NCT03377816: The Role of Emotional Processing in Improving the Quality of Life of Breast Cancer Patients (REPAT)

Statistical Analysis Plan- September 14th, 2017

The following statistical analysis plan was written in September of 2017 as part of the grant proposal for the REPAT study and was incorporated into the study protocol and guided the design of the actual study.

C.5 Statistical Methods:

C.5.1 Sample Size: A power analysis was conducted via Monte Carlo simulation in Mplus showed that a sample size of 240 (120 per condition), provides: (1) >90% power to detect a moderate effect size (Cohen's d = 0.50) of treatment on mechanisms, (2) >90% power to detect a moderate association (r = 0.30) between mechanisms and symptoms, and (3) >90% power to detect an indirect effect from treatment to symptoms via mechanisms. The sample size will also provide >80% power to detect a moderate effect size for the Condition by Ethno-Cultural group interaction.

C.5.2 Data Analysis: Prior to testing hypotheses, we will produce a thorough descriptive profile of the sample and examine the distributions of key variables involved in the hypotheses. We will also examine levels of nonresponse and **missing data**. Prior experience indicates attrition will be low; although, some missing data are expected due to missed assessments and dropout. Data will be analyzed using full information maximum likelihood to address missing data, supplemented with pattern-mixture modeling for non-random missingness. The first part of Hypothesis 1: women in the AT group experience greater increases in emotion processing, HRV, and regulatory cytokine levels and greater decreases in pro-inflammatory cytokines than women randomized to the Mandala condition will be tested using linear mixed models[129]. Models will include a Time x Condition interaction to test whether the change over time in emotion processing and cholinergic anti-inflammatory processes is significantly different between treatment groups.

A significant interaction will be followed up by simple slope tests to characterize the degree of change separately in the AT and Mandala conditions.

The second part of Hypothesis 1: emotion processing and cholinergic anti-inflammatory processes mediate the effects of AT on symptoms (depression, pain, fatigue) will be tested using path analysis.

Specifically, models will be tested where condition (AT versus Mandala) predicts the change in emotion processing or physiological correlates (path a) and the change in emotion processing or physiological correlates predicts the change in symptoms (path b). Mediation will be tested by calculating the indirect effect as the product of coefficients (path a x path b) and utilizing bootstrapping to calculate 95% confidence intervals and statistical significance[130].

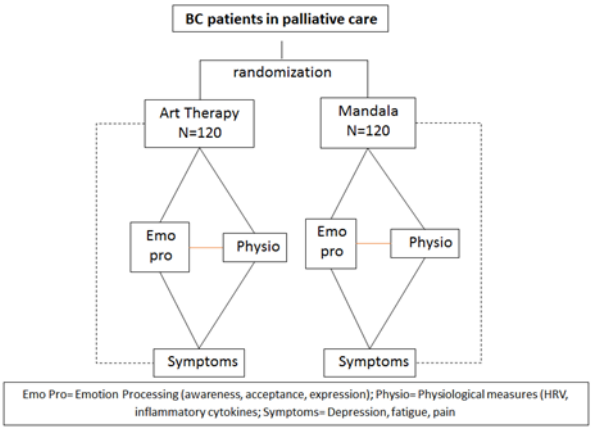

Figure 3: Model hypotheses 1 & 2

Hypothesis 2: changes in emotion processing and cholinergic anti-inflammatory processes will be correlated and have unique effects will be tested by expanding the path analyses from Hypothesis 1 to simultaneously include all proposed mediators on each symptom outcome. Indirect effects with bootstrapped confidence intervals will be calculated as before. The change in mediators will be allowed to freely correlate to examine their relations.

The Exploratory Hypothesis posits a sequential mediation model from treatment (AT versus Mandala) to emotion processing (path a) to cholinergic anti-inflammatory processes (path b) and finally to symptoms (path c). To establish temporal precedence, change in emotion processing from baseline to intervention midpoint and change in cholinergic anti-inflammatory processes from intervention midpoint to completion, and change in symptoms from baseline to intervention completion will be used. Indirect effects will be calculated as the product of three coefficients (path a x path b x path c) capturing the hypothesized sequentially mediated effect. Bootstrapped confidence intervals and significance tests will be calculated. To test the reverse ordering, the same process will be used exchanging the time points and order of emotion processing and cholinergic anti-inflammatory processes.

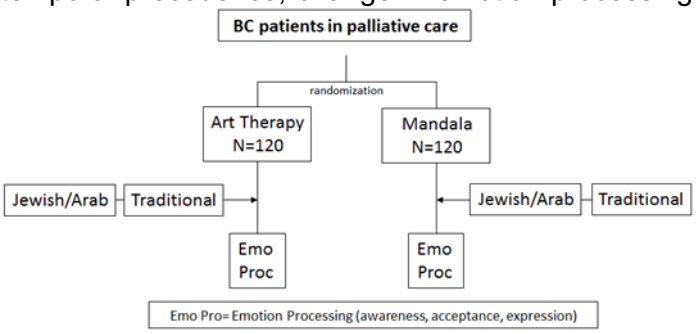

Figure 4: Model Hypothesis 3

Hypothesis 3: the effect of AT versus SHAM on emotional processing will be stronger in women from an ethno-cultural minority group will be tested by expanding the linear mixed models from Hypothesis 1 by including measures of traditional values as a covariate and a Time x Condition x Ethno-Cultural Group (Jewish vs Arab) interaction to test whether ethno-cultural group moderates the Time x Condition interaction from Hypothesis 1. If the three-way interaction is significant, simple slopes will be calculated and graphed to characterize the change in emotion processing by treatment condition and ethno-cultural group.