Pain Reduction Through Empowered Recovery (PRIME) Study
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Study Protocol and Statistical Analysis Plan

JHM IRB - eForm A – Protocol

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1. Abstract

Chronic pain and depression frequently co-occur among older women with disabilities, and each can exacerbate the other in a worsening cycle.[1,2] Beyond each individual category of risk, the intersection of age, sex, and disability place older women with disabilities at even higher risk of having co-occurring pain and depression. In yet another intersection, older Black women are at the highest risk of experiencing co-occurring depressive symptoms and chronic pain as compared to any other gender or race groups.[3–5] To address this population's need for tailored, culturally appropriate non-pharmacological interventions, we propose an intervention based on a multicomponent biopsychosocial approach to reducing chronic pain and depression in older women with disabilities, and have designed this intervention with a foundation of understanding of how social determinants of health impact this population. Based on preliminary work, we identified preferred strategies among older Black women with disabilities to address pain and depressive symptoms, such as empowerment to communicate with providers, physical activity education, and group therapies.[6,7] On the basis of prior work and current literature, the purpose of this study is to evaluate the feasibility, acceptability, and efficacy of a multicomponent behavioral intervention titled: "Women in Pain Reduction & Improved Mood through Empowerment (W-PRIME)." We aim to reduce pain and depressive symptoms in older adult women, 50 years of age and older) with physical disabilities. We will also explore potential inflammatory pathways contributing to the hypothesized effects. We propose a randomized wait list control design to test feasibility and acceptability and obtain a preliminary effect size for the intervention. We will recruit 40 (≥age 50) African American women who report pain intensity of 3 or higher that interferes with their activities, depressive symptoms lasting more than two weeks, physical disability, and live in the community/are not institutionalized. The sample will be recruited through the PI's previous study, community recruitment flyers distributed virtually, word of mouth campaigns, and Johns Hopkins MyChart. Participants will be randomized into either the intervention or the wait list control group. Once the intervention group has completed their visits, the wait list control group will begin their visits. All participants will be offered the same information and format of nurse visits and ACT virtual group sessions. The nurses will systematically tailor the content of the visits to the participants' risk profile and goals based on protocols. All participants will be assessed at the start of the study, at 12 weeks, and 24 weeks. The primary outcomes will be pain and depressive symptoms. Other endpoints include goal attainment, stress (cytokines), and communication with health care providers. We will also

examine the acceptability of the intervention using intervention compliance and one-on-one qualitative interviews.

2. Objectives

Using a randomized, wait list control design, we will test the feasibility and acceptability of W-PRIME among 30 women, 50 years of age and older, with physical disabilities, chronic pain, and depression. Our aims are:

Aim 1: Determine feasibility through retention rates and rates of adherence to the intervention protocol (e.g., participation in all visits/meetings), and acceptability through qualitative interviews.

Aim 2: Determine feasibility and acceptability of sweat patches to identify inflammatory cytokines (IL-6, IL-8, and TNFα). We will measure feasibility by how many women successfully used the sweat patches and through open-ended questions during qualitative interviews.

Aim 3: Compare changes in pain, depression and inflammatory cytokines between W-PRIME participants and wait list control participants to determine effect sizes to inform future research.

3. Background

Co-occurring Pain and Depression

It is well documented that pain and depression are highly related, frequently co-occur and may co-exacerbate physical and psychological symptoms.[8] The overlapping mechanisms remain elusive in clinical cohorts, yet there is evidence implicating alterations in modular neural systems and critical links to chronic low-grade inflammation. Increased levels of stress hormones are a biological response to pain and depression[8–10] and pain and depression share many biomarker similarities.[11] For example, inflammatory markers such as IL6, IL8, and TNFa may contribute to the relationships between behavioral symptoms and pain severity.[12–16] Depression has been associated with central inflammation, and central inflammation influences regulation of the stress-response, as well as neuronal communication. Thus, central inflammatory response likely contributes to alterations in neuronal processing of pain signals and results in a greater risk for chronic pain detection and reduced pain tolerance.[8,9]

There is also evidence suggesting that living with chronic pain can increase the risk of developing depression.[17] Regardless of whether chronic pain or depression comes first, there is substantial evidence showing that their co-occurrence contributes to impaired physical, mental and social functioning, which is greater in severity than when either is experienced alone.[8] Furthermore, older women with disabilities may have additional comorbid conditions that contribute to chronic pain, which may then lead to depression. Given what is known regarding the reciprocal relationship of pain and depression,[18] aging women with disabilities and comorbid conditions may find themselves in a cycle of chronic pain and depression. It is suggested that, because several of the mechanisms underlying pain and depression are shared, some of the behavioral therapies commonly used for depression may also be effective in addressing pain.[8]

Disparities in Pain and Depression in Older Women with Disabilities

An estimated 50 million adults in the U.S. experience chronic pain, and the highest prevalence of chronic pain occurs in women, older adults, and individuals with disabilities.[19,20] Depression rates are also higher in older women than younger women or older men and in individuals with disabilities versus individuals without disabilities.[1,2] Those experiencing comorbid pain and depression are most likely older adults, women, and individuals with disabilities.[21] Disability is defined as "difficulty completing activities or fulfilling expected roles in any domain of life due to a health or physical problem."[22] Pain and depression can exacerbate the inability to fill a social role or complete an activity in individuals with disabilities. In women with physical disabilities, it is further complicated, as women with disabilities may have more inflammatory cytokines that may increase the risk of comorbid pain and depression.[1,2,23] In addition to the biological risk factors, social determinants of health for older women with disabilities may prohibit them from getting the needed pain management and mental health care, which further exacerbates their symptoms. Social determinants of health that further contribute to disparities in pain and depression in older women with disabilities include affordability or accessibility of pain management and mental health therapies (pharmacological discrimination within health care settings, and difficulty with communication with health care providers).[7,24]

Disparities in Pain and Depression in Black Women

The intersection of race, sex, and age put Black women at an increased risk of experiencing undertreated depressive symptoms and pain that can significantly diminish their quality of life.[3–5] Depressive symptoms among Blacks are more severe than other racial/ethnic groups.[25] Although half of adults with depressive symptoms undergo treatment, only 45% of Blacks with depressive symptoms undergo treatment.[3,4,26] Black women experience higher rates of pain[3–5,26,27] yet Blacks are prescribed pain medications less often than non-Hispanic Whites.[3] In our previous work, we identified that older Black women living with undertreated pain and depression described a state of suffering.[6] Some antidepressant medications, opioids, and NSAIDS can improve depression and decrease pain among older adults/older Blacks; however, they may experience high rates of side effects from these medications.[3,28] Hence, non-pharmacological pain interventions can be combined with pharmacological interventions[29] to help alleviate pain and depressive symptoms in older Black women.

Behavioral Interventions

Behavioral interventions have been successful in treating pain or depression, but few studies have addressed both outcome variables, and many have not explicitly reported if they included older women with disabilities or older Black women with disabilities. In an intervention that successfully improved depression in older Blacks, pain was not assessed and the disability status of the participants was unclear.[30,31] In another clinical trial for depression in women, group therapy session significantly reduced depressive symptoms in older, non-Hispanic White women but not older Black women.[32] Many of the behavioral interventions that address pain in older women have been focused on cancer pain or do not specify if older women with disabilities or Black women with disabilities were included in the samples.[33,34] Individuals with disabilities are often not part of the study samples in clinical trials because of the inclusion criteria or other environmental barriers that prevent them from participating.[35,36] We did identify one study that examined efficacy of a depression self-management intervention with group sessions for rural women with physical disabilities, that did show a reduction in depression.[37] Evidence suggests that behavioral interventions for pain in older adults should have a multi-component approach that also addresses secondary conditions such as depression.[38] Self-management and cognitive

therapies are recommended methods to include in behavioral interventions for older adults with pain, it critical however to determine if the methods used are acceptable and feasible for underrepresented groups such as those with disabilities or underrepresented racial/ethnic groups.[38] Self-management strategies and goal-setting have demonstrated improvements in pain and other related outcomes in the older adult population.[39]

Behavioral interventions for both pain and depression in older adults are essential due to the complexities of providing pharmacological treatment for pain and depression. Age is strongly associated with treatment-related side effects of opioids, and the risk is increased by the presence of comorbidities.[38] In our previous work we identified that older women with disabilities were hesitant and at times fearful of taking opioids to manage their pain and/or depressive symptoms due to side effects and/or the potential of drug dependency.[7] In addition, higher pain severity and higher depression scores are associated with opioid misuse among community dwelling older adults.[40] Whether they complement pharmacological treatments for pain and depression or replace them based on participant preferences, behavioral interventions are an effective method of empowering older adults to engage in their own treatment and reduce their pain and depressive symptoms.

Communication with Health Care Providers

Individuals with disabilities may have difficulty communicating with health care providers that can prohibit them from achieving adequate pain management. High-quality relationships and communication between patients and their providers should include partnership and respect, which is essential in developing a tailored pain management plan.[7] People with disabilities and/or chronic pain may have difficulty achieving effective communication with their health care providers.[41–43] In our previous work, we identified that older women who were low income with disabilities identified barriers to communication with their health care providers and described the impact this had on their pain and mental health.[7]

ACT Therapy

Acceptance Commitment Therapy (ACT) is a form of cognitive behavioral therapy that focuses on acceptance of inevitable changes and developing or improving psychological flexibility and quality of life.[44–47] Psychological inflexibility is the inability to act effectively in congruence with a valued life when unpleasant thoughts, emotions, or physical symptoms are present and can be disabling.[48,49] When an individual with chronic pain has psychological flexibility, they are still able to act within their own goals and values system despite the pain and distress they are experiencing.[50,51] Researchers have demonstrated effectiveness of ACT in addressing psychological inflexibility, pain, and depression in older adults, including ACT in a virtual format.[44–46] ACT has also been effective in improving depression outcomes among individuals with physical disabilities.[47] ACT has also effectively been used to improve depression in groups of older women.[52] There is little known about the combination of ACT with other non-pharmacological strategies in reducing depression and pain in older women.

The proposed study is **significant** in: 1) targeting a growing population of women with disabilities who are disproportionately impacted by pain and depression; 2) the purposeful inclusion of older Black women with disabilities in the trial who are often underrepresented in clinical trials; 3) the combination of evidence-based strategies to simultaneously address co-

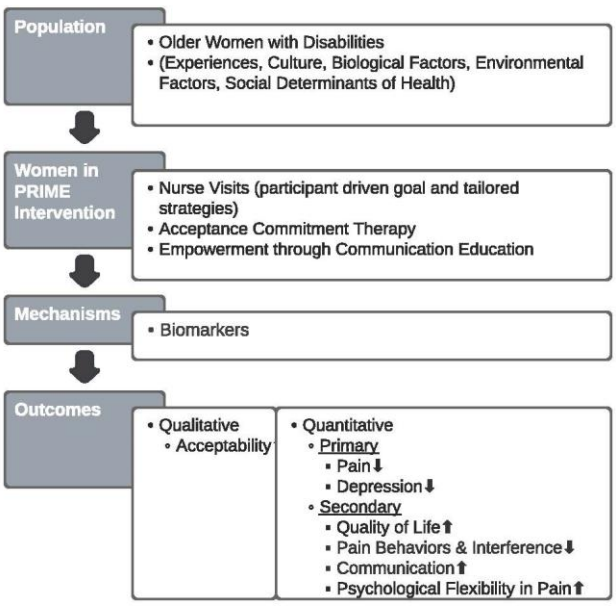
occurring pain and depression; 4) the use of evidence-based non-pharmacological strategies in the intervention serving as an alternative to opioids or other pain medications that present a high risk for side effects in older adult populations;[53–55] and 5) the response to the National Institute on Aging's (NIA) priority of developing effective interventions to maintain health and reduce the burden of disease among older adults (specifically those experiencing health disparities).

Currently, **the PI (Dr. Taylor)** is finishing a pilot randomized trial testing a behavioral intervention that was adapted from a previous successful intervention,[31] which is for older Black women who are frail and have chronic pain and depression. The study team has successfully enrolled participants in this behavioral intervention with a wait list design similar to the proposed study. Through this pilot, she is measuring feasibility and acceptability of the intervention, which we will build on for the proposed study. The multidisciplinary research team has a history of collaborations and demonstrates diverse areas of expertise. Dr. Gill (Co-I) has expertise in biomarkers, sweat patches and work with individuals with disabilities. Dr. Regier (Co-I) is a clinical psychologist with expertise in older adults and Acceptance Commitment Therapy. She will lead the ACT virtual group sessions.

4. Study Procedures

This study will systematically test and refine a multi-component behavioral intervention, referred to as W-PRIME, to improve pain and depression among community dwelling older women with disabilities. W-PRIME includes pain reduction through one-on-one nurse visits structured around participant-driven goals and tailored evidence-based strategies to achieve the goals, which have demonstrated effectiveness in other interventions.[39,56] The improvements of mood will also be addressed in the one-on-one intervention nurse visits. Both pain and depression will be addressed in the ACT group virtual sessions. Lastly, the women will receive training by the nurses to communicate effectively with their health care providers about what their symptoms, goals and treatment preferences are. We will build on the strengths and experiences of the women to increase their empowerment to improve their pain and depression outcomes, which can lead to improvements in overall quality of life. We have used our preliminary work in older Black women with pain and depression[7,57] to develop the W-PRIME intervention. During our time developing the W-PRIME intervention, we identified over 10-20 non-Black older women with disabilities who expressed a desire to participate in the study. Consequently, although we have been pilot testing a behavioral intervention for pain and depression in older Black women, we have identified the necessity of this work in older women with disabilities from other racial/ethnic groups, the desire/need for group sessions, and the importance of developing and building this intervention based on participants' preferences and needs.[47–49]

Figure 1: Theoretical Framework



Conceptual Approach: One of the theoretical frameworks for the study is self-regulation theory, which involves two tenets: 1) participants manage their response based on their experiences (e.g., experiences with communication and pain and depression treatments) and

knowledge of an event and 2) participants' goals are to maintain comfort and decrease the negative effects of an illness (e.g., comorbid pain and depression) on their lives.[58] The intervention is participant-centered and participant-driven. This means that the participants' experiences and existing knowledge about pain and depressive symptoms affect the goals that they set. For example, a participant may have experienced pain, depression symptomsand is no longer able to work in her garden. Her goal may be to be able to garden again. This would provide meaning, potentially decrease the effects of these conditions, and potentially improve her symptoms.

The second theoretical framework for this study is the biopsychosocial approach to chronic pain.[59] Based on the biopsychosocial approach to chronic pain, biological[60], psychosocial, psychological, and cultural factors play a role in a person's pain experience. Due to the heterogeneity of these factors within any given chronic pain population, treatments that are tailored to meet the needs of the participants/patients are more likely to succeed.[38] A tailored pain treatment program will produce the best outcomes because of the vast differences that exist from one individual with chronic pain and/or depression to the next. Figure 1 above represents our conceptual framework for the study. The sample for this study will come with unique experiences and knowledge that inform their pain responses and experiences. The W-PRIME intervention will use self-regulation theory to tailor the nurse visits with participant-led goals and tailored strategies. The intervention is biopsychosocial in that we include cognitive and behavioral components to address both pain and depression. We hypothesize the two main outcomes, pain, and depression, will decrease after the intervention and the secondary outcome of quality of life will improve.

Design Overview

Overall Study Design

The overall design for this study is a wait list randomized clinical trial.

Components of W-PRIME

Before starting the intervention the data collector will meet with participants to collect baseline data and have participants place sweat patches on for 24 hours. The a research team member will pick the patch back up from participants or participants will mail the sweat patches back, whichever they prefer. They will be instructed to wear the sweat patches on the arm or abdomen for 24 hours and avoid tub baths or swimming during those 24 hours.

The W-PRIME intervention has two main components. The first component is five weekly 1:1 individualized nurse visits. The nurses conducting the visits will be from our research study team. Previous work has demonstrated the effectiveness of 1:1 participant goal-driven visits for older adults.[31,56,61] In-person visits provide opportunities to and identify barriers or facilitators to pain management strategies and examine how the participants engage with their environment and what accommodations may be needed. The nurses will all undergo the same training and use the same intervention manual that outlines the overall format of each visit. The participants will be given the option for virtual nurse visits through Hopkins ZOOM; however, in person will be the preferred method. The strategies and educational components will be tailored but the structure of the visits may change. During the first visit, the nurse and the participant will work together to assess participant experiences and develop tailored participant goals regarding their pain and depression. The nurse will work with the participant on strategies that are tailored to the participant, their environment, and their preferences. The nurse will work with the participant during the remaining four visits to make progress toward and achieve the goals. The nurse will

also devote time at each visit to conduct training/education with the participants on communication with health care providers. The nurse will provide tailored education and tools (role play, checklists) to prepare and empower the participants to discuss their concerns, needs and treatment preferences with their health care providers. The second component of the intervention will be the ACT virtual groups. The groups will consist of 3-5 women meeting virtually with a clinical psychologist for ACT therapy sessions. We anticipate Dr. Regier conducting all of the ACT therapy sessions. In the event we need additional clinical psychologists, they will all be trained in providing ACT therapy group sessions Co-I Dr. Regier. There will be a total of six weekly ACT sessions. Dr. Regier will keep track of participants goals and completion of any assigned homework from sessions in REDCAP.

The research coordinator will schedule the sessions when it is convenient for at least three participants. The group will ideally remain the same 3-5 women all six sessions. The six sessions will cover the six core components of ACT, which are acceptance (increasing value-based action), cognitive defusion (change how one interacts with their thoughts), self as context (awareness of self and experiences), values (family, spirituality, career), and committed action (skills, goal setting and shaping methods).[61] The clinical psychologist will encourage participants to reflect on goals they set with the nurse during the session focused on committed action. The research participants will be given forms to complete during the sessions; however, the participants will keep these forms and not turn into facilitator/clinical psychologist. The psychologist potentially will take personal notes during the session but these notes are for the sole purpose of continuity and information for subsequent sessions.

Table 2. Components of the W-PRIME Intervention

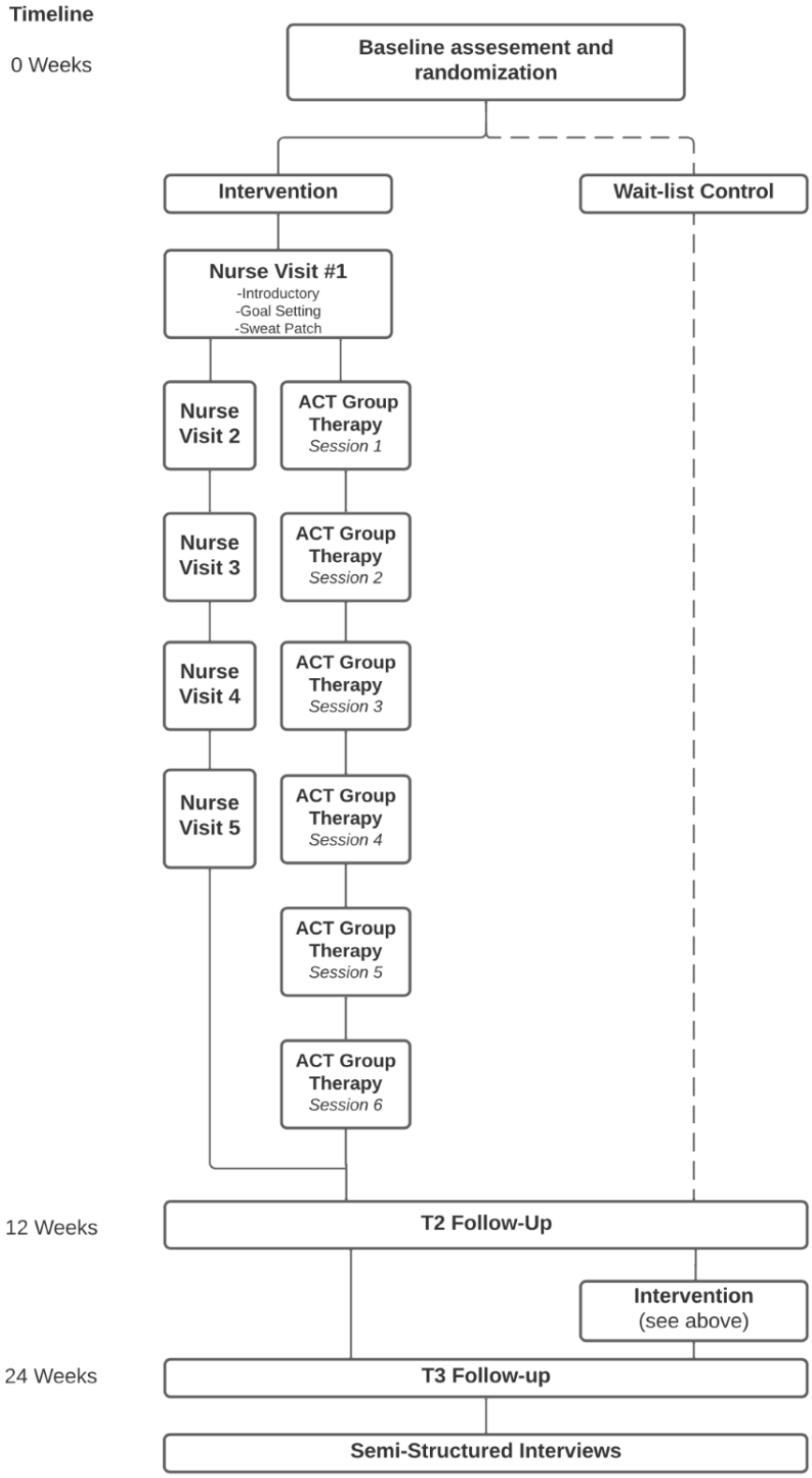
Component 1	**Rationale**	**Potential Impact**
1:1 Nurse Visits (Participant directed, goal setting, evidenced based strategies)	Nurse-led interventions have shown benefits for outcomes among older adults with disabilities. Participant driven interventions show improved sustainability and acceptability. Meeting individuals in their home environments may improve effectiveness and sustainability of intervention. Tailoring strategies to the participants based on their goals, experiences, preferences, and environment. Meeting in home environments decreases the need for transportation barriers often experienced by populations with disabilities[31,50,56,62,63]	Improvements in pain, improvements in depression, improvements in quality of life, decreased inflammatory cytokines. Increased sustainability and acceptability of the intervention.
Communication Empowerment	Accurate and open communication that involves respect leads to better outcomes and improved trust of health care providers[53,54]	Improvements in communication between participants and their health care providers.
Component 2	**Rationale**	**Potential Impact**
ACT Virtual Group Sessions	The virtual option removes structural barriers or extra risk associated with traveling to a group setting[46] ACT addresses the cognitive/mental aspect	Improvements in psychological flexibility, improvements in pain, improvements in depression, decreased inflammatory

	associated with chronic pain and depression[38,44]	cytokines.

Coordination between the components: The nurses and clinical psychologist will meet at least monthly to discuss patient goals and progress. The clinical psychologist will tailor and/or adjust the ACT sessions as necessary based on goal setting and overall experiences of the participants in each ACT group. The clinical psychologist will also update the nurses on what was covered in the sessions, so they have that knowledge and may tailor some of the strategies to align with any new material in the ACT sessions if that is appropriate for the respective participant. The nurses and clinical psychologist will review and brainstorm together to best assist participants who may be having difficulty with any component of the intervention or finding appropriate strategies to address their goals. In Table 2 (above) the components of the intervention and the potential impact are described.

We will also send each participant a monthly or quarterly newsletter with updates about the study and at least one health tip. These newsletters will be sent via mail or email.

Figure 2. W-PRIME Timeline



To maximize scalability, we have designed this multicomponent interdisciplinary intervention to be minimally disruptive or burdensome on participants and standardized yet tailored.

We will use a wait list control design to test the intervention. Outcomes will be measured at baseline for both intervention (n=15) and wait list control groups (n=15) and at 12 weeks (compare intervention and wait list control group) after which the wait list control group will receive the intervention. At 24 weeks, we will measure the outcomes for wait list control group and for sustainability purposes in the original intervention group (Aim 1). During baseline visits and 12 weeks (T2) the sweat patches will be applied by a study team member with the participants. After at least 24 hours, the study team member will go back to participants' homes to obtain the sweat patches when they have worn them for the allotted time (Aim 2). Participants will be given directions regarding the sweat patches. The only restrictions related to the sweat patches are not to submerge in water (e.g., baths or swimming). After participants have the sweat patch removed, it will be placed into a biospecimen bag and stored in our lab for extraction and further downstream analysis. In our lab, the absorbing pads will be cut by sterile tweezers and cutting knives, rolled, and placed into filter tubes with 500 uL sweat washing buffer (1X PBS, 0.5% Tween 20, and 0.2% BSA). Next, the samples will be placed at 4˚C to incubate for 20 minutes and then will be centrifuged at 4,000 x g in a cold centrifuge for 20 minutes. The filtered sweat extractions will be aliquoted and stored in a -80˚C freezer.

During the data collection visits, information will be obtained on demographics, pain, depression, and disability. Goal attainment will be measured at 12- and 24-week data collection visits. The intervention group will start the study and will receive five nurse visits that will be focused on decreasing pain, depressive symptoms, and meeting participant selected goals set in these areas. The wait list control group will receive monthly calls by a study team member to ensure their contact information has not changed and continue a rapport with them. At 24 weeks, we will also conduct virtual semi-structured individual interviews with participants to determine feasibility and acceptability (Aim 3).

Recruitment: In the state of Maryland, over 22% of adults have a disability, African Americans make up 32% of Maryland, females make up 51%, and those 65 years of age and older make up 15.9%, which demonstrates we can access older Black women with disabilities and older women with disabilities of other races. We will recruit participants for the study through community partners, including churches, and senior day centers, and we will use Johns Hopkins MyChart. We will also recruit through word of mouth, and through established community partnerships with the Johns Hopkins School of Nursing RESILIENCE Center. We will also provide our study information to the Johns Hopkins School of Nursing Center for Equity in Aging to share on the website and social media accounts. We will also recruit through senior high rises throughout Maryland, health fairs, and through community organizations such as The National Disability Rights Network Inc., the Baltimore County Department of Aging, and our advisory group Older Women Embracing Life (OWEL), Inc. (See letters of support). We will also recruit from participants who had interest in our previous study but did not enroll and expressed interest in being contacted for future studies. Our previous study IRB number is IRB00226182 and Janiece Taylor is PI. The research study team will call these participants. Our study will also be referred to the CAPABLE Family study (IRB00243117 , PI Sarah Szanton) . Participants who do not qualify will be given a flyer for our study and can contact the study team. The study team will not contact these participants first.

Randomization: The participants will be randomized within variable-sized blocks from four to eight participants. The research coordinator will call the participants and notify them if they will receive the intervention immediately or in 3-4 months. The Research Coordinator will perform monthly calls with the wait list participants to check in and verify if contact information is still the same. These procedures will maintain allocation concealment throughout the trial, consistent with the CONSORT recommendations.[64] No research staff or investigator interacting with potential participants can anticipate treatment allocation of the next assignment because of separate non-study computer files and variable block sizes. Research staff performing outcome assessments will be masked to assignment. Prior to each assessment, staff will use standardized language to request participants not to discuss their treatment allocation with research staff.

5. Inclusion/Exclusion Criteria

Inclusion criteria: 1) Self-reported pain ≥4 out of a 0-10 scale that has lasted longer than 3 months and prohibits at least one valued or daily activity; 2) Physical disability based on the 2008 American Community Survey.[65] The survey includes three questions relevant to physical disability. Answering yes to any of the three questions will deem the participant eligible to participate in the study. Candidates who report yes to any of the three questions will considered for the study; 3) Non-institutionalized and living in Maryland; 4) Score a 5 or higher on the PHQ9 (depression measure) at least two times during a two-week period (screening call and then at first data collection visit via video); 5) 50 years of age and older; and 6) identify as a woman.

Exclusion Criteria: 1) Hospitalized > 3 times in the last year; 2) Participating in physical therapy; 3) Have a terminal diagnosis (<1 year expected survival); 4) ≥ Moderate intellectual impairment (5-7 errors) based on the Short Portable Mental Status Questionnaire (SPMSQ); and 5) unable to understand or speak English. We will exclude anyone with more than three hospitalizations and/or have a terminal diagnosis because of the acuity of their conditions which may limit the effectiveness of the intervention. Physical therapy may impact the outcomes of the intervention and having impaired cognition may make it difficult for participants to engage in the nurse visits, set goals and participate in the ACT sessions.

6. Drugs/ Substances/ Devices

a. Sweat patches will be used for the study. The rationale for using the sweat patches is because it is a sweat collection device is a non-invasive way to collect physiologic data. Recent pilot testing has indicated that the sweat patch can be used in older adults. This research will also add more data to the literature about the useful and effective use of sweat for physiologic data collection

7. Study Statistics

Measurements: We chose measures based on our experiences in community-based trials as well as those that met the following criteria: 1) possess known reliability and validity with older samples; 2) are sensitive to change from an intervention; 3) represent objective as well as subjective indicators of the domains we seek to impact. Finally, we sought to achieve a balance between psychometric quality and practical considerations such as respondent burden.

Demographics and Baseline Measures: We will measure demographics of all participants at the start of the study to obtain characteristics of the sample. We will identify disability status using the Craig Handicap Assessment and Reporting Technique (CHART)[66] and Katz's activities of daily living (ADL) and Lawton's instrumental activities of daily living (IADL).[67,68] The CHART measure is a reliable instrument in samples that included various racial/ethnic groups, including Blacks, and has a test-retest reliability of 0.93. The inter-rater reliability of Katz's ADL and IADL measures ranges from 0.81-0.93.[69,70]

Primary Outcomes: The primary outcomes for the proposed study are pain and depression. We will measure pain intensity using the Patient Reported Outcomes Measurement Information system (PROMIS) Pain Intensity.[71] The PROMIS Pain Intensity instrument asks about pain intensity in the last seven days and right now on a 0-10 scale. To confirm that the women have chronic pain, we will ask them if they have had pain for more than three months that interferes with at least one activity as inclusion criteria. The Patient Health Questionnaire (PHQ-9) is an instrument used to measure depression according to the DSM-IV/V criteria.[72]

Secondary Outcomes: We identified secondary outcomes that may improve post intervention. We hypothesize that perceived communication will be a secondary outcome due to the communication education/guidance that the nurses and clinical psychologist will do with the participants. We will use the Patients Reactions Assessment (PRA) to measure quality of relationships with health care providers and ability to initiate communication. The PRA measures communication and relationship through two domains including information, communication.[73] We hypothesize that the intervention will also reduce pain interference and pain behaviors that are a direct result of pain. Pain interference will be measured using the PROMIS Pain Interference scale, which consists of six items from the PROMIS short form on pain interference. The scores range from 6-30 with higher scores indicating more pain interference. The scores on PROMIS Pain Behaviors scale can range from 7-42 with higher scores indicating more pain behaviors.[74] To our knowledge there are no reports of reliability for these two PROMIS measures in diverse samples of older adults, however, there is evidence to support that both measures are responsive to interventions that target pain.[75] We also will measure psychological inflexibility using the 12-item Psychological Inflexibility in Pain Scale. We hypothesize that the ACT sessions and nurse visits can reduce psychological inflexibility. Quality of life is a secondary measure that may improve with this multicomponent intervention. We are measuring quality of life using the Short Form 36.[76,77]

Mediators: We hypothesize that the biomarkers serve as mediators between the intervention and the primary outcomes. The inflammatory markers may have an effect on the relationships between the intervention and the primary outcomes of pain and depression.

Covariates: We identify that comorbidities and stress may be related to the primary and secondary outcomes.

Table 3 shows the instruments that will be used to measure primary and secondary outcomes.

Table 3: Study Measures				
Construct	**Measured When**	**Instrument used**	**Measure Description**	**Documented Reliability (Cronbach's a)**
Demographics	Baseline, 12	Demographic	Age, race,	

	weeks	Questionnaire	socioeconomic status, marital status	
Baseline Vulnerability	Baseline, 12 weeks	Craig Handicap Assessment and Reporting[66] Activities of Daily Living (ADL) Instrumental Activities of Daily Living (IADL)[78] Short Portable Mini Mental Status Exam[79]	A measure of disability/social role performance ADL/IADL disability A measure of cognitive status	0.93[66] 0.81-0.93[69,70]
Acceptability of intervention	After completion of all data collection (24 weeks)	Individual Semi-Structured Qualitative Interviews	We will ask participants to describe their experiences participating in the study and give feedback on the study protocol etc.	
Primary Outcomes				
Pain Intensity	Baseline, 12 weeks, 24 weeks	PROMIS[80]	Quantitatively measures how much pain a person is experiencing	0.84-0.93
Depressive Symptoms	Baseline, 12 weeks, 24 weeks	Patient Health Questionnaire 9[72,81]	The PHQ9 includes 9 questions related to the Diagnostic and Statistical Measures of Mental Disorders (DSM) diagnostic criteria for major depression.	0.79-0.89 in various racial/ethnic groups[72]
Secondary Outcomes				
Communication with Providers	Baseline, 12 weeks, 24 weeks	Patient Communication Pattern Scale	A 14-item scale to measure perceived abilities to initiate communication with health care providers	Demonstrates strong reliability
Psychological Flexibility in Pain	Baseline, 12 weeks, 24 weeks	Psychological Flexibility in Pain Instrument[76]	The ability to act in alignment of goals, values and in acceptance while living with pain and distress	0.88[76]
Pain Interference	Baseline, 12 weeks, 24 weeks	PROMIS[74]	Six items on how much pain interferes with life and activities	

Pain Behavior	Baseline, 12 weeks, 24 weeks	PROMIS[82]	Self-reported external manifestations of pain	
Goal Attainment	At nurse visit 3 and nurse visit 5	Self-Report[39]	Measures if goals were not met, partially met, or fully met	
Quality of Life	Baseline, 12 weeks, 24 weeks	36-Short Form Survey[77]	Self-reported quality of life	
Mediators				
Biomarkers	Baseline,12 weeks and T3 follow up (for wait list control group)	Sweat Patches[39]	IL-6, IL-8, TNFa	
Covariates				
Stress	Baseline, 12 weeks, 24 weeks	Perceived Stress Scale[83]	Self-reported perceived stress	0.89[84]
Comorbidities	Baseline, 12 weeks, 24 weeks	Charlson Comorbidity Index[85]	Measures chronic conditions from 17 categories	0.74-0.95[85,86]

Sample size: We assume an attrition rate of 20% prior to the 12-week follow-up based on our Co-I's trials such as the CAPABLE trial (which had 13% drop out).[61] Based on these assumptions and experience, an initial sample size of 30 participants (15 in the intervention group and 15 in wait list control) would yield 24 participants (12 intervention, 12 wait list control) after attrition. It is unlikely we will detect a significant difference between the groups due to small sample size and limited follow-up, but this sample size will allow us to determine stable estimates of the degree of change in the outcomes.[87]

We will continue to collect data on participants who cannot continue the intervention. We will also request to do exit interviews with participants who drop out of the study if they agree and their time/situation is conducive.

Analytic Approach: Before any analyses are carried out, the data will be audited for quality and completeness, and evaluation of distributions with reference to planned analysis models. The evaluation of distributions will include the detection of outliers in quantitative data and checking distributions of variables to ensure that they meet the assumptions of planned analyses. Reliability will be estimated for key study measures (item analysis, Cronbach's a). T-tests and chi-square analysis will be used to evaluate group equivalence at baseline. Variables for which the two groups differ will be considered for inclusion as covariates in the analyses. All analyses will follow intent-to-treat principles.

Management of Missing Data. The pattern of missingness will be examined, and baseline responses will be compared between those with and without missing data. Variables related to missingness will be included in the analyses which should yield valid inferences.[88] Multiple imputation will be used to handle missing data in the main analyses. We will complete sensitivity analyses comparing parameter values from the analyses of completers only with parameter

values for analyses using multiple imputation to assess any bias introduced through the use of imputation.

Analyses

Analysis for Aim 1: To evaluate feasibility and acceptability of the tailored multi-component behavioral intervention. Acceptability of the intervention will be examined in multiple ways. We will examine the number of sessions attended, as well as participants' ratings of satisfaction with the intervention. We will examine the association between number of sessions attended and satisfaction with participant characteristics to explore if acceptability varies by participant demographics. We will conduct individual semi structured interviews with participants who have completed all data collection for the study. We anticipate doing approximately 10 interviews; however, we will continue to interview participants until we reach saturation.[89,90] For example, we will ask about appropriateness of the visits, if the participants found the intervention burdensome or helpful and if participants would recommend any changes to the intervention. We will also attempt to interview 2-4 individuals who do not complete the study and are willing to participate in a one-on-one individual interview. We will ask them to provide information on what would have made the intervention more acceptable and useful to them. Detailed, verbatim transcripts of the interviews will be prepared by a professional transcription service as is standard in qualitative research. Details such as long pauses during interview responses, dramatic inflection or change of tone when speaking (e.g., strong emphasis on particular words), emotional content (e.g., laughter, crying) will be noted. Completed transcripts will be checked against the audio recording to ensure accuracy. Qualitative content analysis will be used to code the data. The interviews will be coded line by line and data will be categorized based on differences and similarities, which will be separated into themes, analyzed, and coded.[1] Rigor will be promoted by having data coded by multiple members of the study team. We will complete member checking by calling participants after the interviews to clarify any information necessary. This method of analysis will be used for all qualitative interviews throughout the study. We will use the themes as the foundation for refining the intervention.

Analysis for Aim 2: To assess feasibility and acceptability of sweat patches to identify inflammatory cytokines (IL-6, IL-8, TNFα). We will identify if participants wore their sweat patches for the full 24 hours at each data point that they wear it. In addition, during the qualitative interviews, we will ask participants about their experiences with the sweat patch to identify any barriers to implementing the sweat patch. Data from the sweat patch analysis will be examined to determine if the analysis led to IL-6, IL-8, TNFα, values within expected ranges.
Protein Quantification: Coreplex cytokines panel of (IL-6, IL-8, TNFa), will be analyzed using SP-X Imaging and Analysis System (Quanterix, Lexington, MA). Because the array volumes are approximately 2 billion times smaller than a conventional ELISA, a rapid buildup of fluorescent product is generated if labeled protein is present, and it provides detection ability between 100-1,000 times that of ELISA methods. Samples will be distributed randomly across plates and all assays will be run in duplicate; intra-assay and inter-assay performance will be evaluated.

Analysis for Aim 3: Compare the change over time in pain and depression between the intervention and wait list control groups and estimate the associated effect sizes to inform the power analysis for future research. To examine the effect of the intervention on outcomes (depressive symptoms, pain), generalized estimating equations will be used (GEE) with time (baseline, 12-, 24-weeks), group and the time by group interaction. The time by group interaction

will test if the change over time in the intervention group differed from the wait list control group. We will not be sufficiently powered to detect a significant effect; interpretation of the results will be based on the Cohen's d' effect sizes associated with the time by group interaction for each outcome. One advantage of GEE is it allows all participants' data to be included in the analysis, even those who do not complete the study, providing an intention-to-treat analysis. We will also conduct sensitivity analyses with completers only and compare the effect size to the ITT analysis to estimate the effect size when all participants adhere to the intervention. Some experts discourage calculating an effect size from a pilot trial; however, combined with our preliminary work, we feel that we can utilize the proposed study to calculate an initial effect size for future research.

8. Risks

Medical risks, listing all procedures, their major and minor risks and expected frequency:
Minimal risks to study participants are expected. There is a chance participants may experience some discomfort, or inconvenience in completing sweat patch data collections. Participants may become fatigued or emotionally distressed while completing battery of questions. If strategies include any type of physical activity (e.g., tai chi exercises) participants may become short of breath, fatigued, or may experience pulled muscles or dizziness.

a. Steps taken to minimize the risks.

Participants can decline the sweat patch data collection or stop collecting the sweat patch at any time. Participants can also decline to answer any of the survey questions. Research staff has been trained to interact with participants in a positive, non-judgmental manner that encourages honest communication and a partnership approach to study participation. Participants may decline any exercise strategies suggested by the nurse. The nurses have the necessary training to recognize respiratory distress and how to reduce falls (e.g., removal of clutter, assessing for dizziness and balance) via Zoom. The principal investigator will be made aware of any adverse reactions or events. Participants will receive a follow-up telephone call to assure that the reaction/event has resolved. If the reaction/event persists, a referral will be made to the participant's primary care provider for further evaluation.

Procedures for protecting against and minimizing potential risks:

If any physical problems emerge during any of the home visits, immediate medical attention will be sought for the participant. The risk of invasion of privacy will be addressed with participants during the informed consent process. All personnel involved in the study will be fully trained and certified in the protection of human subjects and HIPAA regulations. We will use a virtual video call software called Zoom. Zoom is encrypted, collects no protected health information (PHI) and any data transmitted during the call is destroyed when the call ends. It is both HIPAA and HITECH compliant. This certification will be kept current throughout the study. As part of the informed consent process, participants will be notified of their rights pertaining to protected health information. Participants will be informed that they can stop the questionnaire and rest at any time. All study participants will be provided referral information to existing health services

as in typical or usual care. Thus, participants have the information to access any services that they may perceive as necessary independent of their study participation.

The risk of breaching study participant confidentiality will be minimized by identifying all participants by code numbers, securing all data collected in locked files in the PI's office, and screening information to locked file cabinets with limited staff access. Pre-coded data collection instruments are prepared for use with study participants at each testing occasion. Identification numbers to assure subject confidentiality will be used. Only one master log of subject names, addresses, telephone numbers, and study identification assignment will be maintained in a password protected computer program. Data collection will be on computer tablets that are password protected. Audio recordings of nurse visits will be routinely conducted for fidelity and quality control review. This recordings will be done on a digital recorder whether the visit is in person or via Zoom. These recordings will be identified by numbers only and stored in files on computers of the project coordinator and Dr. Taylor who will provide fidelity oversight of the interventionists. Access to these computer files will be password protected; recordings will not contain respondent name or other personal identifying information and will not be transcribed. Recordings will be used only for quality control and training purposes and then destroyed (deleted from computers) within one year of trial completion.

Plan for Data and Safety Monitoring: This study is funded TRIPLL by the Translational Research Institute on Pain in Later Life (TRIPLL) Center at Weill Cornell Medical College. The PI will have responsibility for monitoring and oversight of problems and events. The Cornell TRIpLl Center will review study progress and data safety issues at least twice a year and as needed.
e.2 Verification of eligibility criteria: The TRIPLL Center reviews all applications for TRIPLL support that are being considered for funding. The board will verify that the inclusion and exclusion criteria are acceptable, or they will recommend revisions.

e.3 Frequency of Data and Safety Monitoring: Reports are reviewed quarterly, in conjunction with review of TRIPLL supported investigator progress reports. Unscheduled reviews may be conducted if necessary, at the request of the TRIPLL Director, study PI, or NIA program official.

e.4 Content of Data and Safety Monitoring Reports: N/A

Adverse Event (AE) Reporting: The PI will notify IRB of any adverse events. We do not anticipate any adverse reactions to the intervention. Based on our previous work and studies in this area by others, there is only a small risk that participants will become increasingly anxious to the point that it becomes an adverse event (e.g., harmful to self or others) as a consequence of the intervention activity or having a member of the research team in their home. However, interviewers/interventionists are well trained to manage this reaction or make an effective referral if necessary.

Given that interviews for data collection and interventions via video, there is the potential for a member of our research team to encounter a potential emergency that is not related to study participation (e.g., dehydration, environmental risk, medical emergency). Following the emergence of the need to account for such events in behavioral interventions differently than in medical/clinical studies,[46] we refer to such events as "alerts" and have well-developed procedures for their management. However, the reporting of alerts to the IRB of JHU is not required (see Chart below of potential alert events and plan for their management and reporting).

Recruitment, AE, and Alert Reports: Reports presented to the the TRIPLL Center will include data on enrollment (study accrual by month; comparison of expected to actual enrollment; number of individuals screened, number eligible and number ineligible, number randomized by gender, AEs, and alerts). In addition, the TRIPLL Center will receive reports of the number of study participants who discontinue from the treatment group and/or the study and reasons for discontinuation. We propose that reports are provided to the TRIPLL Center twice yearly. In addition, the TRIPLL Center may request reports as needed as well as the unblinding of the data should they deem this necessary

Plan for reporting unanticipated problems or study deviations:

b.2. Protections Against Risk

The Principal Investigator will be notified of any adverse events. Participants will receive a follow-up telephone call to assure that the reaction has resolved. If the reaction persists, a referral will be made to the participant's primary care provider for further evaluation. In situations where there is initial severe distress or when the distress has not been resolved, if suicidal thoughts are present, we will immediately call 911 for further help and stay with the participant until help arrives. **If suicidal ideation or intent is identified, the study team member will follow the study's suicide protocol. The suicide protocol will utilize an adapted version of the Columbia Suicide Severity Rating Scale to assess mild, moderate or severe risk. If risk is mild, the study team member will notify PI, provide mental health resource guide, and advise them to speak to their health care provider. If the risk is moderate, procedures will be the same as mild with additional expression of high concern and strong recommendation to seek care. If the risk is severe, the study team member will call 911 or suicide crisis number or escort to emergency room and immediately notify the PI. We will consult with Dr. Regier on referrals and next steps for any all mild and moderate risk patients.** Furthermore, if any physical problems emerge during any of the visits, immediate medical attention will be sought for the participant.

If participants experience any physical problems during any portion of the study, immediate medical attention will be sought for the participant. See the table below regarding alert and actions to be taken.

Table 4	
Alert	**Action Taken**
Medical Emergency: • Chest pains • Excessive bleeding	If a member of the research team encounters any of these symptoms over the phone, the participant is put on hold and the PI will call 911 immediately. If the situation

• Fall and cannot get up • Difficulty breathing	occurs within the home or during focus groups, the PI and/or research personnel will call 911 immediately and stay with the participant until help arrives. If participants engage in physical activity virtually, the nurse will assess every five minutes for shortness of breath or any pain at all. If participants verbalize this or shortness of breath is observed the nurses will ask participants to stop any physical activity.
Evidence of abuse	Evidence of physical abuse is follows: • Participant states to the PI/research staff that abuse occurs. • The RN observes physical evidence (e.g., black eye, black and blue marks arms/legs. The investigators will contact participants and strongly encourage him/her to contact his/her primary care provider and/or Adult Protective Services (phone number will be provided). Based on the situation, the PI may notify Adult Protective Services. The PI will complete an alert form. Note- The possibility of informing an agency about an abusive situation will be stated in the informed consent.
Extreme Home Hazards • Exposed electrical • External door missing or cannot be locked • Ceiling, floors caved in • No temperature regulation (e.g., no air or heat- must be extreme) • Major infestation	The investigators will refer participants to Baltimore City 311, who can refer participants to possible resources for home repairs and/or infestations.

All personnel involved in the study have been fully trained and certified in the protection of human subjects. This certification will be kept current throughout the study. Education in protection of human research participants: The investigators have completed the Johns Hopkins University School of Medicine Research Compliance course. All research personnel on the proposed study will complete the Johns Hopkins University (JHU) School of Medicine Research Compliance Course. The JHU course consists of the University of Minnesota Web modules on Informed Consent, the Consent Process, After Informed Consent, JHU School of Medicine module on local IRB requirements, and achievement of a passing score on the JHU Knowledge Assessment module. According to the policies of the JHU, approval for this research will be obtained from the JHU IRB office for research using human subjects. Participants will be assigned a code number on initial entry and only the code number will identify all subsequent questionnaires. Information needed for follow-up contact (names and addresses) will be kept separately from all other data.

Legal Risks such as the risks that would be associated with a breach of confidentiality: The risk of breaching study participant confidentiality will be minimized by identifying all participants by code numbers and by securing all data collected in locked files in the PI's office and screening information at the senior center in areas with limited staff access. Pre-coded data collection instruments are prepared for use with study participants at each testing occasion. Identification numbers to assure subject confidentiality will be used. Only one master log of subject names, addresses, telephone number, and study identification assignment will be maintained on site in the locked PI's office. This log, in both hard copy and disk, will be stored in a locked filing cabinet separate from other identifying information. All completed data collection instruments are stored in locked filing cabinets.

Financial risks to the participants: There are no anticipated financial risks to the participants.

9. Benefits

Potential Benefits of the Proposed Research to Human Subjects and Others
Participants will receive study visits from a nurse and participate in ACT virtual group sessions lead by a clinical psychologist, learning strategies to address pain and depression as well as improve communication with health care providers. There are no known direct benefits to participants, but possible benefits may include that participants will learn strategies to help improve their symptoms related to pain and depressive symptoms. Participants will also be contributing to important research that may help improve understanding of physical disabilities, chronic pain, and depression, particularly among older women.

Importance of Knowledge to be gained
This study has the potential to add to the current body of literature on effective ways to address physical disabilities, chronic pain, and depression, particularly among community-dwelling older women.

10. Payment and Remuneration

All participants will receive a $25 gift card upon completion of the nurse visits, $25 gift card upon completion of ACT sessions and an additional $10 if they participate in a qualitative interview post intervention.

11. Costs

There are no costs to participants for participating in the study.

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