.

10. Secondary and Exploratory Analyses (Objective 1)

The same linear mixed modeling approach used for the primary outcome will be applied to each of the separate components of the BPI-SF (Pain Severity and Interference). Similar comparisons using the sequence of linear contrasts and 95% confidence intervals as specified for the primary outcome will be made.

Similar longitudinal modeling approaches will be applied to evaluate treatment effects on other secondary outcome variables. Appropriate models will be applied depending on the scale of the outcome variable, but the model for fixed effects/linear component will remain consistent across outcomes. For opioid use, a binary outcome, we will apply generalized estimating equations along with a logistic link function and unstructured working covariance matrix. For analgesic-related side effect frequency and severity, physical function, overall health, sleep quality, and healthcare utilization, all quantitative measures, we will compare mean response over time by applying generalized estimating equations along with an identity link function and unstructured working covariance matrix. All comparisons will be made using appropriately specified linear contrasts, tested at the 5% significance level, and/or 95% confidence intervals.

Non-opioid analgesic use and use of other pain management strategies will be descriptively summarized by randomization group and time, without any plans to apply inferential statistical methods (hypothesis tests or confidence intervals).

Exploratory Analyses: To assess whether some groups of participants are more likely to benefit from the interventions, we will estimate and compare effects using tests of interaction for a priori identified subgroups based on gender, race, health literacy, access to a PCP, and preference for control over decision-making[4]. To assess for potentially differential intervention effects on the primary outcome across each of the subgroups, we will use ANCOVA models similar to that for the primary analysis, but with the addition of appropriate interactions between intervention groups and subgroups. Separate models will be used to assess each interaction. Interpretation of differential effects of the intervention will be limited to subgroups for which an interaction is significant at the 5% level.

[4] After enrollment was converted to remote due to COVID, which meant that the intervention was experienced *following* the ED visit, the shared decision making items were dropped from the study. Thus, we will not use "preference for control over decision-making" as a variable in our models.

11. Assessing Potential Mechanisms (Objective 2)

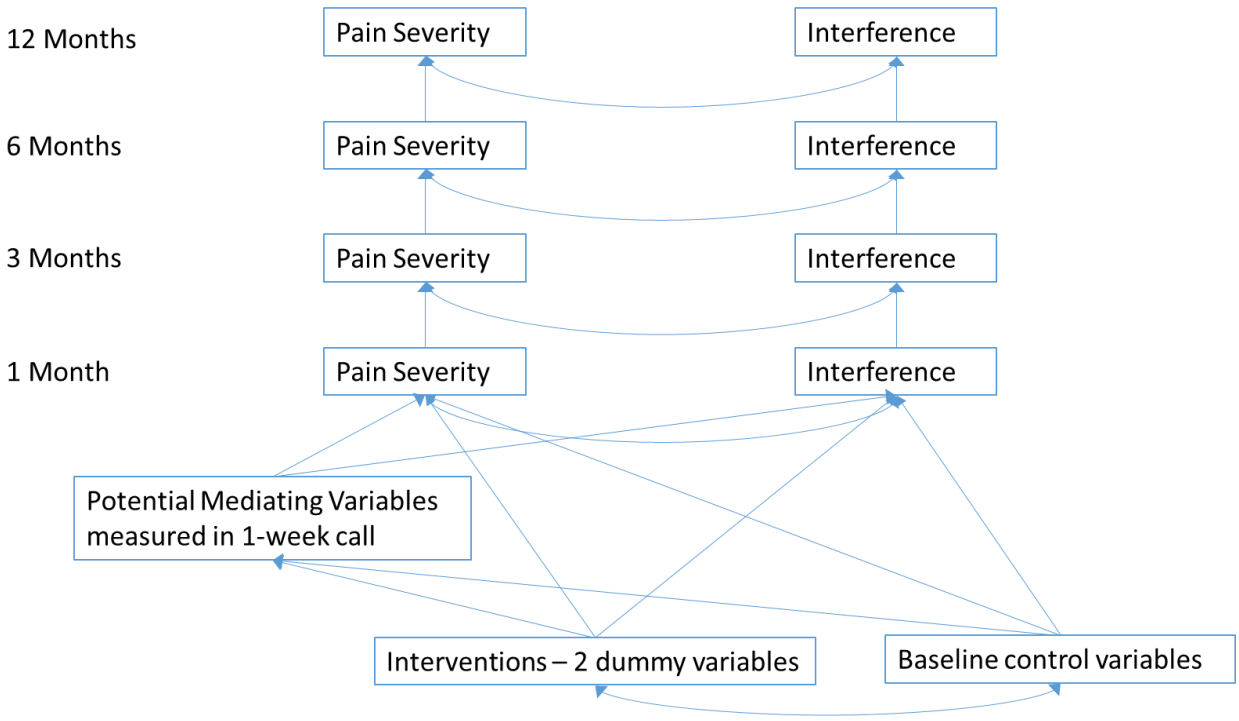
To address the Objective 2, we will apply structural equation models (specifically, longitudinal path analyses with manifest variables) with all variables incorporated appropriately for their scale. The structural equation models will be fit using MPlus software, version 8.3 or higher. The models will use data from all participants and will control for the same baseline variables as for the primary objective. Full maximum likelihood methods will be used, which allow for inclusion of all observed data for participants who contribute incomplete data. The primary model will include direct and indirect effects from the interventions to the longitudinal outcomes through potential mediating variables (self-efficacy and other "process-related" variables measured at he 1-week phone call) to allow for assessment of whether mediation is present, and if so, whether it is complete or partial. No structural relationships will be imposed relating the potential mediating variables to one another, beyond simple correlations. For the longitudinal outcomes, we will include Pain Severity and Interference in the model as separate variables, which we will allow to be correlated at each time point. We will first test each of the path coefficients from the interventions to the mediator variables separately at the p=0.05 level using chi-squared difference tests. We will then test indirect paths to assess mediation. We will compare full and reduced models (with selected paths restricted to be zero) using chi-squared difference tests. Standard model fit indices (i.e., RMSEA, Bollen's incremental index, and the Tucker-Lewis index) will be reported.

A schematic diagram of the general model set up is shown in Figure 1 below. In this figure, straight arrows represent structural paths, curved arrows represent correlations.

12. Summary of Safety Data

Adverse events will be descriptively summarized for the ITT Population, by randomized treatment group, using frequency tables. Summaries will also be presented according to severity and perceived relatedness to the study. No inferential statistics (hypothesis tests or confidence intervals) will be presented for comparing across groups.

Figure 1. Schematic diagram of the proposed longitudinal path model.


12 Months
Pain Severity
Interference
6 Months
Pain Severity
Interference
3 Months
Pain Severity
Interference
1 Month
Pain Severity
Interference
Potential Mediating Variables measured in 1-week call
Interventions – 2 dummy variables
Baseline control variables