

Title: Pain Informed Movement for People With Knee Osteoarthritis

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1. Introduction

With an increasing global prevalence of knee OA (KOA) and no highly effective treatments for pain, there is an urgent need to improve conservative pain management strategies to avoid the associated negative outcomes such as limited mobility and multimorbidity [1]. Current clinical practice guidelines strongly recommend exercise and patient education as the core conservative management strategies [2,3]. Various types of exercises are recommended including neuromuscular exercises which are focused on improving knee functionality [4]. However, these treatments are only moderately effective for controlling pain [5], which therefore begs for a deeper understanding of the mechanisms of KOA pain and filling the corresponding gaps with mechanism-based treatment strategies.

Current recommended methods for conservative management are not predicated on pain mechanisms, while evidence for neural sensitization and dysregulation of intrinsic pain modulation is widely reported [6]. Mind-body approaches have the potential to fill these gaps in the management of KOA through a combination of physical postures, breathing techniques, meditation, mindfulness, and relaxation [7]. The effects are reported to be mechanistically related to the regulation of nociceptive signals [8]. For instance, breathing exercises can lead to the disruption of the association of pain and sympathetic nervous system activation [9], leading to modulation of autonomic functions [10]. Meditation and relaxation can create a state of calm and provide a sensation of being in a place of safety (a parasympathetic state) [11], which can lead to changes in one's pain experience [12]. Mindfulness and mindful movements can improve where and how to focus, develop skills to control the response to pain [13], and influence the pain experience through emotional regulation and interoception [8].

A management strategy that can be a valuable addition to exercise,

Pain Neuroscience Education (PNE) is a technique that shifts the focus from the diseased knee joint and the assumption that pain stems from degenerative structural changes [14]. Unlike standard OA education that has historically had a biomedical influence [14], PNE reconceptualizes pain as a danger signal and introduces intrinsic modulation of pain to influence the pain experience. Omitting biomedical language from KOA education can lead to significantly lower perceptions that physical activity is injurious to the knee joint, lower fear of movement, and improve participation in exercise [14]. Combined with active treatment strategies such as exercise, PNE results in positive changes in pain [15].

The need for high quality research that evaluates the effects of mind- body approaches in managing KOA pain and understanding how they may modify altered nervous system processing is needed. Our group has developed a program we call Pain Informed

Movement, which is a combination of neuromuscular exercise, mind-body techniques, and PNE with the aim of improving intrinsic pain modulation in people with KOA. Although each of these components as a standalone technique can improve pain in KOA, their cumulative effect may be more substantial and has the potential to lead to an enhancement of outcomes, as each component can lead to optimization of the other. Given that the feasibility and acceptability of the Pain Informed Movement program has been previously established [16], further evaluation of this program compared to standard care is warranted. This paper presents a detailed protocol for a pilot randomized controlled trial (RCT) to collect pilot data, as well as initial efficacy data on the comparison of Pain Informed Movement program with neuromuscular exercise and standard OA education in people with KOA. This study has been approved by the Hamilton Integrated Research Ethics Board and registered on clinicaltrials.gov (ID: NCT05730829).

1.1. Study objectives and hypothesis

The objectives of this study are 1) to pilot test the procedures of this RCT and investigate the feasibility with the primary outcome of rate of follow-up, 2) assess secondary aspects of feasibility such as acceptability of the programs, rates of recruitment, adherence, compliance, as well as burden and adverse events) and 3) explore effects of Pain Informed Movement program on subjective and objective measures of KOA pain when compared to a usual conservative management strategy for people with KOA. Given the additional and improved components of the Pain Informed Movement program and its feasibility established in the previous phase [16], we hypothesize that this pilot RCT will show feasibility of comparing the two treatment strategies, and the Pain Informed Movement program will show promising results.

2. Methods

2.1. Study design

This is a pilot study with a nested qualitative component designed as a parallel, randomized, single-centre, two-arm clinical trial with a 1:1 allocation ratio. Informed consent will be obtained from all participants prior to initiating the study. All participants will be invited to complete an exit survey and take part in focus group interviews at program completion. Fig. 1 depicts the trial design. The procedures will be followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Conceptual Framework for Defining Feasibility [17] and Pilot studies and the Standard Protocol Items: Recommendations for Intervention Trials will be used [18]. Following

program completion, the study results will be re-ported using the extended CONSORT guideline for pilot trials as well as the TiDIER guidelines [17,19]. The study protocol is registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05730829) #NCT05730829.

2.2. Study participants

Sample size is based on the primary outcome of complete follow-up using the confidence interval method for calculating sample size in pilot trials [20]. We will aim for 90% follow-up but will consider the trial successful if we achieve 81%. To achieve a margin of error of 9%, with 10% added for attrition, we will require 66 participants (n ¼ 33 per arm).

Participants will be recruited through the email lists of the McMaster University's community and research centers and their social media pages. Additionally, the study poster will be placed on other social media channels (e.g., Twitter, Facebook advertisements) and flyers will be placed in local Orthopaedic surgeon, Rheumatologist, and Physiatrists offices.

The inclusion and exclusion criteria are listed in Table 1.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
≥ 40 years of age with diagnosis of knee osteoarthritis (KOA by) a physician OR ≥ 45 years of age and having activity-related knee joint pain with or without morning stiffness lasting ≤ 30 min (NICE criteria) 2 Having an average pain intensity of at least 3/10 on a numeric pain scale on most days of the past month	1 Cannot communicate in English 3 Has inflammatory arthritis or other systemic conditions 4 Has had lower limb trauma or surgery within the past 6 months 5 Has participated in a KOA exercise program in the past 3 months 1 Has had any injection in the index knee within 3-months prior to baseline assessment 2 Does not have regular access to the internet 3 Inability to get up and down from the floor independently 4 Use of mobility aids 5 Currently participating in any other drug/device/exercise clinical trial related to OA 6 Planned absences (e.g., trips away) of >1 week 7 Currently receiving other forms of care for KOA pain (e.g., from a physiotherapist, chiropractor, athletic therapist, kinesiologist) 8 Does not meet screening for safe participation in exercise according to the Get Active questionnaire from the Canadian Society for Exercise Physiology [25]

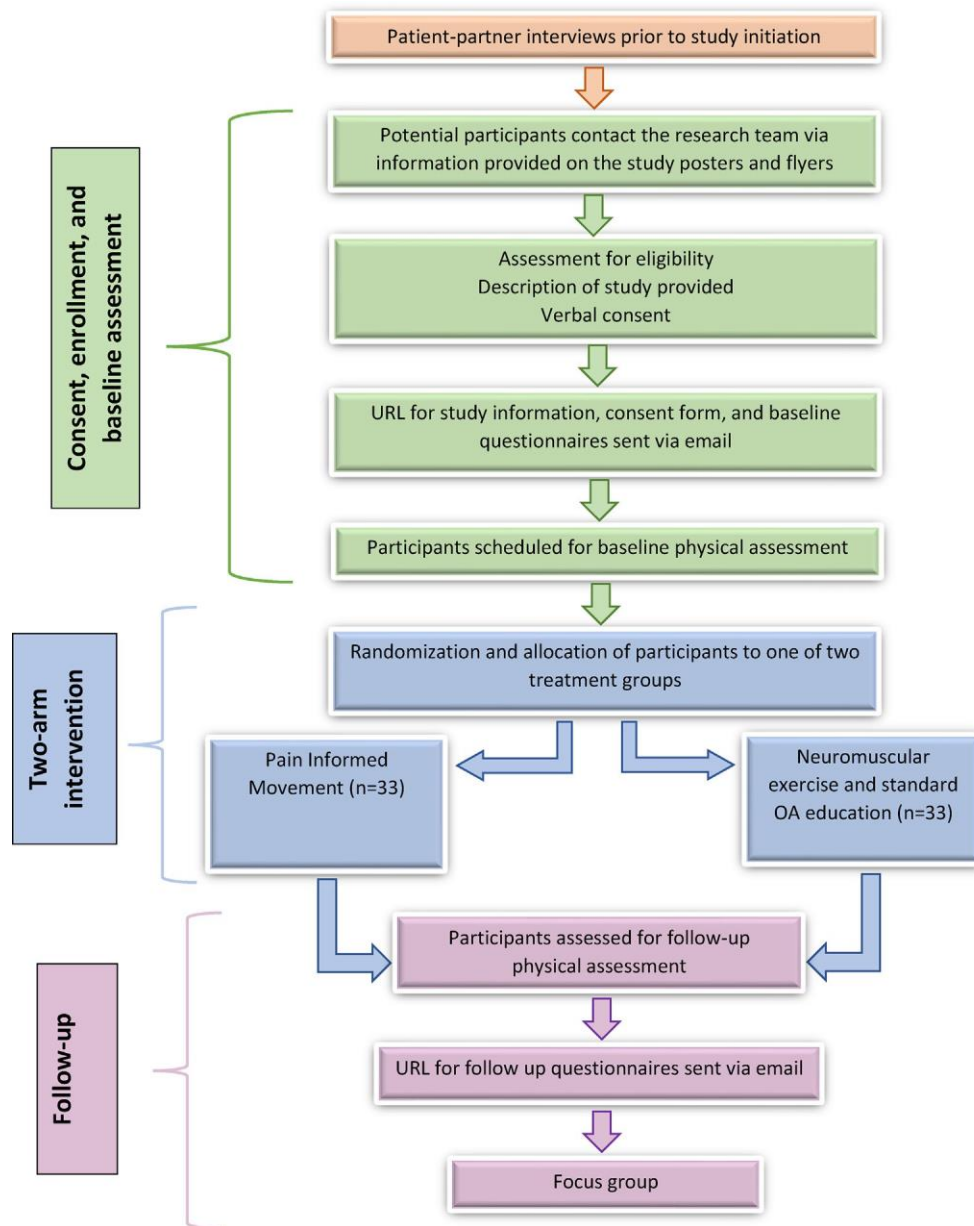
2.3. Screening and assessments

Potential participants will contact the research team through the contact information provided in the flyer and study poster. Screening will be conducted over the telephone and study information will be provided. Consenting and eligible participants will be sent an individualized link to the written consent form, written study information, and baseline

questionnaires. Those who pass the screening, including exercise safety, will be invited to an in-person physical assessment. Upon program completion, participants will be sent the questionnaires again (which also include the exit survey questions) and will attend a second in-person assessment of physical measures. Focus groups will be conducted to further assess the participants' perception of the study. If a participant has bilateral KOA, the most symptomatic knee will be studied. If both knees are equally affected, the dominant knee will be studied, which is the knee with which the individual steps first when initiating gait.

2.4. Randomization and blinding

Participants will be randomized with an allocation ratio of 1:1 into one of two treatment groups (Pain Informed Movement or neuromuscular exercise and standard OA education) using a REDCap randomization module. The process of randomization will be conducted by a member of the research team who is independent of the recruitment process. Additionally, the assessors responsible for conducting baseline and follow-up assessments will be blinded and not involved in recruitment. Blinding of exercise instructors is generally not possible in studies of physical interventions (e.g., exercise) [21]. Participants will be blinded to study hypotheses and the two treatment groups. As both arms of the study are providing exercise-based interventions and education, participants will be provided limited details of each intervention arm so as to blind them from knowing which is the intervention and which is the control. This will help minimize any bias that occurs by knowledge of group assignment and perception of treatment effects.



2.5. Interventions

The intervention will start within two days of the physical assessments with participants receiving educational videos approximately 10–14 days before the first exercise session.

2.5.1. Pain Informed Movement program

Participants in this group will receive an 8 week in-person group exercise program held twice weekly, in which they will receive exercise instructions and PNE. They will also be

asked to complete a third exercise session at home weekly. Participants will be provided with tracking sheets to note their compliance and progress.

The PNE component will consist of several short videos that are provided online for the first five weeks of the program (the videos are divided into short segments, each with a separate subject, totaling 20–30 min/week)). The videos will provide simple explanations of nociception processing by the nervous system, how it can be modulated through upregulation or downregulation of signals to increase or decrease pain and that pain does not accurately signify the extent of tissue damage, particularly when experiencing chronic pain. The videos will also offer techniques to reconceptualize pain and movement not as imminently dangerous. In addition, the videos will introduce and provide a demonstration of mind-body techniques that will be provided progressively each week. The mind-body techniques will include breath awareness and regulation, body awareness and muscle tension regulation, and awareness of pain related thoughts and emotions. The techniques will then be implemented in the in-person exercise sessions where participants are asked to incorporate them into their performance of the exercises. Instructions will be provided on how to ‘nudge the edge’ of pain which is conceptualized as a balance between challenging current physical abilities during the exercises and being successful at not leaving pain provoked and/or function limited after exercise. Participants will be instructed to use breath, body tension, thoughts, and emotions as guideposts to their pain in order to successfully nudge its edge. Participants will be given the opportunity to ask questions during the in-person sessions.

The exercise component (75 min) will consist of three parts (in sequence):

Part one: the first part is the warm-up which begins with a centering practice aimed at regulating physiology. Next, warming movements of the shoulders, legs, and spine will be instructed.

Part two: of the second part is the main exercises (based on the original NEMEX-training program [4] This part is divided into four sections: core stability, postural orientation, lower extremity muscle strength, and functional exercises with an emphasis on proper alignment of the knee over the foot. Within each section, there are two types of exercises and three levels for progression. Participants will be instructed to complete each exercise for two to three sets of eight to 15 repetitions. For the core stability section, one exercise is instructed based on breaths. When an exercise is performed with good quality of the performance, with minimal exertion, and with control of the movement, it can be progressed by increasing repetitions or the load (going through the levels). The exercises will be performed with both the affected and the unaffected leg.

Part three: the third and last part is cooldown which consists of the same warmup movements plus relaxation and guided self-reflection. Participants will be cued to use the PNE concepts and mind-body techniques during the exercise sessions.

Participants will also complete a third home session (weekly) which is facilitated by handout sheets. The exercise component will be delivered by an experienced yoga teacher with training in the integration of pain science and mindful movement.

2.5.2. Neuromuscular exercise and standard OA education

Participants in this group will receive an 8-week in-person group exercise program held twice weekly, in which they will receive exercise instructions and standard OA education. Participants will be provided with tracking sheets to note their compliance and progress.

The exercise component (60 min) of this group will be similar to that of the other group without the added mind-body techniques. Similarly, a third home session (weekly) will be facilitated by exercise handout sheets. The exercise instructions will be delivered by a physiotherapist. The standard OA education will consist of several short videos (20–30 min/week for the first two weeks provided through online videos) and will cover the following topics: pathophysiology of OA, common OA symptoms, risk factors, the effects of exercise, and self- management tips. Participants will be given the opportunity to ask questions during the in-person sessions.

2.6. Safety

Participants will be provided with a tracking sheet to note any adverse events (AEs) throughout the study. The instructors will also monitor for adverse events during the in-person sessions. If any AE happens, participants will be instructed to tell the instructor to modify the exercises or reduce the intensity if necessary. AEs will be defined as any problem that lasts for >2 days and/or causes the participant to seek other treatment.

2.7. Primary and feasibility outcomes

The primary outcome measure is the follow-up rate (i.e., number of participants that completed the program and attended follow-up). Other feasibility outcomes include: acceptability (content, format, frequency, and duration) of the Pain Informed Movement program compared to the control group, recruitment rate, burden of procedures, adherence rate (i.e., number of participants that attended all in-person sessions), compliance to the program (i.e., number of participants that reported completion of at least three exercise sessions per week), and AEs. A priori success criteria will be used to determine feasibility and acceptability of the programs (Table 2).

Table 2:

A priori feasibility criteria.

Outcome	A priori criteria		
	Proceed	Proceed with protocol amendments	Significant amendments required
Follow up	≥90% of participants followed up at 8 weeks	≥50% of participants followed up at 8 weeks	≤50% of participants followed up at 8 weeks
Recruitment	≥40 participants consent to participate/year	≥30 participants consent to participate/year	<30 participants consent to participate/year
Compliance to exercise program	≥80% of participants report exercise at least 3 times a week	≥50% of participants report exercise at least 3 times a week	<50% of participants report exercise at least 3 times a week
Program content acceptability – usefulness	≥50% found treatment useful (Likert ≥4/5)	≥25% found treatment useful (Likert ≥4/5)	<25% found treatment useful (Likert ≥4/5)
Program content acceptability – frequency	≥50% found frequency acceptable (Likert ≥4/5)	≥25% found frequency acceptable (Likert ≥4/5)	<25% found frequency acceptable (Likert ≥4/5)
Program content acceptability – duration	≥50% found duration acceptable (Likert ≥4/5)	≥25% found duration acceptable (Likert ≥4/5)	<25% found duration acceptable (Likert ≥4/5)
Format acceptability – delivery	≥50% found treatment delivery (in-person and home) acceptable (Likert ≥4/5)	≥25% found treatment delivery acceptable (Likert ≥4/5)	<25% found treatment delivery acceptable (Likert ≥4/5)
Adherence to in person treatment	≥75% of participants attended all in person treatment sessions	≥50% of participants attended all in person treatment sessions	≤25% of participants attended all in person treatment sessions
Burden (0 = no burden, 10 = most burden)	Burden of completing questionnaires and physical tests <3/10 for ≥75% of participants	Burden of completing questionnaires and physical tests <3/10 for ≥50% of participants	Burden of completing questionnaires and physical tests <3/10 for ≤25% of participants
Adverse events	No adverse events or only mild transient (e.g., pain increase) for ≥75% of participants	No adverse events or only mild transient (e.g., pain increase) for ≥50% of participants	No adverse events or only mild transient (e.g., pain increase) for ≤25% of participants

2.8. Secondary outcomes and descriptive data

Participant characteristics such as age, sex, gender, education, marital status, race, number of people in household, height, and weight will be collected. A list of secondary outcomes is provided in Table 3.

Table 3: Secondary outcomes.

Outcome	Tool	Description
Comorbidities	Modified Charlson Comorbidity Index (CCI)	Assessed the presence of 19 comorbidities in participants. The CCI has been used in many patient populations, including knee osteoarthritis (KOA). ³⁰
Central sensitization	Mechanical Temporal Summation (TS)	A 512mN weighted probe was applied at the volar wrist opposite to the index knee. Participants were asked to rate their pain between 0 and 100 ³¹ . Then, the same stimulus was applied 10 times at the rate of 1/second (guided by a metronome), and participants asked again to rate their pain. TS was defined as present when, compared with the initial trial, the participant reported increased pain following the second trial. ³¹ The validity of mechanical TS has been reported in people with KOA. ³¹
Endogenous pain modulation	Conditioned Pain Modulation (CPM)	CPM was assessed in the following steps ³² : 1) at the proximal anterior shin on the unaffected knee, an ascending measure of pressure pain threshold (PPT) was evaluated; 2) at the opposite volar forearm, a conditioning stimulus in the form of forearm ischemia was applied using a blood pressure cuff and squeezing a stress ball until a pain rating of 4/10 was reached;

		<p>3) PPT at the anterior shin was repeated with the cuff remaining inflated. ³²</p> <p>4) an index was created by calculating the percent efficiency of CPM (%CPM) as PPT2/PPT1, multiplied by 100; whereby %CPM \leq 100 indicated inefficient pain modulation ³³. CPM testing has demonstrated good intra-session reliability ³⁴.</p>
Pain intensity	Numeric Rating Scale	<p>Average pain intensity in the past 24 hours, past week, and worst pain in the past 24 hours was recorded. Questions were rated on an 11-point scale where participants selected a rating between 0-10, with zero representing 'no pain' and 10 representing the 'worst imaginable pain'. ³⁵. The Numeric Rating Scale is reported to have excellent inter-rater reliability and acceptable validity in people with KOA ³⁶.</p>
Pain catastrophizing	Pain Catastrophizing Scale (PCS)	<p>The PCS ³⁷ is a 13-item self-reporting instrument for catastrophizing in the context of actual or anticipated pain, with higher scores indicating higher pain catastrophizing. The validity of the PCS for measuring pain catastrophizing in people with KOA has been reported ³⁸.</p>
Chronic pain self-efficacy	Self-Efficacy for Managing Chronic Disease 6-item scale (SEMCD-6)	<p>Higher reported scores on the SEMCD-6 indicate higher self-efficacy ³⁹. The SEMCD-6 has high internal consistency with significant correlations with other health outcomes ⁴⁰.</p>
Anxiety and depressive symptoms	Hospital Anxiety and Depression Scale (HADS)	<p>Higher scores on the HADS ⁴¹ indicate increased severity of anxiety and depression symptoms. The HADS is a brief and reliable measure of emotional</p>

		<p>distress in general in chronic populations ⁴².</p> <p>Validity and reliability of the HADS have been previously established ⁴².</p>
Fear of movement	Brief Fear of Movement Scale for Osteoarthritis (BFMSO)	<p>The BFMSO has 6 items that are derived from the Tampa Scale for Kinesiophobia (TSK) and uses a 4-point Likert scale with higher values indicating higher levels of kinesiophobia ⁴³. The BFMSO has been reported to have adequate validity ⁴³.</p>
Knee injury and outcomes	Knee Injury and Osteoarthritis Outcome Score (KOOS)	<p>The KOOS pain and function in daily living and QoL subscales were used to assess self-reported opinions about patients' knee and associated problems. Scores ranged from 0-100 with zero representing extreme knee problems and 100 representing no knee problems ⁴⁴. KOOS has adequate internal consistency and validity in people with KOA ⁴⁵.</p>
Type of KOA pain	Intermittent and Constant Osteoarthritis Pain (ICOAP)	<p>The ICOAP knee version was used to assess the different types of knee pain experienced by participants ⁴⁶. The ICOAP knee version has two sections: 1) 'constant pain' has 5 items that asks about pain that is present all the time, and 2) the 'intermittent pain' has 6 items that asks about pain that comes and goes. The psychometric properties of the ICOAP such as reliability and validity have been previously established ⁴⁷.</p>
Other painful body parts	Body diagram	<p>Participants were asked to indicate any other areas where they experience pain (e.g., neck, shoulders, back) on a body diagram. Body</p>

		diagrams have shown to be a reliable method for indication of painful body parts ⁴⁸ .
Functional leg strength	30 second sit-to-stand test	The 30 Second Sit to Stand Test was used as a performance test ⁴⁹ . The maximum number of chair stand repetitions completed during a 30 second interval was noted. A standard chair height was used. The 30 Second Sit to Stand Test has been reported to be a reliable measure of functional leg strength and endurance ⁴⁹ .
Brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF)	Blood analysis (blood draws under fasting conditions)	Altered levels of BDNF are involved in the pathophysiology of chronic pain ⁵⁰ . NGF has been shown to be elevated in a wide variety of chronic pain conditions including KOA ⁵¹ . Five ml of blood was drawn for analysis of BDNF and NGF and samples were centrifuged at 4 degrees Celsius for 10 minutes at 1000g. Collected serum was stored at -80 °C. Serum levels of BDNF, diluted 1:100, were measured using Biosensis Human/Mouse/Rat BDNF ELISA kits read on a Spectramax i3 spectrophotometer. Serum levels of NGF were measured in duplicate, after diluting 2X in Reagent Diluent, with R&D Systems Human beta-NGF DuoSet ELISA kits read on a Multiskan Go spectrophotometer.
Medication use	Survey question	Participants were asked to indicate any medication that they take on a regular schedule including prescription medications, non-prescription, over the counter, vitamins, herbal, and alternative medicines.

Perspective on knee replacement surgery	Survey question	Three questions were asked: 1. Are your knee symptoms so severe that you wish to undergo knee replacement surgery? ⁵¹ 2. Do you think knee replacement surgery is eventually inevitable? ⁵² 3. In your opinion, what factor(s) can lead to better outcomes after knee replacement surgery?
Perspectives on effectiveness of components of intervention	Survey question	Participants were asked to rank the effectiveness of the intervention components for pain management that they received. i.e. mind-body techniques, pain neuroscience education and strengthening exercises vs OA education and strengthening exercises.

2.9. Exit survey and focus group

At follow-up, a satisfaction survey will be conducted. Participants who indicated upon initially consenting to the study that they would like to participate in a focus group will be contacted. Qualitative description will be used to explore participants' experience and perceptions of the feasibility and acceptability of the Pain Informed Movement program as well as the standard treatment as well as the procedure for the entire study. An interview guide developed by patients and practitioners will be used. The focus groups will be conducted virtually consisting of six to eight participants and will last about 60–90 min. The session will be recorded, and transcripts will be produced to ensure accuracy of the responses.

2.10. Data integrity

The health information collected in this study will be kept confidential on a secure REDCap platform maintained by McMaster University. To ensure confidentiality, each participant will be given a unique identification number. At the end of the study, the anonymized data will be kept and will comprise a resource database. The researchers and the ethics board may access the study records to monitor the research and verify the accuracy of study information. No records with identifying information will be allowed to leave the principle investigator's office. Study information will be kept for 10 years, then will be permanently destroyed.

2.11. Analysis

Descriptive statistics will be used to report feasibility outcomes. The quantitative analysis of secondary outcomes will be by intention-

to-treat principles. Repeated measures analysis of variance (ANOVA) will be used to assess the amount of change in outcome measures and compare them between the two groups using means and 95% CIs. Similarly, within group differences will be analyzed using the paired sample's t-test and will be reported using means and 95% CIs. Where possible we will also report minimally important difference.

The transcripts of the focus group interviews will be analyzed using thematic content analysis to identify suggestions for program modification [46]. Line-by-line reading of the transcripts will be performed and thematic patterns will be explored. Once themes and patterns are identified, each meaningful segment of text will be assigned a conceptual code.

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