As the number of U.S. adults age 65 and older increases, so too will the prevalence and associated mortality of various cancers (1). Along with pain and other symptoms, psychological symptoms are prevalent in cancer patients, especially in advanced stages (2). Depressive disorders in adults with advanced cancer have been estimated to be as prevalent as 31% and anxiety disorders as prevalent as 14% (3).

A range of treatments have been developed to address both physical and psychological symptoms in advanced cancer patients, with massage therapy (MT; an approach involving manual manipulation of soft tissue) gaining increasing attention (4). MT has been associated with reductions in anxiety, blood pressure, and heart rate (4, 5), and a study in the PCRC data repository, the "Reducing End-of-Life Symptoms with Touch (REST)" study, found MT to be associated with improved pain and mood in advanced cancer patients.

In order to maximize the benefits of evidence-based treatments like MT, understanding whether there are subgroups who respond better to treatment than other groups is essential. These subgroups may be identified by treatment moderators, which specify for whom or under what conditions treatment is effective (6). Moderators can help inform clinicians about which clients may respond best to treatment and which clients might be better served by alternate treatments. Moderators can also help inform inclusion and exclusion criteria and choices for stratification in randomized controlled trials (RCTs), which maximizes power (6). Therefore, identifying moderators of MT could have significant research and clinical implications.

Though a meta-analysis has examined moderators of response to massage therapy for various conditions and populations, none of the moderators considered (age of participants, gender of participants, level of practitioner training, and study setting) were significant (5). Psychological symptoms are potentially another key moderator; psychological symptoms at baseline were identified as a moderator for low back pain treatments in a meta-analysis, with those with higher depression and anxiety symptoms showing better treatment responses (7). However, we were unable to identify any research on psychological symptoms as a moderator of treatment effect in MT in advanced cancer patients; published analyses of the REST study do not appear to have examined moderators of MT (8-11). The proposed research attempts to begin to address this gap by conducting a secondary analysis of data from the REST study, which compared MT to simple touch in 380 adults with advanced cancer (10). **Specific Aims** are:

**Aim 1.** To examine whether, across treatment groups in the REST study, baseline presence of depression or psychological symptom frequency are associated with primary and secondary study outcomes.

Hypothesis 1: In both treatment and control groups, the presence of depression and baseline psychological symptom frequency will be highly associated with all outcome variables.

Measures Aim 1: *Presence of depression* was identified on the initial study screen, which includes a yes/no item on whether depression was identified either in the patient chart or the patient interview. *Baseline psychological symptom* frequency was measured with the Memorial Symptom Assessment Scale (MSAS), which includes items on the frequency of five psychological symptoms (worrying, feeling sad, feeling nervous, feeling irritable, difficulty concentrating), and also provides a Psychological Symptom subscale score (the MSAS-PSYCH) based on these 5 items. We will examine the same outcome variables as in the initial REST study analyses (10), except that mood will not be considered (as it is likely highly correlated with baseline psychological symptoms). *Primary outcomes* will be immediate and sustained change in pain and interference of pain, as measured by the pain scale of the Memorial Pain Assessment Card (MPAC) (12) and the Brief Pain Inventory (BPI) (13, 14). *Secondary outcomes* will be 60-second heart and respiratory rates; quality of life (measured by the existential well-being and support subscales of the McGill Quality of Life Questionnaire (MQOL) (15)); physical distress (measured by the Memorial Symptom Assessment Scale (MSAS) (16)), and analgesic medication doses over the prior 24 hours (considered as parenteral morphine equivalents using World Health Organization equianalgesic conversion ratios (17)).

Data Analysis Aim 1: We will generate descriptive statistics and frequency distributions for all variables, then used mixed models methodology to explore both bivariate and adjusted associations.

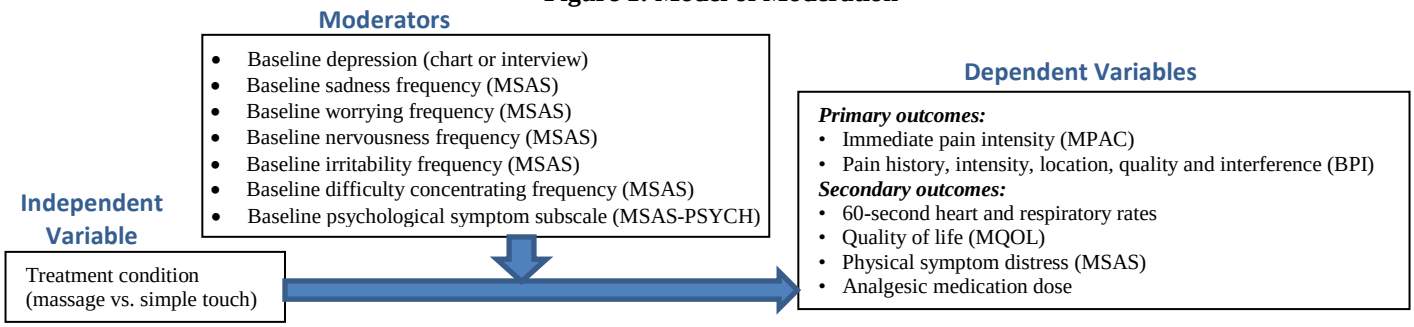
**Aim 2.** To test whether the presence of depression and baseline psychological symptom frequency moderate intervention effects.

Hypothesis 2: The presence of depression and baseline psychological symptom frequency will moderate response to MT, with those with depression or more frequent symptoms showing greater effect.

Measures Aim 2: Same as Aim 1.

Data Analysis Aim 2. We will utilize mixed models methodology, with pain severity, 60-second heart and respiratory rates, quality of life, physical symptom distress, and analgesic medication doses as outcomes, and presence of depression and frequency of psychological symptoms as moderator variables. The models will test separately for the interaction of each baseline psychological symptom measure and treatment assignment. Models will adjust for key covariates used in the initial REST outcome analyses (10): age, gender, general health status, prior massage experience, expected benefit from massage, and worst pain in prior week. Subject intercepts and slopes (if needed) will be treated as a random effect. To account for individual differences, time will be treated as a fixed-effect categorical variable, treatment status as a fixed effect dummy variable, and outcomes treated as either categorical or continuous variables. A moderating effect would be deemed as present if a substantial difference in effect size is observed. Analyses will be adjusted for multiple comparisons using the step-up method to control for the false discovery rate method (18). See **Figure 1**.

**Figure 1: Model of Moderation**




**Ethics:** In order to ensure compliance with accepted standards of human research ethics, we will obtain approval to analyze data from the City University of New York IRB before beginning analysis.

**Next Steps**: Upon completion of the analyses, the PI will prepare and disseminate study findings via peer-reviewed journals and presentation at professional conferences. In addition, the results may also inform future studies of treatment implementation for adults with advanced cancer- particularly whether those with more psychological symptoms require targeted approaches. If we do find that greater psychological symptoms moderate the effects of massage, a brief mental health-focused intervention could potentially be paired with MT, or delivered prior to MT, to further enhance treatment gains. The results from the proposed research could also guide the design of future RCTs of MT in advanced cancer, including whether inclusion/exclusion criteria or stratification should consider psychological symptoms.

**Proposed Project Timeline** (May, 2017 – June, 2018)

| Activities | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre-award: Start Up: IRB | | | | | | | | | | | | | | |
| Receive data from PCRC | | | | | | | | | | | | | | |
| Data cleaning and recoding, as needed | | | | | | | | | | | | | | |
| Data analysis | | | | | | | | | | | | | | |
| Submission of manuscript plan to PCRC | | | | | | | | | | | | | | |
| Manuscript and report preparation | | | | | | | | | | | | | | |
| Manuscript submissions | | | | | | | | | | | | | | |
| Manuscripts under review/published | | | | | | | | | | | | | | |

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# Proposed Budget

| Personnel | Annual Salary | Level of Effort % | Salary | Fringe Benefit | Total Salary |
|---|---|---|---|---|---|
| Angela Ghesquiere- PI | $90,000 | 17.00% | $15,300 | $5,713 | $21,013 |
| **OTPS** | | | | | |
| Supplies | | | | | $309 |
| SUB-CONTRACT- CUNY School of Public Health and Public Policy Katarzyna Wyka- statistician | | | | | $16,738 |
| | | | | Total OTPS | $17,047 |
| | | | | **Total Direct Costs** | **$38,060** |
| | | | | Indirect Costs | $11,940 |
| | | | | **Total Costs** | **$50,000** |

# Budget Justification

**Personnel**

**Angela Ghesquiere, PhD, MSW, Principal Investigator.** Angela Ghesquiere is on a 12-month appointment. She will devote 17% of her effort to this project over the year-long project period. Dr. Ghesquiere is a program manager at the Brookdale Center for Healthy Aging of Hunter College, and is a PhD-level social worker specializing in services research. She has coordinated a number of federally funded studies on older adults' health and mental health. She has training and analysis experience in quantitative research, and has published over 10 articles involving secondary data analysis, including several from intervention trials. Dr. Ghesquiere will lead the project, oversee all analysis activities, help prepare the data for analysis, and lead preparation of all presentations, reports, and peer-reviewed journal-articles resulting from the project.

**Fringe benefits:** The fringe rate for Dr. Ghesquiere's salary is **37.34%**.

**Other Direct Expenses**

**SUB-CONTRACT- CUNY School of Public Health and Public Policy, Katarzyna Wyka, PhD**, **Statistician**. Dr. Wyka is on a faculty appointment. She will devote 10% of her time to this project during the academic year (from September, 2017-April, 2018); costs for Dr. Wyka consist of $6,821 Salary; $3,479 Fringe Benefits (at 51.0%); and $6,438 in Indirect Costs (at the CUNY School of Public Health and Public Policy rate of 62.5%). Dr. Wyka is an Assistant Professor in the Department of Epidemiology and Biostatistics, Graduate School of Public Health and Health Policy, City University of New York. Her expertise is study design and statistical methods for public health research. She has been a statistician on multiple NIH-funded grants, including projects focused on the mental and physical health consequences of psychiatric disorders, chronic diseases, physical activity and nutrition, and has over 20 peer-reviewed publications on these topics. Dr. Wyka will conduct the planned statistical analyses in conjunction with Dr. Ghesquiere, assist with interpretation of the results (including creation of tables and figures for reports) and help ensure the integrity of data management.

**Supplies** ($309): Office supplies (*e.g.* pens, printer ink, paper, paperclips, staples, notepads, etc.) will be purchased to support project activities, such as review of analyses.

**Indirect Expenses**

Dr. Ghesquiere is an employee of the Hunter College of the City University of New York, which has an indirect rate of **56.0%**. As per City University of New York requirements, indirect costs are requested in addition to the direct costs.