Official Title	PC-PEP: Randomized Clinical Trial of an Early vs Late Patient Empowerment Program for Men undergoing Curative Treatment for Prostate Cancer
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PC–PEP CLINICAL TRIAL PROTOCOL

PC-PEP: Randomized Clinical Trial of an Early vs Late Patient Empowerment Program for Men undergoing Curative Treatment for Prostate Cancer

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This study is being conducted in compliance with the Tri-Council Policy Statement, and applicable regulatory guidelines.

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PROTOCOL SYNOPSIS

Title	PC-PEP: Randomized Clinical Trial of an Early vs Late Patient Empowerment Program for Men undergoing Curative Treatment for Prostate Cancer
Funder	Dalhousie Medical Research Foundation, Soillse Research Fund and Research Nova Scotia (#2215)
Primary Objective	To determine if a six-month comprehensive empowerment program (physical exercises, meditation, and social support) with use of information technology improves the mental health in men scheduled for curative prostate cancer treatment.
Secondary Objectives	1. To compare urinary function, sexual function, quality of life related to hormonal treatment, relationship satisfaction, functional, emotional, and social well-being, general physical and mental/cognitive quality of life and psychological needs, and health care utilization – between the early intervention group and the late (wait-list control) group at the six month point.

2. To compare assessments of fitness and cardiovascular risks measured by the six-minute walk test and sit to stand assessment, BMI, strength, flexibility and balance, diastolic and systolic blood pressure – between the early intervention group and the late (wait-list control) group at the six-month point.
3. To compare assessments of stress levels measured by EEG and heart rate variability – between the early intervention group and the late (wait-list control) group at the six-month point.
4. To evaluate patient and program contextual factors and mechanisms that account for differences in outcomes among participants in the program.

Number patients	140
Enrollment Criteria	-Patients must be scheduled for potentially curative prostate cancer treatment including radical prostatectomy or radical radiotherapy (external beam radiation and/or brachytherapy) or both. Hormone therapy is permitted if given along with surgery or radiotherapy. (Exclusion - Men on active surveillance, hormone therapy only, or those with metastatic disease) -Age >18 -Deemed safe to participate in a low to moderate exercise program -Able to read English and access daily emails for six months -Willing to travel to Halifax at baseline, six and 12 months - Have access to a computer/phone/iPad/tablet with internet access for training and program communication
Efficacy Assessments	Mental health will be ascertained via a self-administered online questionnaire (K10 - Kessler Psychological Distress Scale).
Primary Endpoint	Mental distress (K10 score > 20) at six months from randomization (at the end of intervention for the early group and before the late group starts the program).
Other Evaluations	Evaluation of all men in the early and late intervention groups occur at baseline, six months and one year. a. Comprehensive set of validated questionnaires including International Prostate Symptom Scale (IPSS), Expanded Prostate Cancer Index Composite, EPIC-26, Dyadic Assessment Scale (DAS), Screening for Distress Questionnaire (SDQ), Quality of life (SF-12 and FACT-P), self-reported health care utilization b. Standardized six-minute walk test, sit to stand assessment, BMI, strength, flexibility, balance, diastolic and systolic

	blood pressure,standardized six-minute walk test, sit to stand assessment, strength, flexibility, balance, diastolic and systolic blood pressure. c. EEG (alpha, beta, delta, gamma, and theta activity measured every 30 seconds for 10 minutes pre-and post-intervention), heart rate variability using HeartMath monitors.
Rationale for number of patients	This is a 1:1 randomized wait-list controlled trial of men scheduled for curative treatment for prostate cancer. Eligible and consented participants will be randomized with equal probability to either immediate (early) six-month comprehensive patient empowerment program or to the wait-list control (late) arm starting at six months. Men will be stratified by treatment type (surgery vs radiotherapy vs both), whether they are or will be on hormone treatment, and mental distress at baseline. Assuming 30% of all participants will score positive on the K10 (screen positive for mental distress) at baseline (rationale described in Sample Size Calculation heading under the Statistical Considerations section), and assuming the wait list control (late) group will continue to have the same rate of mental distress (30% screen positive) at six months, and assuming the intervention (early) group will drop their distress rate to 10% screening positive at six months, the sample size required is 124 to detect these difference with a power of 0.8 and an alpha of 0.05. With a 5% drop out rate (an additional 6 patients) and some missed assessments due to COVID-19 (additional 10 patients) the total number of participants needed for this trial is 140.
Statistical Analysis Plan for Primary Endpoint	An intent-to-treat approach will be used to analyze the percentage of men screening positive for mental distress (K10>20) at the six-month point. Conditional Logistic Regression Statistical analyses.
Duration of Patient Participation and Duration of Trial	All study participants must commit to three in-person visits in Halifax for assessment over one year, and multiple online survey assessments. Particpants will also be invited to attend a focus group or one-on-one exit interview at the end of the ntervention, which will occur via videoconference. The trial will extend over an estimated 2-3 years to complete accrual and follow up.

LIST OF ABBREVIATIONS

AE – Adverse Event

BMI – Body Mass Index

CEP – Certified Exercise Physiologist

COVID-19 – An acronym that stands for **co**rona**vi**rus **d**isease of 20**19**.

EEG – Electro-encephalogram

HRV – Heart Rate Variability

HT – Hormone Therapy

K10 - Kessler Psychological Distress Scale

PC – Prostate Cancer

PEP – Patient Empowerment Program

PC–PEP – Prostate Cancer Patient Empowerment Program

QOL – Quality of Life

RC – Research Coordinator

RCT – Randomized Control Trial

RP – Radical Prostatectomy

RT - Radiotherapy

SP – Study Physician

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1 BACKGROUND

1.1 RATIONALE

Each year over 20,000 men are diagnosed with prostate cancer (PC) in Canada with the majority undergoing radical surgery and/or radiotherapy (1). One in seven men will be diagnosed with PC in their lifetime (1). Survival rates for newly diagnosed cases of prostate cancer are very high, with an expected 5 survival rate of 95% (1). However, of those treated with curative intent, 90% will suffer significant treatment-related side effects with respect to their psychological well-being, urinary and erectile dysfunction (2,3). Nova Scotia has the third highest new cancer rate, with PC representing the highest incidences of cancer for males (95 per 100,000) but it has the highest relative survival rate for PC in the country (1,4,5). Based on a survey which assessed 100 PC survivors from Nova Scotia who completed a comprehensive on-line quality of life survey (between May 2017 to March 2018), we identified that a high percentage of survivors reported urinary symptoms, intimacy concerns, isolation, insomnia and many other health problems (6). Overall 17% of these survivors screened positive for mental health issues, yet very few were on medication to address these mental health issues. Fewer than 20% have ever attended a prostate cancer support group (6). Since then, almost 400 men have taken the survey, but this estimate has not changed. The high incidence and long survival rates of PC along with treatment related side effects has resulted in a silent epidemic among thousands of Nova Scotian men needlessly suffering alone. Low attendance to support groups among PC survivors throughout Canada (including PC survivors from NS), problems with intimacy/sexuality, fatigue and depression have also been noted elsewhere (7).

Our program of research aims to address the most critical needs for PC patients and survivors: the development and evaluation of interventions to address the quality of life impact of PC. Based on our survey of 400 PC patients and survivors, a review of scientific evidence, and extensive consultation with patients and their families, and health care providers, our team has developed and pilot tested a unique, comprehensive Patient Empowerment Program for patients with PC (PC-PEP) aimed at educating and teaching the men life skills/habits in order to improve their mental health issues, fitness levels and overall quality of life, and to decrease treatment related side effects. The program includes aerobic, strength and pelvic floor exercise, meditation, relationship teaching, and peer support - based on the best of health promotion science. Building on a feasibility trial which we recently completed, this trial will aim to rigorously evaluate the effectiveness of the program to improve mental health issues and physical outcomes. As well, we aim to conduct a rigorous evaluation process, using realist methods, that will guide program refinement to better accommodate the diverse needs of PC patients and survivors in the future, and facilitate its uptake and spread to other settings.

1.2 SCIENTIFIC BASIS FOR A PATIENT EMPOWERMENT PROGRAM

1.2.1 Development of the PC-PEP Feasibility Program

The PC-PEP program was developed based on our patient surveys, extensive input from patients and health care providers, and scientific evidence. In April 2018 our team convened a Maritime-wide prostate cancer integrative care conference in Halifax, attended by 60 people (mostly from NS), including 28 patients, 10 patients' partners, 6 Urologists, 8 Radiation Oncologists, and a range of other health care professionals including nurses, administrators (e.g., Cancer Care Nova Scotia), residents, and MSc. students. At this Conference we shared the results of our patient survey (6) and asked conference attendees to contribute ideas towards improving these quality of life outcomes, especially mental health issues. The group strongly endorsed the idea of a comprehensive patient empowerment program to be offered to all newly diagnosed prostate cancer patients, to educate and teach the men and their partners life skills/habits which are aimed to improve their mental health, fitness levels and overall quality of life, and to decrease treatment related side effects. PC-PEP was designed by drawing on ideas presented from the April 2018 conference, more than 25 years of experience leading support groups for cancer patients by members of our team, and a review of the scientific evidence in support of potential program components.

1.2.2 Building on Pre-habilitation Prior to Radical Prostatectomy (RP)

Participating in preoperative exercise programs, and/or having a higher level of health and fitness immediately prior to surgery, appears to facilitate a quicker recovery and fewer complications in patients undergoing many operations including radical prostatectomy (RP) (8-12). Men undergoing RP who participated in moderate exercise for 60 minutes, 3-4 times a week, for 4-8 weeks preoperatively reported better quality of life outcomes including less anxiety before and six months after surgery, and superior six-minute walk test scores 4 weeks post operation, compared to the more sedentary control group (8). In an Australian feasibility study (n=10) that provided 6 weeks of an aerobic exercise program prior to surgery to recently diagnosed men, the results were similar, and no adverse effects were reported (12).

1.2.3 Benefits of Pelvic Floor Muscle Exercise

In a recent systematic review looking at pre- and post-operative pelvic floor muscle exercise (PFME) it was shown that preoperative PFME improved early (3 months but not six month) postoperative urinary incontinence post RP. Overall pelvic floor programs have been shown to improve sexual function and urinary continence post-prostate surgery compared to 'usual care' void of this training (13).

1.2.4 Stress Reduction thorough Meditation and Relaxation Exercises (and biofeedback)

Anxiety tends to be the most often experienced mental health issue for men with prostate cancer (14). Men may also report irritability or depression (15-16).
Participating in a meditation or mindfulness program has been consistently reported to reduce stress symptoms (16-21), mood disturbance (16-17, 22) anger (20), and fatigue (19) as well as improve quality of sleep (21), facilitate post-traumatic growth (19), promote spirituality (19,23) and enhance quality of life (22) in survivors of various types of cancer. Men with PC who are under medical surveillance reported significantly greater resilience and less anxiety after receiving an intervention of mindfulness meditation (22). Another study showed combining mindfulness therapy with Kegel exercises resulted in significantly improved continence for men after RP (95.6% achieved continence), compared to men who only did Kegel exercises without mindfulness therapy (71.6% achieved continence) (23).

The implementation of meditation biofeedback training using heart rate variability (HRV) has been shown to improve the quality of life in study participants experiencing many conditions such as diabetes (24), hypertension (25), asthma (26-27), PTSD (28), and chronic pain (29). HRV biofeedback training appears to decrease emotional and physiological stress levels (30), symptoms of burnout, anxiety and depression (30-32) and to increase working and episodic memory (33) and emotional well-being (28,34-35).

1.3 PC-PEP FEASIBILITY TRIAL DESCRIPTION AND RESULTS

1.3.1 Addressing Feasibility Concerns

After ethics approval, Privacy Council clearance from NSHA, and registration in clinicaltrials.org, on January 4, 2019 we began a pilot Patient Empowerment Program of 30 PC survivors to assess the following concerns:

1. Recruitment – would patients be interested and participate in this type of programming?
2. Participant adherence and dropout rates with an intense program (70 minutes of programmed activity daily over 28 days)
3. Would participants complete a 28 days program of this type? Would there be any attrition and if so, how big of a drop out will a program of this type incur?
4. Feasibility of intensive pre- and post- intervention testing.
5. Will there be any safety issues arising from teaching strength training in a group format and prescribing home-based strength and aerobic exercise training?
6. How will patients judge the helpfulness of such a program and each of its individual components?
7. Will patients recommend such program to other patients undergoing active or non-active forms of treatment at the end of the program?

8. Will the research team be competent and be deemed competent by the participants in delivering such a program?
9. Will the technology developed (an app to alert participants to do their daily exercises) be suitable and effective for this program?

1.3.2 PC-PEP Timeline

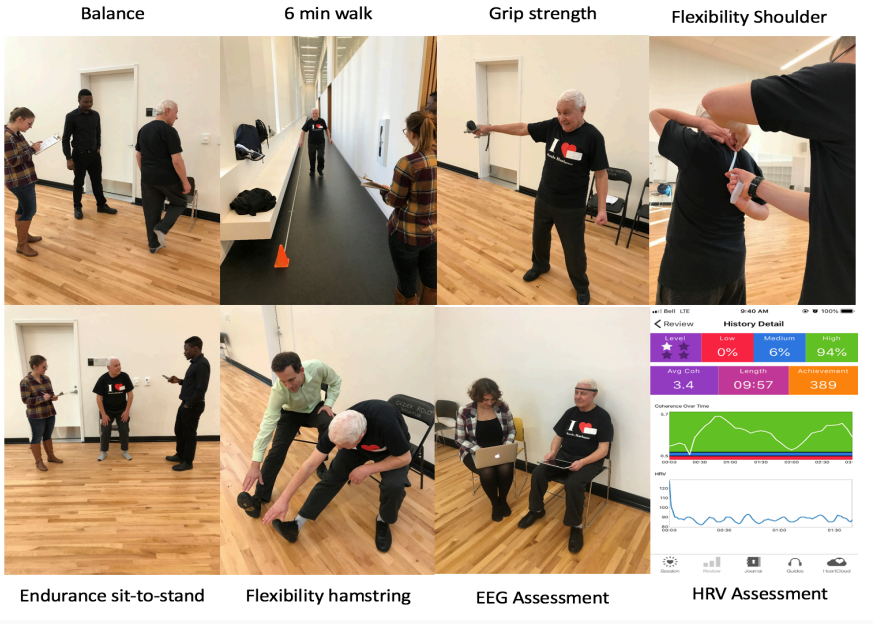
The PC-PEP pilot program ran for 28 straight days from January 12, 2019 to February 10, 2019 for 30 men with a history of non-metastatic prostate cancer. Subjects (n=30) ranged in age from 56-83 years of age, 90% were married, and 67% had a university education. The men varied in their time since diagnosis (four men were less than 7 months, four were between 7 to 12 months, and 22 were greater than 2 years). Participants' treatment history for their prostate cancer diagnosis at pre-intervention was divided between Active Surveillance (10%), Radical Prostatectomy (33%), Radiation External Beam, Brachy or seed implementation (10%), Radiation and Hormonal Treatment (20%), Radical Prostatectomy and Hormonal manipulation (20%), Radical Prostatectomy and Hormonal Manipulation (10%) and Radical Prostatectomy, Radiation and Hormonal manipulation (17%).

All 30 participants completed pre-intervention assessments including:

a) 30 minute quality of life online multidimensional survey which included standardized measures for urinary, bowel, sexual, hormonal function [measured through the International Prostate Symptom Score (I-PSS)], the Expanded Prostate Cancer Index Composite (EPIC-26), mental health assessment (Kessler Psychological Distress Scale-K10), health and well-being (SF-12), current stressors/needs (Screening Distress Scale), relationship Satisfaction (Dyadic Assessment Scale – DAS), overall quality of life (Functional Assessment of Cancer Therapy - Prostate Cancer, FACT-P), demographics (marital status, age, household income, education, occupation) and support group participation.
b) Fitness cardiovascular risks testing (6-minute walk, sit to stand, flexibility, balance, grip strength, height, weight and girth, blood pressure) (see Figure 1).
c) Assessment of stress levels through EEG and heart rate variability monitoring (Heart Math assessment) (see Figure 1).
d) Dietary assessment using a self-reported 24-hour food record.

(These same measurements a-d will be used in this randomized trial)

Figure 1. Fitness, EEG, and Heart Rate Variability Testing in the 28-day PC-PEP pilot program from January 12 to February 10, 2019.



All 30 men first attended a half day education session/intervention which included five sessions taught by professionals:

1. The Science behind PEP taught by a Clinician who treats PC
2. Pelvic floor training by a registered Physiotherapist
3. Mediation instruction by a Psychotherapist
4. Connection/Intimacy by a Professor who taught University courses on Aging and Sexuality
5. Strength training by a Certified Exercise Physiologist (CEP)

1.2.3 Compliance

During the intervention, the men received three daily alerts to do their exercises (either via an app which one of our team members developed for PC-PEP specifically, android and iPhone – 26 participants received app alerts; 4 received text alerts sent by our study's coordinator). They also received a daily video message by email with a list of the daily habits/lifestyle changes recommendations from the PI and the Study Physician. These video messages were between 2-3 minutes long and their usefulness was rated 9.15/10 by PC-PEP participants. Participants were also paired with 2 buddies (also PC-PEP participants) and were encouraged to call each other once a week. This recommendation was highly successful and achieved 100% compliance. The lectures were all videotaped and made available to the participants to use during the program. In the randomized trial, all PEP participants will watch these videos prior to starting the program. The men have graded the didactic and training components of the program as an average of 9.1 out of 10 (lowest scored component was 8.7/10) and the competence of the research team as an average of 9.47 out of 10.

1.2.4 Pelvic Floor Training

Our Specialized Physiotherapist provided a 45-minute overview and live demonstration of pelvic floor anatomy and training. Participants were asked to practice their 'Kegel' exercises three times a day by following an 8-10 minute video we have produced and uploaded for the study participants on the PI's Lab website. The Kegel video instructions changed each week (all uploaded on the website), increasing in intensity during the trial period. Feasibility results of the a-priori repeated measures ANOVA evaluating pre-post mean differences in urinary and sexual function (using the Expanded Prostate Cancer Index Composite, EPIC–Urinary & Sexual domain) found significant improvements in bowel function ($p < 0.05$) and marginal significance in urinary function despite the low statistical power in the feasibility study.

1.2.5 Stress Reduction - Meditation Training

A meditation instructor trained in Mindfulness-based stress reduction with over 30 years of experience, prepared a video of simple mindfulness of body and breath meditations that was made available to the participants. In addition, participants received biofeedback training (30 minutes) during the pre-intervention assessment. Change in pre-post assessment of theta brain wave activity (indicating a meditative brain state) was assessed. No statistically significant results emerged in the analysis of brain waves pre- post intervention ($p=.056$). However, a trend in the improvement direction was observed.

1.2.6 Preliminary Results

Effect on current mental health assessment during the feasibility trial. The results we obtained assessing the effect of the PC-PEP intervention on the pre-post change in mental health status of participants, as measured by a well validated instrument (described below in the methods) showed a statistically significant difference ($p=.031$), despite the small sample size.

Relationship satisfaction: Analyses of relationship satisfaction showed no statistically significant improvement 28 days post intervention.

Strength training: A trained Physiologist evaluated each man and individually prescribed either a low, intermediate, or high-level strength program modified according to the limitations of each man and recommend it to be performed twice per week. An a-priori repeated measures ANOVA revealed statistically significant weight loss, reduced diastolic blood pressure, better endurance sit to stand, and improved hamstring and shoulder flexibility, at post-test comparted to pre-test. The men also agreed to contact two other participants by phone each week. As mentioned earlier, most men received a three-times-a-day reminder text via an app developed by our team or by manual text from our research coordinator (Appendix 10).

All training sessions for strength, Kegels, meditation, connection training/ recommendations were videotaped and uploaded to our lab's website at: http://soillseprostatecancerqualityofliferesearch.che.dal.ca/wordpress/index.php/pc-pep-educational-materials/. Weekly compliance to the program was measured via a weekly self-report online survey. All 30 men completed the post-intervention assessments. No participants dropped out from the program. We collected compliance data (the exact number of days, minutes per day and intensity of engagement in the various aspects of the program). Compliance was consistent among the four weeks with little variation (mostly NS) noted. Overall, the order of compliance for the various aspects of the program (from the highest to the least compliance): strength and aerobic exercises, Kegels, meditation, and intimacy/connection exercises. The buddy system showed maximum compliance. Twenty-five men participated in one of the three focus group sessions held after the program. No adverse events (e.g., injury) occurred. In addition to confirmation of the evaluation results post intervention, the most significant message received during the focus group was the participants' strong indication that they would like the program to have survivors representation so that they may continue to remain enrolled in the program and also help other men and motivate them to do the program as they thought it would be highly beneficial for patients as they go through treatments and afterwards. For this reason, we have 5 men (former PC-PEP members) represented in this grant application; although, we have a list of 20 men (PC-PEP participants) who provided consent and would like to partake in the RCT in some capacity.

1.2.7 Overall Summary of the PC-PEP Feasibility Study

After 28-days of intensive training, the group showed some physical (e.g., weight loss – 3 lbs. weight loss overall, lower diastolic blood pressure, increased flexibility) and improved current mental health assessment as measured by validated self-report questionnaires. The K10 assessment results indicated the presence of screening positive for current mental health issues in 6 men at baseline and in only 2 one month later. Asked whether they would recommend this same program for all new PC patients the men gave an average score of 9.8 out of 10. Self-reported compliance measured weekly was very high throughout the 4 weeks. The feedback from the focus groups was overwhelmingly positive. Some men benefited tremendously from the program more so than what was picked up by assessing group averages. We hope that the reviewing committee for this application would consider viewing one of the 10 patient testimonials we collected by following this link (5 minute length): https://www.youtube.com/watch?v=rAQqejhiXYg&feature=youtu.be. In an interview with the Canadian Press this is what 5 of the participants in our study had to say about the program: https://www.ctvnews.ca/health/unmet-need-new-program-for-men-with-prostate-cancer-shows-promising-results-1.4328403 (36). The results of the feasibility study clearly demonstrate the viability of PC-PEP, and document the interest and commitment of patients and survivors in the program. Our hypothesis is that a comprehensive program such as PC-PEP will improve the mental health of men scheduled for curative PC treatment six months after starting the program compared to standard of care. Our hope is to empower the men at diagnosis and through their

treatment and recovery period, mitigate against treatment related side effects (e.g., urinary incontinence, fatigue), improve their relationships, and ultimately improve quality of life.

2 STUDY OBJECTIVES AND OUTCOMES

2.1 PRIMARY OBJECTIVE

1. To determine whether a comprehensive six-month Prostate Cancer Patient Empowerment Program started prior to treatment, improves the mental health six months later of men undergoing curative treatment for PC, compared to a control group receiving usual care. (All participants receive standard medical care).

2.2 SECONDARY OBJECTIVES

1. Secondarily, we will determine whether PC-PEP also improves the following outcomes relative to controls for:
    a. *Urinary function*;
    b. *Sexual function*;
    c. *Quality of life related to hormonal treatment*;
    d. *Fitness and cardiovascular risks*;
    e. *Relationship satisfaction*;
    f. *Functional, emotional and social well-being*;
    g. *General physical and mental/cognitive quality of life and psychological needs*;
    h. *Diet*;
    i. *Health care utilization*.

2. To determine whether a six-month comprehensive Prostate Cancer Patient Empowerment Program (PC-PEP), delivered to men starting at the six month point improves the one-year point mental health of men who had curative treatment for PC, compared to a control group who received the PC-PEP program during the first six months. We will also compare outcomes relative to controls who did not participate in this trial on secondary outcomes (a) – (h) from Objective 1.

3. To evaluate patient and program contextual factors and mechanisms that account for differences in outcomes among participants in the PC-PEP program.

3 SELECTION AND ENROLLMENT OF PARTICIPANTS

3.1 ELIGIBILTY CRITERA

All potential study participants will be screened by the Research Coordinator and Study Physician (Dr. Rob Rutledge) to ensure that they meet the following eligibility criteria:

3.1.1 Inclusion Criteria

- Age >18
- History of a PC diagnosis
- Scheduled for a Radical Prostatectomy (RP) , or curative intent Radiotherapy (RT = external beam and/or brachytherapy), or adjuvant or salvage RT post RP and complete treatment within 6 months post study enrolment. Patient on hormone therapy (HT) or scheduled to start HT are eligible if they are scheduled to undergo RP or radical RT and complete prostate cancer treatment by 6 months past study randomization.
- Approval from Study Physician that they are safe to exercise. Participants who have recovered from a minor stroke or heart condition in the past will require approval from their Family Physician or Cardiologist to participate in the study.
- Existing (or willingness to create) email account
- Access to a computer/smartphone/tablet with internet access
- Willingness to access and use daily email and/or text messages
- Ability to follow website links to watch YouTube videos
- Ability to understand and speak English
- Ability to participate in low to moderate levels of physical activity
- Willingness to travel to Halifax for an in-person assessment at baseline, six months and one year.

3.1.2 Exclusion Criteria

- Patients treated with hormone therapy only at 6 months post randomization
- Patients on active surveillance (not scheduled for a curative intervention) at 6 months post randomization
- Patients deemed unfit to participate in low level exercise e.g. including but not limited to a myocardial infarction or stroke within the last year, without approval from their Family Physician or Cardiologist that they are safe to exercise.
- Patient with uncontrolled blood pressure. Systolic > 160 or Diastolic > 90.
- Unable to travel to Halifax without incurring travel and accommodation costs for three study visits unless the participant requests to participate in the study and is willing to pay for these expenses in order to participate in the study

- Unable to access the internet and/or lack of a computer/smartphone/tablet to receive emails required for the study intervention, or unable to click on a link to successfully watch a YouTube video.

3.2 RECRUITMENT, SCREENING, AND ENROLLMENT PROCEDURES

3.2.1 Recruitment Methods and Timeline

Recruitment of potential participants will occur through posters, support groups, and education sessions held for PC patients scheduled for curative treatments. Posters (Appendix 1) will be placed within the Departments of Urology and Radiation Oncology, Urologists offices and Cancer Centre's (Radiation Oncology Clinics) throughout the Maritimes. The poster will be available at PC support groups in all three provinces and to Prostate Cancer Canada. In addition to self-referrals, individuals can be referred to the study by their physician or a healthcare provider from their oncology team. Lastly, we will offer this trial to all patients joining an education session to be heald online monthly via telehealth and shared to all patients scheduled for surgery or curative radiotherapy in Nova Scotia. Potential and interested participants will be instructed to contact the Research Coordinator (RC).

At our centre, in Halifax alone, 150 men undergo a radical prostatectomy each year (Dr. Baillie, Head of Urology, personal communication). An additional 250 men receive PC radiotherapy with curative intent. This represents approximately 400 potential participants per year being treated at our centre alone. We have strong support from both the Heads of Urology and Radiation Oncology (leading both Halifax and Sydney Radiation teams). Many non-Halifax Urologists were trained at Dalhousie University and likely will be supportive of this program. Realistically, we aim to accrue 140 (as explained below in section) participants and complete the accrual in 2.5 years (40, 55, and 35 participants per year). A smaller percentage of men who are being treated in New Brunswick or Prince Edward Island and who may will be willing to travel to Halifax for the requisite three (possible 4 visits if they agree to participate in the focus groups and/or face-to-face exit interviews) visits over one year may also be eligible for the study. However, these participants will be informed that their travelling expenses to arrive to Halifax (including related expenses, e.g., accommodation) will not be reimbursed. With their participation, the overall accrual time may be shortened.

3.2.2 Screening and Consent Procedure

1. The Study Physician will explain the study to interested participants via telephone or videohealth. The Study Physician will attempt to screen the participant for eligbility in the trial (Appendix 2) at this time. The RC will provide participants who are interested and eligible with a link to an online REDCap consent form that includes both the study consent form and the Personal Health Information Act (PHIA) Consent form. The PHIA will allow potential participants to give knowledgeable implied consent and details including their name, phone number, and email address. If a potential participant makes initial contact by calling or emailing the RC directly

(by obtaining study information from posters, urology nurses, or other written/verbal information) the RC will assume knowledgeable implied consent to discuss their eligibility and continue with the screening. Knowledgeable implied consent will be assumed to make it more convenient for the patient. This may save some patients a trip to the hospital and avoid unnecessary in-person visits. Since we aim to recruit participants from the three Maritime provinces, assuming implied consent when patients make initial contact via phone/email only may allow for the accrual of a larger demographic of participants who would not have made an in person visit to learn about the study. This process may also improve patient comfort, as participants will all be newly diagnosed cancer patients who may be experiencing distress and who may feel more comfortable talking over the phone. The PHIA consent form will also be made available to Nurses in the Urology Department of the QEII Health Sciences Centre who may introduce the study to patients at the same time as they are providing other standard-of-care education, thus no additional patient contact will occur solely for research purposes. During the COVID-19 pandemic when no in-person recruitment or contact will occur for research purposes, participants will be asked to sign a PHIA consent form on-line at the time they are invited to participate in the study. No candidates will be contacted without voluntarily initiating contact themselves or signing the PHIA form.

2. The Study Physician (RR) will contact the candidates who have signed the PHIA form but have not yet been screen for elgibility criteria to confirm their treatment type and treatment date, interview them for their suitability to engage in low to moderate exercise using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Appendix 3; 37), and screen for other contraindications to exercise. Participants with significant co-morbidities (e.g., moderate or severe cardiovascular disease) will be asked to get a signed letter from their Primary or Specialist Physician clearing them to participate in the program before they can become eligible for the study. Instead of in-person blood pressure assessment, the Study Physcian will obtain their most recent record from their medical records. All potential participants are patients diagnosed with cancer, so they will all have visited a clinic recently and have blood pressure measurements on file. Participants who are eligible, including being able to join a videoconference and deemed safe to exercise will be emailed a link to an electronic version of the informed consent form residing on the NSHA platform, for their review prior to their day 1 assessment or start of the program.
3. All participants who have passed the eligibility criteria and who have completed the online consent forms will be scheduled for a baseline in-person study visit.

3.3 RANDOMIZATION AND STRATIFICATION

3.3.1 Sequence Generation

To minimize the chance of having unbalanced groups, participants will be randomized according to a fixed block design (block length 4), stratifying on the following characteristics: (RP= Radical Prostatectomy, RT = Radiotherapy)

a. Type of curative treatment (RP vs primary RT vs adjuvant/salvage RT post RP)
b. Whether or not they have started or are scheduled to receive hormone therapy. (Note: men scheduled for RP are not expected to start HT)
c. Whether they score positive or negative for mental distress on the K10 questionnaire. (Note: men will have already completed this questionnaire as part of the online survey prior to randomization)

Example Fixed Block (block length 4) Table
'A' represents randomization to early PEP
'B' represents randomization to later PEP

RP and K10 neg – ABBA, BBAA, AABB, BABA, ABAB, BAAB, and so on
RP and K10 pos – BAAB, AABB, BBAA, ABAB, BABA, ABBA, and so on

RT and K10 neg and no HT – BAAB, ABAB, BABA, AABB, ABBA, BBAA, and …
RT and K10 neg and HT – ABBA, ABAB, BABA, ABBA, AABB, BBAA, and …

RT and K10 pos and no HT – ABBA, BABA, ABAB, BAAB, AABB, BBAA, and …
RT and K10 pos and HT – BAAB, ABAB, BABA, AABB, ABBA, BBAA, and …

RP + RT, K10 neg and no HT - BAAB, ABAB, BABA, AABB, ABBA, BBAA, and …
RP + RT, K10 neg and HT - ABBA, BBAA, AABB, BABA, ABAB, BAAB, and …

RP + RT, K10 pos and no HT – ABBA, BABA, ABAB, BAAB, AABB, BBAA, and …
RP + RT, K10 pos and HT – BAAB, ABAB, BABA, AABB, ABBA, BBAA, and …

Only one member of the team (the Principal Investigator), will have access to the randomization table. The PI will not be involved in the consent process (delivered by the RC and CEP).

3.3.2 Randomization Assignment and Concealment Mechanism

Once the participant completes the comprehensive survey, the RC will let the PI know the participant's treatment type, whether they are on or scheduled for HT, and their K10

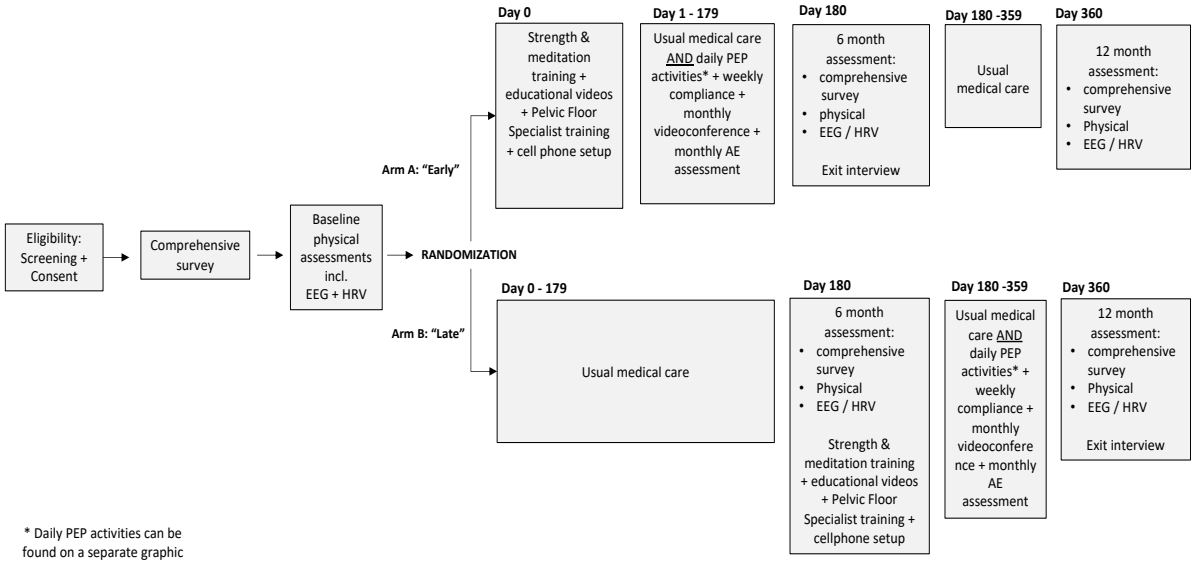
score. The PI will then let the RC know the next available assignment on the randomization chart (i.e. 'A' for early PEP, and 'B' for late PEP starting at six months).

The participant will be booked for physical assessments and EEG/HRV testing on Day 0 in Halifax (Figure 2). Neither the participant nor the CEP will know their assignment (early vs late) until after the initial assessments have been done.

The participants randomized to the Early PEP program (A) will then be asked to stay with the CEP to undergo a full exercise assessment and receive a prescribed home-based exercise program.

The participants randomized to Late PEP (B) will be told (after they complete their initial assessment) to follow the instructions provided by the medical system, and that they will be scheduled to meet with the research team again in 6 months time.

Figure 2. Study Overview Timeline; Early Arm versus Late Arm



4 CLINICAL INTERVENTION (Patient Empowerment Program)

The PC-PEP program includes the following components:

1. Specific training and instructions on how to follow a "home-based" individualized aerobic program aiming to achieve 150 minutes of exercise per week;
2. Specific training and instructions on how to follow an "at home" individualized strength program twice per week as part of the 150 minutes of weekly exercise;
3. Specific training and instructions on how to engage in pelvic floor strengthening exercises and follow an "at home" program three times a day;
4. Specific training and instructions on how to meditate and follow an "at home" program for a minimum of 10 minutes per day;
5. Specific training and instructions on how to use other healthy lifestyle habits related to diet, sleep, and social connection and make them part of routine living.
6. Additional social support by being asked to call two other participants each week during the 6-month intervention period. Participants will also be encouraged to join a confidential videoconference hosted monthly by the PI, Study Physician and PC survivor 'Mentors'.

4.1 INTERVENTIONS AND ADMINSTRATION

4.1.1 Aerobic Training Recommendations

The SP will provide a medical overview to the CEP for every participant. The CEP will assess each participant and create an individualized aerobic exercise plan for the six-month period based on the safe training principles (e.g. slowly increasing intensity and duration of workouts over time). If possible, the participants will try to work their way up to the recommended 150 minutes per week. Participants will be encouraged to exercise daily via emails and short videos and to choose fun and social activities to maximize adherence.

4.1.2 Strength Training Recommendations

The CEP will also assess each participants ability to follow a home-based strength program using elastic bands for some exercises. The CEP will teach the proper technique and prescribe a set of exercises for each participant including the number of reps, sets and intensity (work: rest ratio) of each exercise (see Appendix 8 for an example handout). The CEP will relay the prescription to the Research Team who will create a YouTube video specific for that participant. The video reinforces the correct technique of each exercise and encourages the men to stay within their physical limits. The men are asked to do their strength training program twice per week with a target of 30 minutes per session as part of the 150 minutes of aerobic exercise. Over time they can increase the

intensity of the program on their own by increasing elastic band tension or number of sets or reps, or duration of session. The CEP will be available as a resource to the men throughout the study duration.

Participants Undergoing Radical Prostatectomy (RP)

Men undergoing RP, a pelvic surgery, will need to adjust their exercise program. The Research Coordinator will remind the men to taper down their exercise regimen four days prior to the surgical date (note the daily email system will be set up according to surgical dates). Once the men are admitted to Hospital for their surgery, they will follow the directions of their Health Care Professionals about when and how to reinstitute an exercise program (typically six weeks after their operation). Gentle aerobic activities (e.g. walking) will start first, and only after they have been cleared by their Urologist can they restart the strength training sessions, for instance by starting with the upper body exercises.

Participants Undergoing Radiotherapy (Brachytherapy or External Beam)

Brachytherapy entails placing radioactive sources directly in the prostate gland through needles inserted in the perineum. Men have swelling and tenderness in the lower pelvis for at least a month. Men can exercise lightly throughout the recovery period. However, they will be instructed to follow the directions of their Radiation Oncologist before reinstituting their strength training exercises.

Participants undergoing external beam radiotherapy can continue with the aerobic and strength exercises without modification. If / when they develop fatigue or other issues, they will take instruction from their health care team.

4.1.3 Pelvic Floor Muscle Training

All participants will be encouraged to follow pelvic floor training (Appendix 7) three times a day during the intervention period. They will be taught the concepts and techniques by:

a) Watching a video explaining the anatomy and physiology of the pelvic floor and the rationale for the exercises, as well as practical exercises they can use to decrease the likelihood of leaking.
b) Meeting with a Pelvic Floor Specialist via videohealth or telephone for a one-hour individualized teaching session.
c) During the six-month intervention they will receive a daily email. On the email is a link to a 5-10 minute video outlining the pelvic floor exercise for that day. Every two weeks the video changes, slowly increasing in intensity, and teaching different techniques. They are expected to follow the video instructions three times a day.

NOTE: As per standard of care, all men who undergo surgery will meet with a Pelvic Floor Specialist 3-4 weeks after surgery for up to 6 weekly training sessions or as per their Urologist's recommendations.

4.1.4 Meditation Instruction

Participants will receive a heart rate variability (HRV) monitor produced by the HeartMath Institute to use at home throughout the 6-month intervention. This will allow them to have consistent biofeedback and further help them learn how to relax (increase their HRV). The monitor can be a stand-alone hand-held unit, or as a Bluetooth compatible free unit synched to the patients iPhone or android device. The HeartMath Institute monitors were chosen based on their hardware and software's reliable and frequent use in other clinical studies (30, 32, 38). Over 300 peer-reviewed studies have used HeartMath products and the technology is based on 25 years of scientific research (34). The monitors were also well received by participants during the feasibility study. Each patient connects a small probe to their earlobe which is painless and non-invasive. The probe detects their heart rate pattern and sends the signal to the device. The software produces an ongoing read out of the HRV and a display of a slow breathing pattern. Those who are using their cell phones will be encouraged to send a summary of their session to the RC. Summary includes length of session and average heart rate coherence. These data will be deidentified and housed on NSHA servers.

Patients will receive instruction on how to meditate (and increase their HRV) by:

a) Watching a video produced by the HeartMath Institute (slow breathing, coupled with positive emotional image, and visualization of warming up the heart region)
b) Daily emails will include a link to a 5- or 10-minute meditation sequence
c) The start of each pelvic floor exercise video starts with two minutes of simple meditation instruction

4.1.5 Healthy Lifestyle Promotion

Participants will be encouraged to follow a healthy lifestyle by:

a) Watching a video of the science underlying the PEP program (includes the modifiable risk factors for PC including diet, smoking, obesity, and sleep. Men who are smoking will be asked to contact their provincial smoking cessation program)
b) Joining an in-person or videoconference session at the start of the program with the Study Physician
c) Daily emails and short videos include reminders to adhere to the recommended lifestyle habits including dietary tips.
d) Monthly videoconference sessions led by the Study Physician, other participants, and others (PI, Mentors)

4.1.5.1 Smoking Cessation

In the online baseline questionnaire, participants will be asked about their smoking habits (Appendix 4). Participants who indicated that they currently smoke or consume tobacco products will be directed to Tobacco Free Nova Scotia (TFNS). TFNS offers free, confidential, personalized support to help people quit smoking and stay quit. Participants

will be asked to call 8-1-1 to register with the service at the beginning of their 6-month intervention period after they watch the educational videos and receive other health promotion advice (Day 0 for 'Arm A: Early Intervention' or Day 180 for 'Arm B: Late Intervention). Participants from provinces outside of Nova Scotia will still be asked to call 8-1-1 while at the QEII Hospital for their first study visit, after which TFNS will refer them to their specific provincial smoking cessation program. A 2016 study found that Canadian provinces with smoking cessation initiatives for cancer patients offered a referral to 22-80% of ambulatory cancer patients who screened positive for smoking and 21-45% of those patients accepted the referral (39). Therefore, participants may be referred to smoking cessation services through standard medical care, in which this will act as extra support to further encourage acceptance of referral to TFNS or other provincial service.

4.1.6 Connection and Relationship Teaching

Participants will learn about and be encouraged to increase the multidimensional connection and intimacy in their lives by:

a) Watching a video produced by the PI
b) Joining an in-person or videoconference session at the start of the program with the Study Physician
c) Daily emails and short videos include reminders to express and ask for more connection in their lives. For instance, every Sunday the pilot participants were asked to call a family member or friend who lives at a distance
d) Monthly videoconference sessions led by the Study Physician, other participants, and others (PI, Mentors)

4.1.7 Social Support

To maximize compliance with an intense program and to improve the depth and breadth of social support we're asking all participants to

a) Call two other co-participants each week. Co-participants are matched by demographic features. They are instructed to ask their 'Buddies' how they are doing with the program and to report their own compliance.
b) Join a monthly videoconferencing session

4.1.8 Monthly Videoconferencing with active PEP participants

The www.Zoom.us platform is an easy-to-access platform to allow distant participants to join in on a videoconference. Participants will be encouraged watch or listen to the videoconference, and if they feel so inclined, to join in on the conversation. The conference will occur for one hour on the first Tuesday of each month at 7pm AST/ADT and will be available to the participants in the active phase of the protocol. This conference will provide an opportunity to discuss issues arising on the trial and include tips on how to address health concerns and on how to maintain compliance with the

protocol. Participants who are willing will be encouraged to share their experience of going through treatment.

The Study Physician and PI will host the meetings and will be joined by PC survivors who have been screened. The survivors will act as 'Mentors' by providing stories of their personal experiences. Mentors may offer their contact information during the conferences or on the study's website, and participants can choose to reach out to the Mentors for ongoing support. The Mentors will not be offering medical advice. Mentors will be registered as "volunteers" with the NSHA and thus they will be required to sign an NSHA Pledge of Confidentiality agreement. Any action considered as a breach of confidentiality will result in immediate termination of their role as "Mentor/Volunteer".

Participants themselves will be offered the opportunity to become mentors after a minimum of one year of follow up from time of their randomization.

Maintaining Privacy during Videoconferences

The Zoom videoconferencing software has a number of privacy features including:

a) Only participants who have a password can access a meeting. Each meeting has its own unique password
b) Participants can join by telephone only and 'listen' to the conversation, with the option of speaking.
c) The RC can provide a unique username to each person like a 4-digit number. The username is what appears as the participants name for those who decide to join by videoconference.
d) Each participant can mute their microphone and turn off or cover their camera.
e) Once the appropriate participants have joined a meeting the meeting can be 'locked' so that no one else can join the meeting
f) The Zoom software does not capture any personal information of the participant. Each person simply goes to a webpage and enters in the meeting-specific password.
g) The videoconferences will not be recorded.
h) Participants will be reminded to maintain the confidentiality of all other participants both at the start and end of each meeting.

Figure 3. Schedule of weekly PEP activities during the 6-month intervention period.

4.1.9 Using Technology for Support

To increase compliance with this intense program, participants will receive a daily email outlining the activities recommended by the program for each day. These email notices will point out different resources (including video links) to help the men with their implementation of the program's recommendations. Participants who use a smart phone will also receive a text three times per day reminding them to do their pelvic floor exercises. Participants who do not have a smart phone will choose their preferred platform for their three times a day reminder (e.g. text message, or email). Smartphones will not be provided to participants as part of the study.

Bank of Emails and Videos

	MON	TUES	WED	THUR	FRI	SAT	SUN
Meditation (minimum 10 min/day)	✓	✓	✓	✓	✓	✓	✓
Pelvic Floor Exercises* (8-10 min/day)	✓	✓	✓	✓	✓	✓	✓
Aerobic Exercises (30 min/day or as total time; allowed to miss a day)			✓			Something different	
Strength training	Work out #1			Work out #2			
Connection suggestions	Call 2 co-participants	✓	✓	✓	✓	Fun activity of choice	Call someone at a distance
Compliance survey							✓

To standardize the program for all participants (for both early and late groups, and over the entire accrual period), we will create a bank of 180 emails for each day of the six months of intervention. Each email will have an accompanying 2-4-minute YouTube video.

Once a participant has watched all day 0 educational videos and spoken with the Study Physician, they will be asked to start the program. Each day the RC will email each

participant who is on the active phase of the trial. At the end of active phase, the participants will no longer receive emails and no longer be invited to join the monthly videoconferences.

4.2 DESCRIPTON OF ARM A – 'EARLY' INTERVENTION

All participants prior to randomization will have taken the comprehensive online survey (Appendix 4) and completed the physical assessments (Appendix 5) with the CEP and the EEG/HRV with the RC.

Participants will learn about their randomization assignment at the end of the pre-intervention assessment by the CEP. Those randomized to 'Early' PEP will stay with the CEP for the strength training session. The schedule for Arm A participants is as follows:

4.2.1 Education Phase for 'EARLY' ARM 'A' Prior to Day 1

a. Strength training session The CEP will create an individualized strength training program (one session to be done every Monday, and a different session to be done every Thursday). A YouTube video of these two sessions will be produced by the Research Team who will send the links and a paper copy of the list of exercises to the participant. The strength training session can be conducted while maintianging 2 meters distance at all times and participants use new exercises bands that have not been used by any other people.
b. At the pre-intervention session the CEP will also offer advice and a suggested weekly aerobic exercise regimen.
c. The participant will by given an appinment with the Pelviv Floor Specalist. who will provide individualized PFME teaching. This will be done via videohealth or telephone.
d. The participant will be directed to watch three videos (total 1 hour viewing time) and given a chance to ask any questions the participant may have at that time:
    i. Science behind PEP
    ii. Pelvic Floor training
    iii. Meditation
    iv. Connection
e. A research staff member will review the PEP program with the participant. Once the participant is satisfied with their instructions, they will start the intervention phase.

4.2.2 Intervention Phase for EARLY ARM (days 1-180)

The men randomized to the Early intervention will complete the following activities during the first six months at home:

1. Between the strength and aerobic program to try to achieve or work towards 150 minutes/week of exercise**. They will be encouraged to do some form of exercise every day, even if it is just easy walking.
2. Do an "at home" individualized strength program twice per week, one program on Monday and a different program on Thursday.** Men can choose to deviate from these specified programs by doing more than twice per week strength training, working out in a gym alone (+/- with the advice of a personal trainer) as long as they do strength training twice per week.
3. Engage in pelvic floor strengthening exercises three times a day, for 8-10 minutes per session
4. Meditate for a minimum of 10 minutes per day
5. Read an email and listen to a video (embedded in the email) every day which includes healthy lifestyle habit suggestions and social connection teaching.
6. Call two other participants each week.
7. Join a monthly confidential videoconference hosted by the PI, Study Physician and PC survivor 'Mentors'.
8. Fill out their compliance survey (5min) weekly (Appendix 6).

***Men undergoing surgery will be instructed to decrease their exercise and strength program the 3 days prior to the procedure, and to slowly increase their aerobic component after the surgery on the advice of their Urologist. Men undergoing RP or Brachytherapy will not restart their strength training until they have been given permission by their Urologist or Radiation Oncologist, for instance six weeks after surgery.*

All men undergoing surgery will see a Pelvic Floor Specialist starting 3-4 weeks after their surgery and weekly for six weeks to undergo PFME teaching.

4.2.3 Post Intervention Assessment Phase for EARLY ARM (Day 181)

The men randomized to the Early intervention (Arm A) will complete the following assessments during a single visit on Day 181 (+/- 2 days):

1. Comprehensive online survey (same as the pre-invention survey)
2. Program evaluation survey
3. In-person audiotaped interview evaluating the program
4. Physical Assessments with the CEP
5. EEG/HRV assessment

During the assessment, research staff members will wear a new pair of medical gloves and a new disposable medical mask. Participants will also be required to wear a mask. Only one participant will be present during each assessment. Staff will be required to maintain a distance of 2 meters from each other and from particiapnts whenever possible. Equipment will be sanitized thoroughly after ever use. These procedures will occur during every study visit.

Arm A men will then follow usual care as prescribed by the medical system until day 359.

4.2.4 End of trial Assessment for EARLY ARM (Day 360)

On Day 360 (or within a few days) the Early' men will come in for a single visit to complete

1. Comprehensive online survey (same as the pre-invention survey)
2. Physical Assessments with the CEP
3. EEG/HRV assessment

Please refer to Figure 2 for a timeline diagram of 'EARLY ARM' schedule.

4.3 DESCRIPTON OF ARM B - 'LATE' INTERVENTION

Participants will learn about their randomization assignment at the end of the initial physical assessment with the CEP. Those randomized to 'Late' PEP will be told to follow the instructions provided by the medical system. All men undergoing surgery will see a Pelvic Floor Specialist starting 3-4 weeks after their surgery and weekly for six weeks to undergo PFME teaching.

Late arm men will receive no further instruction about how to empower themselves until they meet again with the CEP for assessment on day 180 (or within a few days) for a strength training. During that visit the men will complete.

1. Comprehensive online survey (same as the pre-invention survey)
2. Physical Assessments with the CEP
3. EEG/HRV assessment

4.3.1 Education phase for LATE ARM (Just prior to Day 180)

a. Strength training session. The CEP will create an individualized strength training program (one session to be done every Monday, and a different session to be done every Thursday) for the participant after assessment of their health by the study's physician just prior to day 180. The study's physician and CEP will ensure the exercise program offered/recommended is suitable for the level of fitness of the participant. A YouTube video of these two sessions will be produced by the Research Team who will send the links and a paper copy of the list of exercises to the participant
b. At the same session the CEP will also offer advice and a suggested weekly aerobic exercise regimen.
c. The participant will be directed to watch three videos (total 2 hour viewing time)
    i. Science behind PEP
    ii. Pelvic Floor training
    iii. Meditation
    iv. Connection

d. After they watch the videos the participant will videoconference or telephone call the Study Physician and/or PI to discuss information provided on the videos and ask questions. The SP/PI will review the PEP program. Once they are satisfied with their instructions, they will start the intervention phase.

4.3.2 Intervention Phase for 'LATE' ARM (Days 180-360)

The men randomized to the Late intervention will complete the following activities between 6 to 12 months post diagnosis, at home:

1. Between the strength and aerobic program try to achieve or work towards 150 minutes/week of exercise. They will be encouraged to do some form of exercise every day even if just easy walking.
2. Do a "at home" individualized strength program twice per week, one program on Monday and a different program on Thursday. Men can choose to deviate from these specified programs e.g. do more than twice per week strength training, work out in a gym alone or with the supervision of a personal trainer as long as they do strength training twice per week.
3. Engage in pelvic floor strengthening exercises three times a day.
4. Meditate for a minimum of 10 minutes per day
5. Read an email and listen to a video (embedded in the email) every day which includes healthy lifestyle habit suggestions and social connection teaching.
6. Call two other participants each week.
7. Join a monthly confidential videoconference hosted by the PI, Study Physician and PC survivors 'Mentors'.
8. Fill out their compliance survey (5min) weekly (Appendix 6).

4.3.3 Post Intervention Assessment Phase for LATE ARM (Day 360)

The men randomized to the Late intervention will complete the following assessments during a single visit on Day 360 (or within a few days):

1. Comprehensive online survey (same as the pre-invention survey)
2. Program evaluation survey
3. In-person audiotaped interview evaluating the program
4. Physical Assessments with the CEP
5. EEG/HRV assessment

Please refer to Figure 2 for a timeline diagram of 'LATE ARM' schedule.

5 CLINICAL EVALUATIONS

5.1 PRIMARY ENDPOINT (MENTAL DISTRESS) EVALUATION

The primary outcome is current mental health status as measured by the Kessler Psychological Distress Scale-K10 assessment at the six-month point self-administered by all participants- at the end of the intervention period for Early men and prior to the Late men starting the program. K-10 is a 10-item questionnaire intended to yield a global screening measure of current mental health illness based on questions about anxiety, depressive symptoms and psychological distress that a person has experienced in the most recent 4-week period (40). Scores on K-10 range from 10 to 50. Scores of 20 or above indicate the presence of a mental health illness ranging from mild (20-24), moderate (25-29) or severe (30 or above). This is a screening instrument that practitioners consider to help them make a clinical judgement as to whether a person needs mental illness treatment (41). K-10 has been widely implemented, including in the World Health Organization World Mental Health Survey, Center for Addiction and Mental Health (Toronto, Ontario), as it is widely used all over the world in epidemiology and clinical research (42) and prior research has shown the K-10 to be an excellent screening tool for mental health illness (43-44). In a study (n=3,697) assessing the screening for mental health illness among older adults (65 years old and plus), the K10 was found to exhibit sensitivity to internalizing disorders as they occur across the lifespan (45).

If the sum of the ten questions is greater than 20 on the K10, the participant is deemed to screen positive for mental distress, and those whose total is 20 or less are deemed to screen negative for mental distress.
The Study Physician will contact those who have screened positive for mental distress and will recommend or refer them to the psychosocial cancer team at the Nova Scotia Cancer Centre.

5.2 SECONDARY ENDPOINT EVALUATIONS

Secondary outcome measures will include physical fitness assessments, relaxation brain-waves activity (EEG) measurement (alpha, beta, delta, theta, gamma averages over listening to 10 minutes relaxation music and instructions), Heart Rate Variability, and quality of life patient reported survey outcomes pre- and post- PC-PEP. Three a-priory hypotheses will examine changes between pre and post physical strength, EEG brain activity during meditation and quality of life patient reported outcomes. We predict improved physical and quality of life outcomes in those randomized to the ‘early’ intervention arm compared to those randomized to the ‘late’ intervention.

5.3 SCHEDULE OF EVALUATIONS

X^A = applies to participants in 'ARM A Early' only
X^B = applies to participants in 'ARM B Late' only

Note: Compliance surveys will be administered weekly during the intervention part of the study (Day 0 – 180 for Arm A Early and Day 180 – 360 for Arm B Late). Assessment of AEs will occur monthly throughout these intervention periods.

5.4 PRE- AND POST-INTERVENTION MEASUREMENTS

5.4.1 Physical Fitness Assessment

All physical fitness assessments will be performed by a CEP. Measurements will be recorded for weight, height, hip, and waist. Body composition and abdominal obesity will be assessed via calculating body mass index (BMI) from weight and height measurements, and waist-to-hip circumference (WHR). According to recommendations from the World Health Organization, abdominal obesity is defined as a BMI >30.0 and

Evaluation	**Screening** **(Day -7 to -1)**	**Baseline/ Study Visit 1** **(Day 0)**	**Study Visit 2** **(Day 180 ± 3)**	**Study Visit 3** **(Day 360) ± 3)**
Inclusion/exclusion criteria	X			
Contact information + planned date of PC treatment	X			
PAR-Q+ assessment	X			
Medical history	X			
Informed consent		X		
Comprehensive online questionnaire	X		X	X
Physical assessments		X	X	X
EEG/HRV assessments		X	X	X
Randomization		X		
Adverse Events			X	X
Exit Interview			X^A	X^B

WHR >0.90 for males (46). Aerobic fitness will be determined using the six-minute walk test (47). Static postural and balance control will be assessed using the one-legged stance test (48) while the timed sit-to-stand test will be used to evaluate lower limb strength (49).

5.4.2 Relaxation – Brain Activity Assessment

EEG assessment of the relaxation state will be measured using the Muse™ (InteraXon, Inc., SCR_014418, Toronto, Ontario, Canada) neurofeedback device (Appendix 9). It is a headband that detects and measures brain activity via seven dry sensors located at various points across the forehead and behind the ears. These measures of brain activity will be used as an indication of skill of mindfulness and meditation. The Muse™ device has been used in previous research studies related to treatment of traumatic brain injury in civilian and military populations (50). A validation study reported that the Muse™ device accurately captured event related potential components during rapid tests, demonstrating its application in clinical studies (51). Furthermore, the Muse™ takes minimal time to set-up compared to larger electrode EEG devices, costs significantly less to purchase and administer, is portable, non-invasive, and user-friendly (51). The Muse™ device was chosen because it will allow us to collect EEG data from a large number of participants at a low cost. The analysis from the Muse™ data will provide the results we are interested in: how many restful periods were achieved, how frequently, and how many times during the 10 minute session was the individual able to bring their attention back to the present moment and relax (go into theta brain activity). Muse™ captures in an excel file its own data which is exported to the study data base housed on the NSHA servers.

5.4.3 Online Questionnaires

All online questionnaires will be administered via Research Electronic Data Capture (REDCap) and they will include the evaluation of the following areas (please see Appendix 4 for a complete list of online questions):

1. *Demographics* – e.g., education, household income, relationship status, etc.
2. *General Health Questions* – e.g., presence of health conditions, medication usage, etc.
3. *Cancer-Specific Questions* – e.g., date of diagnosis, cancer stage, Gleason score, etc.
4. *Urinary Tract Symptoms*: For the assessment of lower urinary tract symptoms and impact on quality of life, participants will be asked to complete the Expanded Prostate Index Composite (EPIC-26) (52) questionnaire and the International Prostate Symptom Score (IPSS) (53, 54). The EPIC is a validated questionnaire that was derived from the UCLA-Prostate Cancer Index (UCLA-PCI) (55) to assess health-related quality of life after treatment for cancer. The 26-item domain-specific patient-reported questionnaire has been tested on patients treated with RP and it has demonstrated satisfactory results in both validation analyses and respondent compliance with survey completion (52).
5. *Modified Charlson Comorbidity Index questionnaire (CCI):* The CCI is based on a history of concomitant disease (e.g., diabetes, renal failure, cardiovascular disease, etc.) and malignancy and it was a tool initially developed and validated in women being treated for breast cancer (56). However, since its inception, it has gone on to be used in various clinical populations and has been widely administered to predict short-term outcomes (57 – 62).

6. *Quality of Life (QoL):* Questions taken from several questionnaires will be used to assess the different components of QoL:

    a) Functional Assessment of Cancer Therapy-Prostate (FACT-P) – This questionnaire has been shown to be one of the best psychometric tools for measuring the psychosocial (e.g., emotional distress, social functioning, etc.) aspect of QoL in patients with PC (63).
    b) Short Form 12 (SF-12) Health Survey – This questionnaire will be used to assess general health QoL (64, 65). The SF-12 has been considered the most superior generic instrument for measuring health related QoL in individuals with PC (55, 65, 67).
    c) Kessler Psychological Distress Scale (K10) – The K10 is a validated and widely used clinical instrument for the assessment of psychological symptoms, which has demonstrated high factorial and construct validity (68, 69).

5.4.4 Measuring Compliance

Each week the participants will self-report the number of times they did aerobic exercise, strength exercise, pelvic floor exercises, and meditation – and the average number of minutes they spent during each session - by completing an online survey (please see Appendix 6 for a list of questions for the compliance survey sent out weekly via email).

6 STATISTICAL CONSIDERATIONS

6.1 SAMPLE SIZE AND ACCRUAL

A meta-analysis of 4494 PC patients reported in 27 articles shows the incidence of pre-treatment anxiety to be 27% and of pre-treatment depression to be 18% (69). Kessler Psychological Distress Scale-K10 (our primary outcome questionnaire) picks up both depression and anxiety so the rate of clinical positive K10 score at diagnosis is likely lower than 45% (the sum of 27% and 18%). In our feasibility study of a diverse group of 30 prostate cancer survivors (22 of which having been treated more than 2 years since their diagnosis) 6 men scored positive for mental distress (K10 measurement) at baseline (20%). We hypothesize, based on literature findings, our participants' mental health status will likely be poorer at the time of their diagnosis, likely higher than 20%. So, as a conservative estimate (between 20% and 45%) we predict that the rate of screening positive on K10 for mental distress will be 30% of all our study participants at baseline.

At the six-month time point we expect the control group (Late arm) will maintain a 30% positive distress rate as they will be dealing with the long-term side effects of their treatment and multiple other stressors. Supporting this assertion comes from two trials

showing that up to 23% of men who undergo PC treatment continue to screen positive for mental health issues 12 months after and onwards (71-72). Screening positive for mental distress are likely to be even more prevalent at the six-month point than at 12 the month point, again supporting an estimate of 30% distress rate in the control group (Late arm) at six months (71-72).
We expect those in the intervention arm (Early Arm) to have improved their mental health status at six months because the intervention is designed to address multiple issues (in the physical, cognitive, and social realms) that lead to depression and anxiety. In our feasibility study, the K10 distress rate decreased from 20% to 6% (a 66% reduction) in just 28 days. If in the proposed trial the estimated improvement is a similar 2/3 reduction in distress rates, we calculate the distress rates will drop from 30% at baseline down to 10% at six months. To summarize, at six months we expect 30% of the control group to score positive for mental distress compared with 10% in the intervention group. With a 2-sided test, an alpha level of 0.05, and estimated power of .80 power analysis based on an anticipated incidence of screening positive for mental health issues among men diagnosed with prostate cancer six months after diagnosis of 30% (control arm) vs incidence of 10% (intervention arm) indicated a total of 124 participants is needed to detect a minimum effect ($F = 0.35$), which is considered to be meaningful (60-62). Although during the PC-PEP feasibility study there were no dropouts (n=30), we will accrue an extra 6 participants to account for any possible dropouts. The COVID-19 pandemic has presented additional challenges in accrual. We expect a small number of participants to miss 6-month or 12-month follow-up assessments due to concerns regarding the virus. We also originally planned to acrue a small number of participants from New Brunswick and Prince Edward Island, however due to restrictions in travel across provinces, it is difficult for these participants to arrange and commit to all study visits in Halifax. We plan to accrue an additional 10 participants to account for these participants missing assessments. Therefore, the total number of participants we plan to accrue is 140.

6.2 STATISTICAL ANALYSES

6.2.1 General Considerations

General description of the statistical methods is outlined below. A more detailed statistical analysis plan (SAP) will be developed early in the study which includes details on coding, data handling, output tables and figures, and technical specifics on all variables. All SAP associated documents will be finalized without knowledge of any emerging results from the study.

6.2.2 Comparisons

Following our design, we will conduct three sets of analyses comparing outcomes for (1) the intervention (early) group versus control (late) group in the first half year (PC-PEP vs usual care); (2) Late group (i.e. late intervention) versus the post early group period in the second half year following diagnosis; and (3) difference in outcomes for early versus late

PC-PEP. This provides assessments of the effectiveness of early PC-PEP versus usual care (Obj. 1), late PC-PEP versus men who have already completed PC-PEP (Obj. 2), and late versus early PC-PEP (Obj. 2).

6.2.3 Primary Analyses

Descriptive analyses will first be conducted to assess the extent of balance between intervention and control groups with respect to treatment modalities and base-line characteristics. As a consequence of our blocked randomization, analyses of primary and secondary outcomes need to account for potential clustering of the data and accrue the benefits of blocking on baseline variables. Accordingly, conditional-fixed effect, generalized linear regression models will be used. Appropriate link and error distributions will be employed, as appropriate, for each dependent variable. An intent-to-treat approach will be used, as we wish to assess effectiveness. Adjustment for prognostic covariates will be employed to address observed imbalances between randomized groups. Post-hoc analyses to describe heterogeneity in treatment effects will also be conducted to support our Objective 3 investigation. Statistical analyses will be performed using R ver. 3.6.0 and SPSS ver. 24.

6.2.4 Qualitative Analysis

Face-to-face interviews will be conducted with two purposively selected subjects in each of the treatment and control arms of 3 randomization blocks (see yellow bars in Table 1, for a total of 12 interviews). We anticipate that one of the two will be a man who had high perceived benefit of PC-PEP, and the other a man who had lower perceived benefit; however, we will also draw on results from post-hoc analyses and results from previous interviews to guide subject selection. In addition, two focus groups will be conducted with personnel delivering PC-PEP (at months 14 and 22). All interviews/focus groups will be audiotaped and transcribed verbatim before being reviewed and coded by members of the research team. Analysis will be guided by realist evaluation processes based on a cycle of hypothesis generation, testing and refinement of Context-Mechanism-Outcome (C-M-O) configurations (73-74). In keeping with this approach, we will generate C-M-O configurations using both qualitative and quantitative data (post-hoc analyses) . Patient interview materials will be qualitatively analyzed by two members of the research team, independent of each other. They will generate preliminary codes based on 4 patient interviews, then meet to compare and develop a coding framework to code the remaining data. A detailed coding procedure will be followed, and codes will be compared among the raters and re-coded if necessary, to identify and capture patterns and trends rooted in the data. Data will be stored, managed, and coded with the latest NVivo qualitative software.

Additional thematic analyses or analyses informed by the abovementioned critical paradigm may also be performed. A series of tables and summaries will be constructed to highlight key results across data sources for each age group and treatment type and develop detailed case reports to facilitate knowledge mobilization of study findings at local and provincial levels.

6.2.5 Secondary Analyses

Secondary outcomes will be assessed through descriptive statistics: adherence counts, frequencies, means, standard deviations, range of responses, proportion of participants who adhered to the various aspects of the program (engaging in the exercises prescribed at the rate prescribed).

A series of a-priori repeated measures t-tests will be used to assess pre- and post-physical strength and relaxation secondary outcomes. We hypothesize that if the program is successful, there will be differences (e.g. improved physical fitness and ability to relax). Urinary and mental health symptoms will also be assessed using repeated measures t-tests. We hypothesize that if the program is successful, there will be differences (e.g., improved urinary continence and less psychological distress). Analyses will be assessed using R ver. 3.6.0 and SPSS ver. 24.

7 ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1.1 Adverse Events

A clinical adverse event (AE) is any unfavourable or unintended sign or symptom associated with the study intervention and occurring in a participant assigned to the intervention. Participants will be able to self-report AEs to the study team at any time throughout the study. The chance of an adverse event on this study is expected to be low and very likely related to aerobic or strength training. All reported AEs will be recorded for type, severity, relationship to exercise program (aerobic, strength), expectedness, serious AE (yes/no), timing, action taken (if any) and outcome.

All AEs reported from the date of informed consent until 28 days after the end of the intervention are considered. Men randomized to the ‘late’ group from the time they complete their initial physical assessment until the start of the intervention at the six-month point. AEs are also assessed by CEP at the time of each physical assessment (baseline, six months and one year) and during strength training.
The risk of an adverse event from pelvic floor exercises, meditation, or social support is so low, that no AEs related to these activities are anticipated.
The study intervention does include home-based aerobic and strength exercises, which pose some possible AEs. Notwithstanding, this is a relatively low-risk group of men (who also have been deemed fit to undergo potentially curative surgery and/or radiotherapy) and all potential candidates will have been screened by the study physician by review of their medical history and through in-person assessment by the CEP to assess cardiovascular contraindications to exercise. Our approach should systematically identify and screen out any individual for whom this study is contraindicated.
It is possible that the participants may experience the following expected non-serious adverse events as a result of participating in this study: musculoskeletal injury (sprain, strain), joint pain, falls, and/or muscle soreness. These will also be listed in the informed

consent form and discussed with the participant prior to their signed consent. Participants will be instructed to contact us immediately if the experience symptoms/events beyond what is typically expected from exercising.
Rare but serious AEs are also possible, however unlikely. Those that may occur during either physical assessment (six-minute walk, sit to stand test, etc.), during the strength training session with the CEP, or during the home-based program include myocardial infarction (heart attack), stroke, unconsciousness, bone fracture or other serious injury. These serious AEs, along with unanticipated adverse events not listed in the protocol or consent form but still believed to be as a result of participation in this study, will be reported according to section 7.1.3.
Events during physical assessment and strength training are rare (<1/100,000 in well men and 1/10,000 in sick men). The CEP will monitor the participants closely in a location with an automatic external defibrillator, five minutes away from the emergency department.
The CEP will provide advice about home-based exercise including the principles of staying within personal physical limits, slowly increasing the intensity of the program over time, and reviewing the warning symptoms of heart attack and stroke.

7.1.2 Indications for Stopping Exercise

The participants will be instructed about when to stop exercising. Absolute Indications to Stop Exercising (during assessment): Suspicion of myocardial infarction, onset of angina (chest pain), signs of poor perfusion (pallor, cyanosis (blue skin), or cold and clammy skin), severe or unusual shortness of breath, central nervous system problems (incoordination, dizziness, confusion, visual problems), participants request to stop, extreme fatigue, skeletal fracture
Relative Indications to Stop Exercising (at home): Increasing chest pain, shortness of breath, wheezing, leg cramps (intermittent claudication), fatigue, signs or symptoms of exercise overload.

7.1.3 Reporting Requirements

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by other means must be recorded in the patient's medical record and in the study's database. Participants will be asked to ensure they have been or will be seen by a physician for full assessment and documentation of the event. All AEs will be reviewed by the Study Physician and PI. The PI is responsible for notifying the REB about the AEs in accordance with local regulations.
Reporting Deaths. All deaths on study will be reported through and including from time of consent for 13 months. The Study Physician will investigate the circumstances of the death and include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of the possible causality. The Study Physician and PI will promptly report these findings to the REB.

Statistically Analysis of Adverse Events: Adverse event rates will be summarized with frequency and percentage within each arm and across arms. The men randomized to the 'late' arm will have a one-time assessment of AE during their first six month 'waiting' period.

9 WITHDRAWAL OF PARTICIPANTS

9.1.1 Protocol Violation

Participants who do not comply with activities outlined in the intervention arm will remain on trial. They will be highly encouraged to complete the six- and 12-month assessments and provide their feedback on the exit interview.

9.1.2 Withdrawal of Participants

Participants are free to withdraw from the trial at any stage without providing a reason and without consequence. If a man withdraws from the study, any data collected on him up to that point in the study will go forward for study analysis. If a man withdraws from the intervention but provides consent to complete subsequent follow up measurements, he will continue to attend study assessments and data will be used for intention-to-treat analysis.

11 PROTECTION OF HUMAN SUBJECTS

11.1.1 Harms

The majority of the practices in the protocol have no possible harms, except exercise. However, exercise has been shown to be a safe and effective means of preventing and improving a multitude of physical and psychological treatment and disease-related side-effects across the cancer trajectory (e.g., on and off treatment). For example, research has shown that cancer survivors who exercise not only have a reduced risk of disease recurrence (75) and all-cause/cancer mortality (75, 76) but also have reduced side-effects of their cancer and/or its treatment such as fatigue (77-79), anxiety (80,81), depression (79, 81), and cancer-related pain (82). Thus, while there is always the risk of increased short-term fatigue, stiffness muscle soreness, and injury with any exercise program, exercise has been shown to be a safe supportive care intervention for cancer patients and survivors and the potential benefits (e.g., improved physical, social and emotional functioning and overall quality of life) outweigh the risks. Furthermore, each participant will be required to have a physician's approval to participate, and our CEP will design an individualized program to minimize risk.

Participants will be asked to fill out several questionnaires regarding their health, substance use, etc. Some participants might find some of these questions uncomfortable,

distressing, or upsetting to answer. Participants can choose not to answer any questions that they do not wish to answer.

There are no known risks with having one's brain waves measured, but some may find the head band around their head uncomfortable. We will do our best to adjust the head band so that it is comfortable on the participant's head. The head band will not cut or mark the skin.

Some participants may also find the procedure of having the muscle activity in their pelvic floor measured with the medical biofeedback apparatus embarrassing or uncomfortable. We will provide participants with a hospital gown to protect their modesty. If participants feel uncomfortable with the procedure, they are free to withdraw from the study at any time without penalty.

In addition, the participants will be told to alert the PI, SP or RC of the study via email or telephone call of any unexpected adverse effects (e.g., exercise induced, mental stress or disease progression may develop). Contact information will be provided to the participants on the first day of the study. Participants will also be encouraged at the training sessions to call and discuss their feelings being unearthed by the process if they feel they want to.

11.1.2 Benefits

As a result of following the 180-day study intervention, participants may experience improved physical fitness, quality of life, lifestyle changes, and social connection. In addition, findings from the current study will improve our understanding of PC and this information will be used to improve the care at NSHA.

11.2.3 Liability

There are no statements in any documents that attempt to limit the liability to which the investigators or affiliated institutions are subject.

11.2.4 Confidentiality

The data will be stored on a secure server with NSHA. Data will be downloaded for analyses by the Principal Investigators, Research Coordinator, and analyzed by a Data Analyst. The computers used for data analyses are password protected and stored in locked offices within the hospital. After study closure, all study related information will be transferred and stored within the Department of Research Services for 7 years. At the end of the retention period, the Department of Research Services will arrange for destruction in accordance with applicable standards.

11.2.5 Disclosure of Any Financial Compensation

Participation in the study is completely voluntarily. Participants will be given no monetary compensation for taking part in this study. Participants will be reimbursed $14.50 for parking for 4 study visits to the hospital.

12 PUBLICATION OF RESEARCH FINDINGS

12.1 Dissemination Plan

We will produce an Interim Annual report on the data collected a year before trial completion and a Complete Annual Report at the end of the trial, release the results of the study to public and media outlets. This is in addition to producing scientific manuscripts on the evaluation of the PC-PEP and the contextual psychosocial determinants of QOL in community members, policy makers and support group representatives. The Soillse Scientist's lab will post updates on a website and allow the free dissemination of Annual reports resulting from this initiative. The members of the research team have demonstrated effective knowledge translation and exchange practices in previous work. We will publish the results of the proposed study in high impact journals and present the results to international conferences. We will train one MSc graduate and one Undergraduate student with the proposed methods and data of this study

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