ABSTRACT OF RESEARCH PLAN

PROJECT TITLE:

Cognitive Behavioural Therapy to Prevent Persistent Post-Surgical Pain following Surgical Repair of Extremity Fractures: A Feasibility Study

Abstract of research plan:

Each year, over 12 million individuals in the United States sustain a fracture of the extremity and many of these fractures are managed operatively. Outcomes are, however, variable and many patients continue to experience persistent pain and disability at one year after surgery. For example, 37% of patients with surgically managed tibial fractures remain off work, 37% report moderate to very severe pain, and 35% report moderate to extreme pain interference at one year. Among patients with open upper or lower extremity fractures, 65% report moderate to very severe pain and 35% report moderate to extreme pain interference at one year. There is a substantial and growing body of orthopedic literature documenting the importance of psychological factors in predicting recovery from surgery; however, to date, there are no evidence-based approaches that have been shown effective for improving recovery among high-risk patients.

We propose a multi-centre, pilot randomized controlled trial (RCT) to evaluate the feasibility of a definitive trial to explore the effect of cognitive behavioural therapy (CBT) in patients with operatively managed extremity fractures who are at high risk of poor outcome due to unhelpful illness beliefs.

The primary objective of this pilot RCT is to determine: 1) our ability to set up the CBT intervention at each participating site; 2) our ability to recruit patients across clinical sites; 3) site investigators' adherence to the study protocol; and 4) our ability to follow patients to one year.

SECTION 3

FACILITIES – Laboratory Space and Major Equipment

This trial represents a joint collaboration between investigators at the Michael G. DeGroote Institute for Pain Research & Care and the Centre for Evidence-Based Orthopaedics at McMaster University. The Principal Investigator (Dr. Busse) and the Co-Principal Investigator (Dr. Bhandari) have developed a close collaborative relationship through their mutual participation in a number of previous research initiatives.

McMaster University was established in 1887 as a school for arts and theology. Since that time, McMaster University has expanded to include science, engineering, and health sciences programs. The Michael G. DeGroote School of Medicine was founded in 1966 and the Faculty of Health Sciences was established in 1974. In 1967, Dr. David Sackett founded Canada's first Department of Clinical Epidemiology and Biostatistics at McMaster University. Dr. Gordon Guyatt, a Distinguished Professor at McMaster University, made history when he coined the term "evidence-based medicine" in 1991. Since then, McMaster University has been a leader in cutting-edge medical research and, in particular, evidence-based medicine. McMaster University is home to multiple research centers focusing on clinical research that continue to attract leading researchers and students in their fields.

The Michael G. DeGroote Institute for Pain Research & Care at McMaster University was established to explore the causes of pain, new strategies for its prevention, and develop innovative care for patients. Researchers affiliated with the Institute and involved with the current grant proposal are Jason Busse, Mohit Bhandari, PJ Devereaux, Eleni Hapidou, and Randi McCabe. Other members of the Institute include methodologists, clinician-scientists with expertise in pain management, research coordinators, a medical librarian, graduate and post-graduate students, and administrative support. The Institute is currently leading the implementation of a $25M SPOR grant awarded by CIHR to develop a National network to advance evidence-based management of chronic pain.

The Centre for Evidence-Based Orthopaedics (CEO) is affiliated with the Department of Surgery, Division of Orthopaedic Surgery at McMaster University and provides expertise, infrastructure, and support in all aspects of clinical research management. This includes project development, project management, data management, biostatistics, report preparation and writing, and support for grant applications. Under direction of the Founding Director (Dr. Bhandari) and the Research Methodologist (Dr. Sprague), the CEO has gained recognition as a leading research center for rigorous, large-scale surgical clinical trials, many of which have received funding from the National Institutes of Health, the US Department of Defense, and the Canadian Institutes of Health Research. At this time, there are no centers with equivalent expertise in orthopaedic surgical trials.

The CEO contains modern research infrastructure and experienced research personnel, including research methodologists, surgeon-scientists, project managers, research coordinators, post-graduate students, data managers, statisticians, and data analysts. Research personnel are available 7 days a week to cover all ongoing research projects. The CEO has strong collaborative relationships with other McMaster University researchers including the Clinical Advances Through Research and Information Translation (CLARITY) Research Group; Health Information Research Unit; Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Research Group; Programs for Assessment of Technology in Health (PATH) Research Institute; Population Health Research Institute (PHRI); Surgical Outcomes Research Center (SOURCE); Perioperative Surgical Research Group; and the School of Rehabilitation Science. In addition, the CEO has a global network of over 300 clinical sites who have enrolled patients into the clinical studies led by investigators within the CEO.

The CEO has office space and the required equipment for the research personnel assigned to the proposed study. All personnel will have access to desks, computers, printers, fax machines, telephones and

teleconferencing capabilities, secure storage areas, office supplies, and courier supplies. They will further have access to specialized software for the Electronic Data Capture system (iDataFax, RedCap), statistical analysis (SPSS, SAS), and up to date operating systems, as well as a secure file server. The CEO has standard operating procedures in place that guide the conduct of our high-quality orthopaedic research studies.

All of the institutions who will be participating as clinical sites (R Adams Cowley Shock Trauma Center, London Health Sciences Centre, Royal Columbian Hospital, and Hamilton Health Sciences – General Site) have the required infrastructure to successfully complete the proposed study. All are major trauma centers that have a sufficient volume of orthopaedic trauma patients to enable them to achieve their enrollment targets for this study. Furthermore, each site employs a team of dedicated orthopaedic research personnel who have the experience required for the day-to-day administration of the study. These research personnel have office space that is equipped with the required computer and telecommunications infrastructure, and have ample locked storage space to house confidential study materials. All of the selected clinical sites have successfully collaborated with the CEO on numerous multi-center orthopaedic studies.

SECTION 4

RESEARCH PLAN

A. SCIENTIFIC AIMS

Each year, over 12 million individuals in the United States sustain a fracture of the extremity and many of these fractures are managed operatively. Outcomes are, however, variable and many patients continue to experience persistent pain and disability at one year after surgery. Among patients with open upper or lower extremity fractures, 65% report moderate to very severe pain and 35% report moderate to extreme pain interference at one year.[1] There is a substantial and growing body of orthopedic literature documenting the importance of psychological factors in predicting recovery from surgery; however, to date, there are no evidence-based approaches that have been shown effective for improving recovery among high-risk patients.

We propose a multi-centre randomized controlled trial (RCT) to evaluate the effect of cognitive behavioural therapy (CBT) in patients with operatively managed extremity fractures who are at high risk of poor outcomes due to unhelpful illness beliefs.

The primary objective of this RCT is to determine the effect of CBT versus standard of care on persistent post-surgical pain (PPSP) in patients with operatively managed extremity fractures who are at high risk of a poor outcome due to unhelpful illness beliefs.

The secondary objectives are to assess the impact of CBT versus standard of care on health related quality of life (HRQL) and return to function in patients with operatively managed extremity fractures who are at high risk of a poor outcome due to unhelpful illness beliefs.

Our null hypothesis is that there will be no difference between patients who receive CBT versus standard of care (control) on PPSP (primary outcome), HRQL or functional outcomes (secondary outcomes).

In order to demonstrate feasibility to larger funding agencies (e.g. NIH, CIHR) for a definitive trial, we are requesting funding from the OTA for a 40 patient pilot study. Measures of feasibility will include the: 1) ability to set up the CBT intervention at each participating site; 2) ability to recruit patients across clinical sites; 3) adherence to the study protocol; and 4) ability to follow patients to one year. If our pilot results indicate that no substantial changes are needed to the study design, we will include the pilot data in the primary and secondary outcome analyses for the full trial to optimize trial efficiency.

B. BACKGROUND & SIGNIFICANCE

In North America, chronic non-cancer pain affects approximately 30% of the population, with similar rates in Europe and Australia.[2-6] Surgery and trauma are frequently cited as triggering events responsible for the development of chronic pain. A survey of 5,130 patients attending 10 outpatient clinics located throughout North Britain found that 41% attributed their chronic pain to a traumatic event or surgery.[7]

Surgical repair of long bone fractures constitute the majority of emergent surgical procedures at trauma centres. A systematic review of 20 observational studies of traumatic tibial fracture repairs found the mean incidence of PPSP was 47.4% (range: 10% to 86%) at an average of 23.9 months after surgery.[8] Although several risk factors for PPSP have been identified many, such as younger age and female gender, are non-modifiable and thus not amendable to intervention.[9-11] However, there are emerging data that suggest patients' beliefs and expectations may be associated with clinical outcomes, including self-reported pain.[12,13]

The relationship between psychological factors, behaviors, and cognitive processes with the sensation of pain is well documented. Stress, distress, anxiety, depression, catastrophizing, fear-avoidance behaviors, and poor coping strategies appear to have a significant positive relationship with both acute and chronic pain.[14] Evidence

suggests that these psychological factors can cause alterations along the spinal and supraspinal pain pathways which influence the perception and experience pain.[15]

The effect of patients' beliefs and expectations on chronic pain is an under-investigated area. A recent systematic review on measures of patient expectations on recovery found only four studies in the perioperative setting, none of which examined the relationship with PPSP.[13] We previously developed the Somatic Pre-Occupation and Coping (SPOC) questionnaire, which identifies unhelpful illness beliefs among approximately a third of surgically managed patients with traumatic, extremity fractures.[16] We have also shown that high somatic pre-occupation and poor coping (as measured by the SPOC questionnaire) are strongly associated with PPSP, functional limitations, unemployment, and reduced quality of life 1-year after a traumatic fracture repair.[16-18] This suggests the possibility that trauma patients with unhelpful illness beliefs could be identified early in the treatment process and targeted for concurrent therapy designed to modify such cognitions to improve their prognosis. With approximately 12 million fractures annually in North America alone, even a small relative reduction in PPSP and disability following traumatic fracture repair would yield substantial socioeconomic savings.

C. PREVIOUS WORK DONE ON THE PROJECT

We enrolled 1319 patients with open and closed tibial shaft fractures amenable to operative fixation in a multi-centre, randomized controlled trial (SPRINT - Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures).[19] Of this population, 359 patients were asked to complete a novel 60-item questionnaire at their 6-week post-operative follow-up which was designed to capture recovery expectations and illness perceptions on fracture healing; 316 provided complete data. We removed redundant items and questions that showed no variability in responses, and conducted factor analysis, which resulted in 27-items that mapped onto four domains: somatic complaints, energy, coping, and optimism. We therefore named our instrument the Somatic Pre-Occupation and Coping (SPOC) questionnaire.

We subsequently administered the SPOC questionnaire to a sample of lower limb trauma patients, and demonstrated strong psychometric properties including test-retest reliability (intraclass correlation coefficients for the total SPOC and all subscales ranged from 0.72 to 0.91) internal consistency (Cronbach's Alpha= 0.94), and construct validity.[17]

Most recently, we enrolled 2,428 patients with an open extremity fracture in a multi-centre, randomized controlled trial (FLOW -Fluid Lavage of Open Wounds).[1] Of this population, 1,360 patients agreed to complete the SPOC questionnaire at their 6-week post-operative follow-up. At 1-year post-surgical fixation, 725 of 1,111 (65%) patients reported moderate or extreme pain associated with their fracture. Addition of SPOC scores to an adjusted regression model to predict persistent pain improved the c-statistic from 0.66 to 0.73 ($p<0.001$ for the difference) and found the greatest risk was associated with high (≥78) SPOC scores (OR 5.29, 95% CI 3.75 to 7.46). Thirty-six percent (406 of 1125) reported pain interference at 1-year. Addition of SPOC scores to an adjusted regression model to predict pain interference improved the c-statistic from 0.66 to 0.74 ($p<0.001$ for the difference) and found the greatest risk was associated with high SPOC scores (OR 5.83, 95% CI 4.12 to 8.26). In our adjusted multivariable regression models, SPOC scores at 6-weeks post-surgery accounted for 11% of the variation in SF-12 physical component summary scores and 13% of SF-12 mental component summary scores at 1-year.[18]

These findings highlight the importance of patient beliefs in recovery from orthopaedic trauma. Targeting and modifying unhelpful beliefs may provide an effective strategy to improve outcomes among high-risk trauma patients. We have received a seed grant funding from the Michael G. DeGroote Institute for Pain and Research Care to facilitate development of the protocol for the proposed study.

D. METHOD

Study Design

We propose a pilot randomized controlled trial of 40 patients at 4 clinical sites (10 patients per site) with operatively managed extremity fractures who screen positive for unhelpful illness beliefs (SPOC scores ≥78). This pilot trial will evaluate the feasibility of a larger definitive trial comparing the effect of CBT versus standard of care on PPSP, HRQL, and function.

Eligibility Criteria

Wide eligibility criteria will be used to increase the generalizability of the trial. The inclusion criteria are: (1) adult men or women aged 18 years and older, (2) screen positive for unhelpful illness beliefs (SPOC scores ≥78), (3) extremity fracture requiring surgery, (4) cognitive ability and language skills to participate in the CBT intervention, and (5) provision of informed consent. The exclusion criteria are: (1) anticipated problems with the patient complying with the study protocol or maintaining follow-up.

Participating Sites

Four clinical sites in the United States and Canada will participate in the pilot study: R Cowley Adams Shock Trauma Center, Maryland; University Hospital, London; Royal Columbian Hospital, New Westminster; Hamilton Health Sciences – General Site, Hamilton.

Screening, Enrollment, and Randomization

All patients between the ages of 18 or older with an extremity fracture requiring surgery will be screened for eligibility. Reasons for ineligibility will be documented in the study electronic data capture (EDC) system. Potentially eligible patients will be approached to participate in the trial. Once patients have provided written informed consent, they will be assigned a unique study identification number. The Research Coordinator (RC) at each participating site will retain a list with patient identifiers and study identification numbers in a secure location. To ensure concealed allocation, eligible patients who provide informed consent will be randomized using an online randomization service (www.randomize.net/). Due to the nature of the intervention, it will not be feasible to blind participants or CBT therapists to treatment allocation.

Interventions

Consenting participants will receive either 6 individualized sessions of CBT or standard of care (control). The CBT intervention will consist of 6 weekly one hour sessions that will focus on addressing maladaptive beliefs related to pain and recovery as well as teaching skills to enhance coping and management of pain symptoms. The specific focus of CBT sessions will be informed by each individual patient's responses on the SPOC questionnaire.

The intervention will follow a session-by-session protocol that will include the following components: emotional processing of the experience of pain and introduction to the cognitive-behavioural model, introduction to the biopsychosocial model of pain, cognitive strategies, behavioural strategies, mindfulness and acceptance, optimizing functioning and preparing and managing for the future. Between-session exercises focused on practicing and applying the skills learned during sessions are a key component of CBT and patients will be encouraged to apply these skills in their everyday lives. Each session will include a review of material from the previous session, review of between-session practice, introduction of new skills/material, and establishment of new of between-session homework. CBT will be provided by experienced therapists and guided by a CBT manual that we have developed for this study. The control group will receive usual care, as per local clinical practices at each site.

Follow-up and Data Collection

A study RC will follow participants in person at 6-weeks, and 6, 9 and 12-months surgery at outpatient clinic visits (Table 1). Participants will complete follow-up forms in person or by telephone if they are unable to return to clinic. Participants may elect to withdraw from this trial at any time. If a participant withdraws prior to

completing the trial, the site RA will attempt to collect final data and the reason for withdrawal.

Outcomes

The primary outcome of the pilot study will be a composite measure of feasibility, including: (1) initiation of the CBT intervention; (2) rate of recruitment (number of participants recruited over a 6-month period), (3) protocol adherence (errors in treatment adherence); and (4) follow-up (proportion of participants followed at one year).

The primary clinical outcome is PPSP at one year after surgery measured using the Brief Pain Inventory scale. Secondary outcomes include SF-12 physical component summary (PCS) scores, the EuroQuol-5D (EQ-5D), and functional outcomes (defined by participants' return to work, household activities, leisure activities, and when they achieve 80% of their pre-injury level of function). Outcomes will be assessed at 6, 9, and 12 months' post-surgery.

Sample Size

Our sample size is based on the confidence interval around the proportion of complete follow-up. We will consider the pilot successful if we achieve at least 90% follow-up at one year for our primary definitive trial outcome (PPSP). If at least 32 out of 40 patients complete 1-year follow-up, we will consider the trial feasible. If fewer than 32 of 40 participants complete 1-year follow-up, the upper boundary of the confidence interval will be below 90% and we will consider the trial unfeasible.

Feasibility Analysis*:*

We will present point estimates of recruitment and feasibility events, including adherence to protocol and follow-up rate at one year, as proportions with 95% confidence intervals. The success of the pilot study will be based upon the following *a priori* thresholds: 1) successful administration of CBT at each site, 2) 40 patients recruited within 6 months, 3) treatment compliance in a minimum 36 of 40 participants (90%), and 4) 32 of 40 participants (80%) achieving follow-up at one year. The pilot study results will be evaluated to identify recruitment issues, data management issues, and inform anticipated follow-up rates. We will also calculate the absolute difference in rates of PPSP at 12 months between treatment groups to inform our sample size estimation for the definite study.

Efficacy Analysis for Definitive Study

We will use descriptive statistics to analyze the baseline characteristics reported by treatment groups as count (percent) for categorical variables and mean (and standard deviation) or median (and interquartile range) for continuous variables, as appropriate.

Generalized linear models will be constructed to compare EQ-5D and SF-12 PCS scores over time considering factors of time, treatment and the interaction between time and treatment. We will evaluate time to return to functional status and return to normal activities as compared between treatment groups using Kaplan-Meier survival analysis (Cox proportional hazards model), as well as the comparison of two independent proportions. Specifically, the proportion of patients reporting development of PSPP, return to functional status, and work in the CBT group will be compared to the proportion of patients reporting development of PPSP, return to normal activities, and work in the control group at 6 months, 9 months and 1 year follow up. All patients enrolled into the trial will be included in the analysis, regardless of attendance for CBT, or any other deviation from protocol. The level of significance will be set at alpha = 0.05. All analyses will be performed with the SAS, version 9.4. A statistician who is unaware of treatment group allocation status will perform all statistical analyses.

Timelines

This project will be conducted over a 2 year timeline. We have allocated 6 months to start-up activities at the four clinical sites, 2 months to complete patient recruitment, 12 months to complete patient follow-up, and 3 months to complete data analysis, and site close-out activities. Our team, with its well-established research infrastructure, is committed to maintaining this timeline.

E. REFERENCES **(not to exceed 2 pages)**

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F. FIGURES/TABLES

Table 1: Recruitment and Follow-up Schedule

Schedule of Events	Baseline	Randomization & Intervention	6 Month Follow-up	9-Month Follow-up	12-Month Follow-up
Assess eligibility	X				
Informed Consent	X				
SPOC	X				
Demographic and baseline data	X				
Randomization		X			
Intervention		X			
Brief Pain Inventory	X		X	X	X
SF-12	X		X	X	X
EQ-5D	X		X	X	X
Functional Outcomes	X		X	X	X

BUDGET

SALARIES AND WAGES (List all personnel for whom money is requested)	% effort on project	Requested from OTA (round to $)
Research Assistant ($19.00/h+13% fringe benefits) $21.47/h for 1.2 days (9h)/wk	25 %	$ $ 20,096
Statistician ($60.00/h + 35% fringe benefits) $81.00/h for 15h (Yr1) and 30h (Yr2)	5 %	$ 3,645
	%	
	%	
Fringe Benefits _____% of Salaries and Wages Salaries and Wages plus Fringe Benefits	TOTAL	$ 23,741

PERMANENT EQUIPMENT (append justification)	
Subtotal	$ 0

CONSUMABLE SUPPLIES (exclude animals and animal care)	
Printing and Other Supplies ($625.00/year for the duration of the 2-year study)	$ 1,250
Subtotal	$ 1,250

ANIMALS AND ANIMAL CARE	
Subtotal	$ 0

ALL OTHER EXPENSES	
Clinical Site Payments ($1,000.00/patient to cover RC costs to recruit and follow 40 total participants	$ 40,000
CBT Sessions ($100.00 per session for 6 sessions each for 20 total participants)	$ 12,000
Participant Parking ($25.00 for parking for 20 participants to attend each of 6 CBT sessions as part of the intervention)	$ 3,000
Subtotal	$ 55,000

TOTAL DIRECT COSTS $ 79,991