RESEARCH PROTOCOL

The *"What is a Protocol?"* file on the HREB ethics website requested that applicants provide information about both the scientific and ethical aspects of their proposal. We will therefore divide this protocol description into those two sections.

1. Scientific Elements

(a) Background Research

In 2010 - 2011, more than 762,000 total knee arthroplasty (TKA) surgical procedures were performed across Canada (1). This number is expected to increase dramatically in the coming years with the growing older adult population and with the recently quantified TKA projections for younger patients (2). The growth of this procedure has resulted in increasing reports of dissatisfaction and poor outcomes such as increased pain, unmet expectations, reduced daily functioning (3), and compromised psychological health (4). Although suboptimal outcomes are not unusual in surgical procedures, there is a discrepancy in the proportion of poor outcomes associated with TKA compared to other arthroplasties. For example, 18-20% of patients following TKA report dissatisfaction (3, 5) compared to only 7% following a total hip arthroplasty (6). In response to these discrepant findings, there have been a significant number of studies that have identified psychological and psychosocial factors that are implicated in poor outcomes of TKA, even when controlling for medical factors such as surgical technique (7). This is not surprising given that more than 50% of adults undergoing TKA suffer from osteoarthritis, which has high comorbidity rates with mental disorders (8). Although psychological factors have been identified as contributing to poor outcomes, it is not clear whether an evidence-based psychological intervention can positively impact post-TKA sequelae. This study aims to pilot the effectiveness of an empirically supported intervention, mindfulness based stress reduction (MBSR), on post-TKA outcomes using a superiority randomized controlled trial (RCT) design.

TKA Outcomes. It is common for patients to have a successful TKA surgery but report dissatisfaction post-operatively (9), which has been largely attributed to post-operative pain (10) and restrictions in functioning and engaging in daily activities (3). Pain catastrophizing, defined as a tendency to magnify the threat of pain, is associated with the intensity of post-operative pain (11). Further, pre-surgical pain catastrophizing has also been linked to post-surgical pain and function (12). In some cases, the symptoms of pain following TKA surgery may become prolonged and debilitating, to the point where patients develop a chronic pain condition (13).

Predictors of Outcomes. It is essential to identify predictors of poor outcomes of TKA for targeted prevention initiatives. Female patients (14) and specifically those from low-income households (14) are at increased risk of reporting dissatisfaction following TKA. Dysfunctional coping style (15, 16) and lower internal locus of control (16) have been associated with poor TKA outcomes, and preoperative patient expectations are linked to dissatisfaction following TKA (5, 15). A growing body of research has demonstrated that psychological factors such as pain catastrophizing (17, 18), depression

(18), and anxiety (19) are significant predictors of persistent pain following TKA.

Interventions to Improve TKA Outcomes. Most of the targeted TKA pre-operative interventions to date have been education-focused (20, 21). A systematic review revealed that although pre-operative education can reduce anxiety, there is little evidence that it improves post-operative outcomes (26). Additional interventions, such as pre-operative exercises (22) or resistance training (23) exist, but the literature is mixed on whether they improve outcomes of TKA such as pain or physical functioning (24, 25). Although a large and growing number of studies have identified psychological and psychosocial factors as indicators of poor outcomes, research has not yet examined interventions targeting these risk factors directly.

Mindfulness Based Stress Reduction. In 2008, Drs. Ludwig and Kabat-Zinn published an editorial in JAMA describing the benefits of mindfulness (i.e., purposeful attention to the present with non-judgmental acceptance) in medicine and the growing body of evidence to support positive physical, mental, and psychosocial outcomes following mindfulness interventions. MBSR is the most widely used empirically-supported intervention that employs mindfulness techniques to address health holistically (27). A MBSR program typically consists of 8 weekly 2.5 hour sessions, home practice (typically 45 minutes per day, 6 days per week), and one day retreat. During the program, participants engage in a number of mindfulness practices (e.g., body scan, mindful movement, meditation) and discussions of their experiences, with the aim enhancing awareness to moment-to-moment experiences in a non-judging and accepting manner.

Health Outcomes. The growing body of literature is demonstrating the positive effects of MBSR on a variety of health outcomes (28). For example, a comprehensive systematic review that examined 115 randomized controlled trials found that, compared to wait list controls, MBSR significantly improved depression, anxiety, stress, quality of life, and physical functioning (28). With respect to pain-related outcomes, MBSR has been found to significantly reduce pain intensity and improve health-related quality of life among patients with chronic pain conditions, with the largest effect sizes demonstrated among those with arthritis (29), who comprise the largest proportion of TKA surgeries. Similar improvements in physical symptoms such as pain intensity, fatigue, and quality of life were demonstrated following MBSR among patients with chronic headaches (30). MBSR is also associated with reductions in pain catastrophizing, which is highly implicated in TKA, in chronic back pain patients compared to usual care or a cognitive-behavioural therapy group (31). Going beyond chronic pain conditions, MBSR has commonly been used as a weight-management strategy (32). According to a recent review, mindfulness interventions result in improvements in binge eating and dietary intake (34). This is of interest as obesity has been identified as a complicating factor in TKA influencing post-operative health outcomes (35), length of stay, and higher medical costs (36).

Preliminary Surgical-Related Outcomes. Despite this compelling evidence, there is little research examining MBSR in surgical contexts. One preliminary study investigating MBSR postoperatively following a spontaneous subarachnoid hemorrhage surgery found it resulted in significant decreases in ratings of depression and physical

stress, suggesting it was successful in both reducing psychological symptoms and improving homeostasis control mechanisms of the autonomic nervous system (37).

(b) General Overview of the Research Plan

The current research will consist of a pre-surgical MBSR course compared to a treatment-as-usual condition to evaluate post-surgical outcomes, including post-operative pain (severity and catastrophizing), improved physical functioning (interference and illness impact), post-surgery complications, and psychological factors including enhanced quality of life, reduced emotional distress (anxiety and depressive), enhanced cognitive skills, and improved sleep. The data will reveal if MSBR is feasible in a TKA population and determine if there are post-surgical benefits, as compared to the treatment as usual (TAU) group.

(c) Objectives, Research Design, and Hypotheses

Objective: The primary objectives are (a) to determine if an 8-week pre-operative MBSR program is feasible in a TKA population, and (b) to determine if this program results in reductions in post-operative pain (pain behavior, pain catastrophizing), improved physical functioning (pain interference, psychosocial illness impact), enhanced quality of life (global health), reduced emotional distress (anxiety and depression), enhanced cognitive skills (Cognitive Concerns), and improved sleep (fatigue, sleep disturbance) compared to TAU.

Research Design: Forty-five participants on the waitlist for a TKA will be recruited from Concordia Hospital Hip and Knee Institute – a facility that performs 800 TKA's per year. Participants will be divided into two groups: the MBSR group prior to surgery (30 participants, divided into two MBSR groups), and the TAU (15 participants; MBSR after surgery). The individuals in the MBSR group will receive a pre-operative 8-week community-based MBSR course, which includes group classes lasting 2.5 hours a week, 45-minutes of home practice 6 days per week, a 1-hour orientation session at the beginning, and a full-day silent retreat at the end. During the orientation, participants will complete the study measures for this study. Two weeks prior to the surgery at the pre-anesthesia clinic, patients will receive another short self-reported questionnaire between the MBSR intervention and TAU groups. Patients will subsequently receive post-operative questionnaires at the following regularly scheduled post-operative appointments: 6-8 weeks after surgery, and at 6 month and 1 year follow-ups. Clinic personnel, who are blinded to assignment, will administer these measures with all other regularly distributed clinical measures. Clinic personnel will also review the chart to inform researchers as to what physical condition contributed to the need for a TKA. The TAU group will have the opportunity to enroll in an MBSR course following the completion of the study (after approximately 1 year), at no cost.

Hypotheses: We predict that pre-operative MBSR will improve post-surgical outcomes including reductions in post-operative pain (pain behavior, pain catastrophizing),

improved physical functioning (pain interference, psychosocial illness impact), enhanced quality of life (global health), reduced emotional distress (anxiety and depression), enhanced cognitive skills (Cognitive Concerns), and improved sleep (fatigue, sleep disturbance) compared to TAU group.

MBSR is an empirically-supported intervention that has been used to examine various health outcomes and psychological factors in both health conditions (e.g., chronic pain; 29, anxiety and depression; 28, and binge and emotional eating; 32) and more recently, surgical populations (spontaneous subarachnoid hemorrhage surgery; 37). We are therefore confident that MBSR will improve the psychological factors and the physical health factors we described above.

(d) The Selection of Participants / Sample Size Calculations

TKA patients will be recruited from the TKA waitlist at Concordia Hospital Hip and Knee Institute– a facility that performs 800 TKA's per year. A Concordia Hospital Hip and Knee Institute staff member or a psychology graduate student on the project will contact all participants, ensuring the inclusion/exclusion criteria are met. Participants will be ensured that their participation is completely voluntary, and will be reminded that assignment to treatment conditions is completely random; therefore, participants will not feel obligated to participate, but will know receiving MBSR before their surgery is not guaranteed.

The sample size was estimated based on G*Power statistical software using a 2:1 approach with a large effect size (Cohen's $d = 0.8$). We will recruit 30 patients for the intervention where they will be divided in 2 groups that will consecutively run. The third TAU group will include 15 patients. This will yield 45 total participants. A 2:1 approach is used to assess within person change pre- and post-surgically given the pilot nature of the study and to protect against up to 20% attrition in the intervention group.

(e) Behavioural and Diagnostic Data

A variety of data will be collected during the initial telephone screening to ensure that participants meet our inclusion criteria. A phone screen template will be used to standardize the recruitment process. Because phone screening is conversational, the study description on the phone screen form has phrases that are italicized, and these are the key points that the phone screen interviewer will convey. We will be collecting information about age, sex, and language that they can read and understand. We will ask whether they are currently on the waitlist for a TKA, and whether they surgery they are waiting for is their first surgery (i.e., not a revision surgery). We will also be asking whether participants have ever been enrolled in an MBSR program or any other mindfulness course before, and if so, when it took place. All of these questions are very important in deciding whether participants are eligible for participating in this study.

After participants are screened for eligibility and provide verbal consent, they will be mailed out packages explaining MBSR in more detail, include two copies of consent forms, and a return envelope. After randomization, those in the MBSR group will complete study measures prior to their pre-operative MBSR course (at an orientation

session). These measures include: Patient- Reported Outcomes Measurements Information System (PROMIS) scales (Cognitive function, Fatigue, Pain Interference, Pain Behavior, Sleep Disturbance, Psychosocial Illness Impact, Global Health, Anxiety, and Depression scales (see: www.healthmeasures.net for information pertaining to NIH PROMIS initiative), a demographics form, the 13- item Pain Catastrophizing Scale (38), and the Five Facet Mindfulness Questionnaire (41). Two weeks prior to the surgery at the pre-anesthesia clinic, patients will receive another short self-reported questionnaire, as well as a questionnaire asking about participation in any other prehabilitation courses offered through the Hip and Knee Institute or any other centre. In PAC, clinic personnel will review the chart to inform researchers as to what physical condition contributed to the need for a TKA. Patients will subsequently receive post-operative questionnaires at the following regularly scheduled post-operative appointments: week 6-8, 6 month, and 1 year. Clinic personnel, who are blinded to assignment, will administer these measures with all other regularly distributed clinical measures, and they can complete while waiting for their appointment.

(f) Data Analysis

We will be looking at changes in outcomes from before to after the MBSR intervention in (a) the MBSR compared to TAU participants, and (b) within the MBSR participants. We will focus on within-persons mean differences using paired samples t-tests within the intervention group. To determine the impact of MBSR on the postoperative TKA outcomes, we will conduct multivariate analyses of variance of conceptually linked dependent variables (i.e. pain variables, mental health variables) with significant results followed up by Tukey post-hoc tests.

(g) Timeline

We hope to begin recruitment after we have obtained ethics approval from both the University of Manitoba and Concordia Hospital Hip and Knee Institute in August 2017. We hope to run the MBSR courses in Fall 2017, run by a teacher (Bernice Parent) with extensive MBSR and yoga training. We anticipate the total duration of this study will August 2017 to August 2019. We will renew our ethics protocol annually, as per HREB requirements.

(h) Definition of Adverse Events

The adverse events should be limited to a reaction to the MBSR course. Participants will be fully informed about MBSR, and what participation in the course will include. In the unlikely event that a participant feels extreme discomfort in a meditation position (e.g., their knee hurts too much), the MBSR instructor has been trained to manage these situations. If additional support is warranted, appropriate resources will be implemented as described in the ethics form.

(i) Budget

Professional Assistance:

MBSR instruction:
$18,500 in fee payment to qualified MBSR instructor.
[(45 participants x $400/participant) +$500 orientation fee = $18,500]
A certified, trained MBSR instructor is required to deliver the MBSR course. The course will be offered to the TKA patients at no cost to themselves, so as to maximize enrollment. No honorariums will be provided to the participants, as the waiver of the MBSR fee is already significant. The MBSR instructor's time, her securing of accommodations in which to hold the sessions, and providing all necessary resources (i.e., workbooks) are included in the fee of $400/participant. The instructor's time for conducting the 1 hour orientation meetings for all 3 groups is $500.
See letter from MBSR instructor for quote (appended to this application).

TKA clinic assistance:
[($60/hr x 143 hrs) + $150) = $8,730]

$8,730 is required for the assistance of the TKA clinic staff. As TKA patients will be recruited from the clinic, access to standard clinic measures will be required, and administration of the additional study-specific measures will be performed by clinic staff at the patient's scheduled appointments, compensation to clinic staff is required. Clinic staff have identified the following time commitments:
1. Pulling waitlist patient info (contact #'s & expected date of sx): 4 hrs
2. Query to pull pre-op Oxford (and other) data for 30 pts: 4 hrs
3. Administer, fill & send post-op questionnaire packages at 6 wks, 6 mo, 12 mo: ½ hr per visit = 45 hrs
4. Query to pull all post-op Oxford, Satisfaction data for 30 pts: 30 hrs
5. Calling and recruiting of patients (mail-out consent & pre-op packages) ½ hr per patient (say 25% rate of enrollment) + mailing costs (~$5 per, incl. return shipping) = 60 hrs + $150 mailing
The typical research staff rate is $60/hr, covering wages and a portion of overhead, for a total of $8,580, plus $150 for mailing.

All materials and supplies are currently available and do not require additional budgeting.

Anesthesia residents and graduate student involvement are covered by respective departmental obligations and do not require additional budgeting.

NOTE: This budget exceeds the limit of $25,000 available from the UCRP; however, Drs. El-Gabalawy and Kornelsen will cover the $2,230 of above-budget costs from their start-up funding.

2. Ethical Elements

(a) Potential Benefits to Participants and Others

Ours will be the first study to test pre-surgical MBSR on post-surgical TKA outcomes. TKA patients are a group of patients growing exponentially and are known to have poor health outcomes. MBSR is a relatively risk-free, empirically supported intervention that has potential to alleviate or lessen these outcomes. Therefore, it should be of interest to TKA patients, especially considering the benefits can be applied to all aspects of their lives, not just in regard to their upcoming surgery. This study may also provide insight on the feasibility of such an intervention to this surgical population. It may allow further research into an adapted version of the MBSR, which could enhance accessibility and service delivery. It may also have broader health and economic implications.

(b) Potential Harms to Participants and Others

There is a possibility that some participants might find a particular meditation posture (e.g., sitting) uncomfortable; however, appropriate modifications will be suggested by the MBSR instructor. Patients may experience temporary discomfort from answering questions related to emotional health; however, resources will be provided if warranted. In exceptional circumstances staff Psychologist, Dr. Renée El-Gabalawy (co-PI), will be contacted by research personnel.

(c) Alternative Treatments or Procedures

The participants randomly assigned to the MBSR group will receive MBSR prior to surgery and the participants who are assigned to treatment as usual will receive MBSR 1 year after surgery.

(d) Minimization of Potential Harms

Concerns regarding MBSR will be minimized through the prescreening and through the forms that thoroughly explain MBSR. All participants who consent will receive these documents and be reminded that if they have any concerns about participation, to not hesitate to ask.

Privacy/confidentiality concerns will be minimized by assigning all participants an alpha-numeric code that will be linked to their data. A file linking the participant's name to his or her code will be kept on a password-protected computer in a secure, locked laboratory room.

(e) The Process for Seeking Consent

All participants will first provide verbal consent during the prescreening period and completed written consent prior to participating in this study; the consent forms were included in this ethics application and will be mailed out to participants along with a return envelope.

References

1. Canadian Institute for Health Information (CIHI). Hip and knee replacements in Canada: Canadian Joint Replacement Registry 2013 Annual Report. URL: www.cihi.ca/cjrr.)
2. Kurtz SM, et al.: Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. Clinical Orthopadeics and Related Research 2009; 497:2606-2612
3. Bourne RB, et al.: Patient satisfaction after Total Knee Arthroplasty: Who is satisfied and who is not? Clinical Orthopaedics and Related Research 2010; 468:57-63
4. Blackburn J, Qureshi A, Amirfeyz R, Bannister G: Does preoperative anxiety and depression predict satisfaction after total knee replacement? Knee 2012; 19:522-524
5. Scott CE, Howie CR, MacDonald D, Biant LC: Predicting dissatisfaction following total knee replacement: A prospective study of 1217 patients. The Journal of Bone and Joint Surgery 2010; 92:1253-1258
6. Anakwe RE, Jenkins PJ, Moran M: Predicting dissatisfaction after total hip arthroplasty: A study of 850 patients. J Arthroplasty 2011; 26:209-213
7. Fisher DA, Dierchman B, Watts MR, Kenneth D: Looks good but feels bad: Factors that contribute to poor results after total knee arthroplasty. The Journal of Arthroplasty 2007; 22:39-42
8. Axford J, et al.: Prevalence of anxiety and depression in osteoarthritis: Use of the Hospital Anxiety and Depression Scale as a screening tool. Clinical Rheumatology 2010; 29:1277-1283
9. Ali A, et al.: Dissatisfied patients after total knee arthroplasty. Acta Orthopaedica 014; 85:229-233
10. Baker PN, can der Meulen JH, Lewsey J, Gregg PJ: The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. J Bone Joint Surgery 2007; 89:893-900
11. Vissers MM, et al.: Psychological factors affecting the outcome of total hip and knee arthroplasty: A systematic review. Semin Arthritis Rheum 2012; 41:576-578
12. Sullivan M, et al.: Psychological determinants of problematic outcomes following Total Knee Arthroplasty. Pain 2009; 143:123-129
13. Harden RN, et al.: Prospective examination of pain-related and psychological predictors of CRP Slike phenomena following total knee arthroplasty: A preliminary study. Pain 2003; 106:393-400
14. Nam D, Nunley RM, Barrack RL: Patient dissatisfaction following total knee replacement: A growing concern? Bone Joint J 2014; 96:96-100
15. Wylde V, Dieppe P, Hewlett S, Learmonth ID: Total knee replacement: Is it really an effective procedure for all? The Knee 2007; 14:417-423
16. Lopez-Olivo MA, et al.: Psychosocial determinants of outcomes in knee replacement. Annals of the Rheumatic Diseases 2011; 70:1775-1781
17. Roth ML, et al.: Demographic and psychosocial predictors of acute perioperative pain for total knee arthroplasty. Pain Research and Management 2007; 12:185-194
18. Lewis GN, Rice DA, McNair PJ, Kluger M: Predictors of persistent pain after total knee arthroplasty: A systematic review and meta-analysis. British Journal of Anaesthesia 2015; 114:551-561

19. Studner O, et al. Demographics and perioperative outcome in patients with depression and anxiety undergoing total joint arthroplasty: A population-based study. Psychosomatics 2013; 54:149-157
20. Riddle DL, et al. Pain coping skills training for patients with elevated pain catastrophizing who are scheduled for knee arthroplasty: A quasi-experimental study. Archives of Physical Medicine and Rehabilitation 2011; 92:858-865
21. Daltroy LH, et al. Preoperative education for total hip and knee replacement patients. Arthritis Care and Research 1998; 11:469-478
22. Wallis JA, Taylor NF: Pre-operative interventions (non-surgical and non-pharmacological) for patients with hip or knee osteoarthritis awaiting joint replacement surgery – a systematic review and meta-analysis Osteoarthritis and Cartilage 2011; 19:1381-1395
23. Calatayud J, et al. High-intensity preoperative training improves physical and functional recovery in the early post-operative periods after total knee arthroplasty: a randomized controlled trail. Knee Surgery, Sports Traumatology Arthroscopy Epub ahead of print
24. Beaupre LA, Lier D, Davies DM, Johnston DB: The effect of a preoperative exercise and education program on functional recovery, health related quality of life, and health service utilization following primary total knee arthroplasty. The Journal of Rheumatology 2004; 31:1166-1173.
25. Ackerman IN, Bennell KL: Does pre-operative physiotherapy improve outcomes from lower limb joint replacement surgery? A systematic review. The Australian Journal of Physiotherapy 2004; 50:25- 30.
26. McDonald S, Hetrick S, Green S: Pre-operative education for hip or knee replacement. Cochrane Database of Systematic Reviews 2004;1
27. Kabat-Zinn J: Full catastrophe living. Using the wisdom of your body and mind to face stress, pain, and illness. 1990; Bantam, New York
28. Gotnik RA, et al. Standardised mindfulness-based interventions in healthcare: An overview of systematic reviews and meta-analyses of RCTs. PLOS One 2015; 10: 1-17
29. Rosenzweig G, et al. Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice. J Psychosom Res 2010; 68:29-36
30. Bakhshani NM, Amirani A, Amirifard H, Shahrakipoor M: The effectiveness of mindfulness-based stress reduction on perceived intensity and quality of life in patients with chronic headache. Glob J Health Sci 2015; 8:142-151
31. Turner JA, et al. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. Pain 2016; Epub ahead of print
32. Katterman SN, et al. Mindfulness meditation as an intervention for binge eating, emotional eating, and weight loss: a systematic review. Eat Behav 2014; 15:197-204
33. Smith BW, Shelley BM, Leahigh L, Vanleit, BV: A preliminary study of the effects of a modified mindfulness intervention on binge eating. J of Evidence-Based Complementary and Alternative Medicine 2006; 11:133-143
34. O'Reilly GA, Cook L, Spruijt-Metz D, Black DS: Mindfulness-based interventions for obesity related eating behaviours: a literature review. Obes Rev 2014; 15:453-461

35. Rodriguez-Merchan EC: The influence of obesity on the outcome of TKR: Can the impact of obesity be justified from the viewpoint of the overall health care system? HSS Journal 2014; 10:167-170
36. Kremers HM, et al. The effect of obesity on direct medical costs in total knee arthroplasty. J Bone Joint Surg America 2014; 96:718-724
37. Myung Joo H, Lee SJ, Chung YG, Shin IY: Effects of mindfulness based stress reduction program on depression, anxiety and stress in patients with aneurysmal subarachnoid hemorrhage. J Korean Neurosurg Soc 2010; 47:345-351
38. Sullivan MJ, Bishop SR, Pivik J: The Pain Catastrophizing Scale: Development and Validation. Psychological Assessment 1995; 524-532
39. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in diseases. Pain 1983; 197-210
40. Mackenzie, C. S., Poulin, P. A., & Seidman-Carlson, R. (2006). A brief mindfulness-based stress reduction intervention for nurses and nurse aides. Applied Nursing Research, 19, 105-109. DOI:10.1016/j.apnr.2005.08.002
41. Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self- report assessment methods to explore facets of mindfulness. *Assessment, 13*, 27- 45.