Pilot and Feasibility Studies

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PTSD Coach as an early mobile intervention to improve cancer-related anxiety and psychosocial oncology uptake in patients newly diagnosed with head and neck cancer: pilot randomized controlled trial

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Abstract

Background This pilot study aimed to provide supportive evidence for the feasibility of conducting a full-scale intervention trial with patients newly diagnosed with head and neck cancer (HNC). This included assessing the acceptability and potential usefulness of the PTSD Coach mobile app as an early self-management intervention that gives information about anxiety symptoms, offers self-assessment of symptoms with feedback, tools to self-manage anxiety, and connects to support.

Methods A three-arm randomized controlled trial was conducted. The primary pilot study questions related to feasibility were: (1) can we recruit enough (i.e., $n=60$ over 8 months or 8/month) and retain a sufficient proportion (i.e., ≥ 85% at three months post-randomization, having completed the primary outcome) of patients with HNC in all trial arms? (2) Will there be at least a 90% completion rate of PTSD Coach within 3 weeks from randomization? (3) Will at least 85% of the content for each module of PTSD Coach be completed? (4) Will there be at least a 90% completion rate of the attention-control tasks (i.e., 45 min/week over 3 weeks)? (5) What would be the anticipated sample size for a full study? (6) We also explored a signal for intervention effects on 1-, 3-, and 6-month levels of cancer-related anxiety, quality of life, anxiety and depression, self-stigma of seeking help, and professional psycho-oncology service uptake.

Results Participants comprised 39 patients (11 experimental group (EG), 13 attention-control (AC), 15 usual care (UC)), primarily male (82%). Enrolment was lower than expected, with strategies implemented to increase the study's participation rate (i.e., shortening the questionnaire, more relevant AC games, pacing study components, and enlarging eligibility to 4 weeks post-diagnosis instead of 2). Retention rates, intervention completion rates, and completion time were adequate. The intervention was acceptable with all patients (100%) who received PTSD Coach reporting

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it a positive experience and that they would recommend it to others. When compared to UC, there was a signal for the PTSD Coach group to report lower 3-month cancer-related anxiety (PCL-S; eta squared = 0.013), lower anxiety and depression (HADS; eta squared = 0.015), anxiety (HADS-A; eta squared = 0.028), and higher functional wellbeing (FACT-FW; eta squared = 0.09), based on effect sizes calculated across all three groups. The sample size for a full study was estimated to be 118 to 154 per group.

Conclusion A repeat pilot study with an expanded oncology population is warranted to further investigate feasibility prior to a full Phase III study. PTSD Coach could be a valuable self-management tool as an initial stepped-care approach intervention in patients newly diagnosed with HNC.

Trial registration ClinicalTrials.gov, NCT03651570. Registered June 26, 2018.

Keywords PTSD, Mobile application, E-intervention, M-health, PTSD Coach, Oncology, Psychosocial uptake, Self-management, Head and neck cancer

Key messages regarding feasibility

• What uncertainties existed regarding the feasibility?

To our knowledge, there has been no previous phase II pilot feasibility randomized controlled trial (RCT) regarding the use of an early intervention with PTSD Coach to reduce anxiety and stigma of seeking help among patients with head and neck cancer (HNC).

• What are the key feasibility findings?

Findings were mixed in terms of feasibility. The intervention was acceptable with all patients (100%) who received PTSD Coach reporting it a positive experience and that they would recommend it to others. Enrolment was lower than expected. Retention rates, intervention completion rates, and completion time were adequate.

• What are the implications of the feasibility findings for the design of the main study?

A repeat phase II pilot RCT with an expanded oncology population (e.g. general oncology patients instead of HNC patients only or including more recruitment sites with the same population) is necessary to demonstrate the feasibility of our intervention prior to a full phase III trial.

Background

Patients with head and neck cancer (HNC) experience some of the highest levels of psychological distress, symptom burden, and morbidity compared to patients in general oncology [1, 2]. Targeting anxiety in patients with HNC may be important early after diagnosis, as it is highly prevalent (i.e., point prevalence of 32% and 22% upon cancer diagnosis and immediately post-treatment [2]) and is a key predictor of longer-term psychologically distressed trajectories and global quality of life (QoL) compromise [3]. This is a novel idea since the current literature tends to focus on the treatment of major depressive disorder (MDD) [3], which typically occurs in the post-treatment period [4]. Given the life-threatening nature of an HNC diagnosis, anxiety is often characterized by increased arousal, intrusive thoughts, emotional numbness, and avoidance, negative alterations in cognition and mood, and marked alteration in arousal and reactivity, symptoms consistent with posttraumatic stress disorder (PTSD) [5]. These symptoms appear in varying degrees in the initial period post-cancer diagnosis [4] and can compromise a variety of outcomes [1]. Despite their high psychological symptom burden, only 31% of patients with HNC seek professional psycho-oncological (PSO) support (i.e., care from a psychiatrist, psychologist, or social worker), with only 44% of those clinically highly anxious seeking this help. In general patients with cancer, PSO under-utilization has been associated with barriers such as stigma around mental health and PSO, inadequate knowledge about availability of services, desire for self-management, and distance for patients living in rural areas [6–8].

PTSD Coach is a free, mobile mental health application (app), developed by the United States Department of Veterans Affairs [7] and translated into French by the Canadian Veterans Affairs and the Department of National Defence and Canadian Mental Health Association [8]. The app can be downloaded on Apple or Android mobile devices. It contains four modules: (1) Learn, (2) Self-Assessment (3) Manage Symptoms, and (4) Find Support. The Learn module consists of psychoeducational information regarding the nature and course of PTSD symptoms, the role of a mental health professional, and how to get help. It has been developed with the goal of providing sound information and destigmatizing mental health care. The Self-Assessment module allows users to track PTSD symptoms (using the PCL; [9]) over time and gives personalized feedback about levels of their symptoms. The Manage Symptoms module provides evidence-based coping tools to help manage a variety of PTSD symptoms including intrusive, avoidant, anxious, depressive, and hyper-arousal (e.g., anger and sleep difficulties) symptoms.

Growing evidence supports the potential for adopting e-interventions in psycho-oncology and their promise

to address barriers to PSO use through information provision, psychoeducation, self-management tools, and personalized feedback on distress levels, among veterans [9] and the general population [10–13]. Furthermore, a pilot study of PTSD Coach, which was adapted for cancer survivors (i.e., Cancer Distress Coach), in 31 patients with lymphoma, breast, or prostate cancer post-treatment [14] has shown acceptability, high satisfaction and usefulness ratings, and a preliminary positive signal for reducing cancer-related anxiety at 4- and 8-week follow-ups. Importantly, 72.4% of patients reported that the app served to destigmatize distress and made them more open towards PSO (69%). To this day, no Phase III randomized controlled trial (RCT) has examined if PTSD Coach could be efficacious in the oncology population.

Considering the emerging literature on the potential impacts of anxiety in patients with HNC as well as the promising results using PTSD Coach in general oncology patients [13], the present pilot study addressed the need to respond to the high levels of anxiety in patients newly diagnosed with HNC and in a proactive manner, while also addressing barriers to PSO uptake in this highly burdened population in a cost-effective, accessible way. We tested an anxiety self-management tool that also addresses stigma as the first step in an eventual stepped-care model with increasing treatment intensity [15], implemented as a routine part of cancer care as promoted in Canadian Partnership Against Cancer guidelines [16]. Given the stigma associated with mental health and possible under-reporting of psychological symptoms by men who are over-represented in the HNC population compared to women by three to one [16], we also measured cortisol and interleukin-6 (IL-6) as bio-immunological indicators for stress. Before completing a full-scale efficacy trial, a pilot trial was needed to determine the feasibility of trial methods and procedures and acceptability of PTSD Coach in this population.

The *primary pilot study questions* were related to feasibility: (1) can we recruit enough (i.e., $n=60$ over 8 months or 8/month) and retain a sufficient proportion (i.e., $\geq 85\%$ at 3 months post-randomization, having completed the primary outcome) of patients with HNC in all trial arms to allow completion of a full study in a timely fashion? (2) Will there be at least a 90% completion rate of PTSD Coach within 3 weeks from randomization (pre-treatment, chosen as we plan to use PTSD Coach as early as the time when patients are newly diagnosed with HNC)? (3) Will at least 85% of the content for each module of PTSD Coach be completed? (4) Will there be at least a 90% completion rate of the attention-control tasks (i.e., 45 min/week over 3 weeks)? (5) What would be the anticipated sample size for a full study? (6) We *explored a signal for intervention effect* on 1-, 3-, and 6-month levels of cancer-related anxiety, quality of life, anxiety and depression, self-stigma of seeking help, as well as professional psycho-oncology service uptake.

Methods

Design

We conducted a Phase II pilot study of a parallel three-arm RCT [17, 18] with patients newly diagnosed with HNC. The EG received usual care plus PTSD Coach, the AC received usual care plus a game app, and the usual care group (UC) received usual care alone. Recruitment, retention, and completion parameters were tracked throughout the study. Self-report questionnaires were completed at baseline and 1-, 3- (primary), and 6-months post-randomization. The design followed the 2008 CONSORT Guidelines for conducting trials assessing non-pharmacologic treatments [17, 18] as well as the extension for pilot RCTs [19].

Eligibility and exclusion criteria

Inclusion criteria

Patients were (1) newly diagnosed with HNC (all HNC sites; TNM Classification [20]); first occurrence, progression, or recurrence) within 2 weeks at referral; (2) willing to complete PTSD Coach or the Game app within 3 weeks as they awaited treatment onset; (3) 18 years or older; (4) alert and capable of giving free and informed consent; (5) able to speak and read English or French.

Exclusion criteria

Patients were excluded if they had a Karnofsky Performance Status (KPS) [21, 22] score of less than 60 (measures functional status and is a prognosis indicator; rated by referring oncologists/nurses or Research Coordinator (RC)) or expected survival less than 6 months according to medical judgment. Excluding patients with the poorest performance status at baseline was important to minimize the drop-out rate due to health deterioration [23–26].

Recruitment

Physicians and nurses working in the Otolaryngology–Head and Neck Surgery (OHNS) clinics at two McGill University-affiliated hospitals, Jewish General Hospital and McGill University Health Centre, were asked to identify and refer potential patients. Records of consecutive patients were kept tracking the reasons for patient ineligibility and refusals.

Data collection

Study patients were evaluated at 4 time points (baseline, 1-, 3-, and 6-month post-randomization). Baseline questionnaires were completed immediately after informed

consent was given, with the research assistant (RA) present to answer questions. Patients completed the post-intervention questionnaires at home and mailed them to the RC in a pre-stamped, pre-addressed envelope. The RC reminded patients to complete questionnaires using a standardized script. Saliva and blood samples were collected at baseline and at 1 month follow-up, as described below. The 1-month follow-up questionnaire comprised a Pilot Study Questionnaire (PSQ) with open-ended questions to measure acceptability. We tracked treatments received at the hospitals during the follow-up via chart reviews and self-reports.

Randomization

All researchers and research staff were blind to the randomization sequence (ratio 1:1:1), carried out in random permuted blocks of 2, 4, and 6 using a web-based central randomization system (CRS) from an office unconnected with study conduct, as per CONSORT 2010 Statement [27, 28]. Group allocation took place immediately after consent was obtained. The RA informed patients of their group allocation once they had completed their baseline questionnaires. EG (or AC) patients then assisted in downloading PTSD Coach (or Game app), either on their smartphone or on a device that we lent them for use during the study (i.e., over 6 months).

Conditions

Experimental Intervention Group (EG)—PTSD Coach

During the initial meeting, patients were provided with informed consent and completed questionnaires. PTSD Coach was then downloaded onto the patient's or study-provided mobile device. Patients were shown how to use the app and were asked to complete at least one module per week (2 modules in the first week) for a total of 4 modules. Patients used the app (as in the AC) while waiting for appointments (average wait of 45 min) and were able to use it freely when at home.

Attention control group (AC) intervention—game app

AC patients were assigned to three apps involving playing a game (i.e., Candy Crush, Tetris, or Tiny Wings), during the waiting time before and between medical treatments in the hospital, on the same weekly schedule as the experimental group. The apps contained no element of PTSD Coach and were selected based on popularity and capacity to interest. Patients were asked to use each app for 15 min in succession, during a 45-min weekly session over 3 weeks, as in the EG.

Usual care control group (UC)

Participating recruitment centers were already offering a best-of-care approach. They were large university-affiliated hospitals (McGill University Health Centre and Jewish General Hospital) with well-established PSO services (including psychiatrists, psychologists, social workers, nurses, and volunteers). However, the OHNS Departments did not offer systematic interventions on anxiety and self-management, nor did any intervention address stigma.

Other support

All patients were free to use hospital- or community-based supports, which were tracked throughout the study.

Feasibility and acceptability measures

Feasibility was assessed by participant enrolment rate and retention rate at 1-month, 3-month, and 6-month follow-up, completion rates of PTSD Coach within 3 weeks from randomization, of PTSD Coach content, and AC completion time as planned. Progression criteria (i.e., criteria that, if they are met, indicate that a larger phase III trial is feasible), included (1) recruiting enough (i.e., $n=60$ over 8 months or 8/month) and retaining a sufficient proportion (i.e., $\geq 85\%$ at 3 months post-randomization, having completed the primary outcome) of patients with HNC in all trial arms; (2) at least 90% completion rate of PTSD Coach within 3 weeks from randomization; (3) at least 85% of the content for each module of PTSD Coach are completed; (4) at least 90% completion rate of the attention-control tasks (i.e., 45 min/week over 3 weeks). Acceptability was assessed through a Pilot Study Questionnaire (PSQ) designed for this study and administered at the 1-month follow-up, with questions adapted from the Client Satisfaction Questionnaire–8 [29] and open-ended questions to assess PTSD Coach strengths and weaknesses. This questionnaire also collected information regarding whether participants felt they benefitted from the application and would recommend it to others.

Treatment adherence

Data on usage was captured through a patient journal to note the date and time used, ensuring inter-group dose equivalency between EG and AC conditions (at least 45 min per week over 3 weeks; scripted prompts if needed). Patients were contacted weekly to collect this information. RAs reminded patients to use the app when they presented to their appointments. PTSD Coach would be deemed feasible if at least 85% of the content for each module had been completed.

Addressing bias

First, while patients were not blinded to their assigned group, details about the intervention were kept minimal, omitting the word "PTSD Coach" from consent forms to avoid prompting patients to use the program if they are

assigned to the AC or UC. Second, healthcare providers and investigators were blind to group allocation and questionnaire data during the pilot (only the RAs saw the data, for data checking and data entry). Patients receiving PTSD Coach were instructed not to discuss the intervention with other patients and staff, which was assessed through questions in follow-up questionnaires. Finally, we monitored the use of the apps through journaling (i.e., daily minutes used) in the EG and AC groups with benchmarks for adherence and equivalency.

Exploratory measures

Measures were selected based on psychometric properties, paper-pencil self-administration, and use with patients with HNC. All measures give continuous scores. *Cancer-Related Anxiety.* Anxiety symptoms were assessed with the PCL-S [30, 31], a 17-item self-report measure covering PTSD symptoms of intrusive negative thoughts, avoidance of negative thoughts, and hyperarousal [32] over the past week on a 5-point scale ranging from 1="not at all" to 5="extremely". Total scores range from 17 to 85 and a 10–20-point change is considered clinically meaningful (Internal consistency: 0.87–0.94; Test-retest reliability: 0.92 (immediate), 0.87-0.88 (1 week)). The *Functional Assessment of Cancer Therapy–General (FACT-G)* [33] was used to assess QoL, as well as physical and functional well-being (total score; internal consistency: 0.89, test-retest reliability: 0.92). The *Hospital Anxiety and Depression Scale (HADS)* [34, 35] was used to measure psychological distress. It contains two 7-item subscales (anxiety and depression) and does not rely on physical symptoms such as fatigue and weight loss, which typify both depression and advanced cancer (Internal consistency: 0.78–0.93 [36]; Test-retest reliability: 0.80 [36]). The *Self-Stigma of Seeking Help* (SSOSH) is a 10-item scale used to assess self-stigma associated with seeking psychological help. Each item ranges from 1=strongly disagree to 5=strongly agree (internal consistency: 0.91, test-retest reliability: 0.72) [37]. *Rates of PSO Program uptake* (psychiatry, psychology, and social work) were collected via chart review.

Biological samples

Cortisol and IL-6 concentrations

Salivary cortisol. Saliva is considered a reliable and valid measure of unbound biological active blood cortisol [38]. Cortisol was measured 4 times per day for 2 days at baseline and at 1-month follow-up using salivate. This allows the calculation of the average slope over the 2-day sample period. Saliva time was standardized, and the samples were collected by patients themselves at home upon awakening and at 30 min post-awakening, 4 p.m., and 9 p.m., via children's swab. They sent the samples via mail (provided envelope) or brought them directly to the research lab upon their next hospital visit. Participants used the Salimetrics kit recommendations for collection. *Serum IL-6.* Blood samples (4 ml) were collected using a serum separator tube at baseline and at 1 month follow-up [39].

Sociodemographic and medical information

To describe the sample, a questionnaire was used to collect information about sociodemographic data, physical level of functioning (ECOG performance status) [40], and group allocation preference. At each evaluation point, professional psychological support (individual, couple, or group psychotherapy, psychiatric medication) used outside the protocol was documented via questionnaire and chart review. Illness and treatment information was gathered through medical charts at each evaluation point (date of diagnosis, disease stage I–IV, surgery, radiotherapy, chemotherapy).

Use of anxiolytic/antidepressant medication and psychosocial support (individual/couple/group; frequency/duration) were tracked in all groups throughout the study via questionnaire and chart review. For the psychotropic and psychotherapy variables, we constructed a summative score per person tallying the endorsement of treatments received since baseline. For example, the psychotherapy 1-month count variable could range from 0 (did not receive any since baseline) to 1 (received treatment between baseline and 1 month); the psychotherapy 3-month count could range from 0 (did not receive any since baseline), 1 (received treatment either at 1 month or at 3 months), or 2 (received treatment at both 1 and 3 months); and the psychotherapy 6-month count could range from 0 (did not receive any since baseline), 1 (received treatment at one endpoint), 2 (received treatment at two endpoints), or 3 (received treatment at all 3 endpoints).

Sample size rationale

We planned to recruit 60 participants (20 per arm) in our Phase II pilot, offering acceptable precision in attrition rate estimates in pilot studies and allowing a manageable number of participants to recruit. It would also allow for confirmation of the estimate of the standard deviation [41]. To estimate the sample size for a full study, we first calculated the 80% upper confidence limit (CL) for the baseline s.d. on the PCL-S, our primary outcome. This upper limit s.d. is considered a necessary conservative parameter for use in power calculations, as s.d. is known to be notoriously unreliable in small samples) [41]. Informed by this value, we then calculated the anticipated sample size using G*Power 3.1 [42] and an effect size (Cohen's *d*) of 0.40, comparable to other e-health

interventions [43–45], with 80% power, alpha 0.05 (two-tailed test), and a 15% to 35% attrition rate.

Statistical analysis

Analyses were conducted using SPSS version 29 [46]. Feasibility and acceptability indicators were analyzed using frequencies and percentages. For scale scores, the main analysis involved ANCOVA to gauge potential experimental group differences on each endpoint outcome, controlling for baseline. We also report eta squared as a measure of effect size when more than two groups are involved (small eta squared is 0.01, medium 0.06, and large 0.14). Eta squared refers to the proportion of variation in the outcome explained by the independent variable trial group.

Results

Feasibility

We recruited 39 participants over a 16-month period: 11 were randomly assigned to the experimental group (EG), 13 to the attention-control (AC), and 15 to the usual care (UC). An average of 2.4 participants were recruited per month with an overall enrolment rate of 40% (see Fig. 1). Participants were mostly men (82%). Nearly 80% ($n=31/39$) owned a smartphone. Other sociodemographic characteristics can be found in Table 1.

One-third into recruitment, we made minimal changes to our study including shortening the questionnaire, including more relevant games in the AC group (i.e., adding Solitary and Sudoku), pacing the introduction of study components (questionnaire and biological samples) to avoid overwhelming participants, and enlarging eligibility to 4 weeks post-diagnosis instead of 2. Accordingly, in the last 3 months, we were able to significantly increase our recruitment rate to 65%. The most effective recruitment strategy was the direct presence of RAs in the clinics (100% recruited this way; 0% via posters and direct physician/nurse referrals).

The 1-month timepoint had a good retention rate (85%; EG 73%, AC 77%, UC 100%) followed by 72% at 3 months and 62% at 6 months post-randomization. Half of the drop-outs by 1 month were due to health deterioration. The proportion of randomized patients using PTSD Coach was 73% with drop-outs having occurred early prior to intervention onset; 100% of those who started PTSD Coach proceeded to complete it within 3 weeks from randomization (see Fig. 1). More than 85% of the content for each module of PTSD Coach was completed. Time to complete PTSD Coach was on average 20 min per week over 3 weeks instead of the originally planned 45 min per week. Time for the AC game app was corrected to be on average 20 min per week over 3 weeks; 77% of randomized AC patients started the attention-control tasks and 100% of those who began, completed their assignments. No patient reported speaking to other patients or staff (for the EG) or hearing from other patients or staff about the intervention (for the AC and UC).

For the exploratory biological measurements, salivary cortisol collection was completed by 77% at baseline with 70% completion at 1-month post-randomization, compared to blood sampling acceptance (69% baseline; 44% 1-month).

Acceptability

Based on our Pilot Study Questionnaire (PSQ) all patients (100%) who received PTSD Coach reported it a positive experience and would recommend it to others in a similar situation. They reported the sessions as helpful in open-ended questions, analyzed through thematic analysis: patients became more aware and better understood their anxiety, they learned about the impact of stress on their treatment experience, they learned new tools to manage stress, and became aware and were appreciative of the availability of professional help. PTSD Coach modules 2 and 3 were preferred since they evaluated and gave informative feedback about distress levels and tools to help reduce it.

Signal for impact

See Table 1 for descriptive statistics for all outcomes and Table 2 for estimated mean differences, controlling for baseline, comparing EG vs. AC and EG vs. UC groups.

For the PCL-S at the primary endpoint of 3 months, the estimated difference between EG vs. AC groups was −3.69, CI (−17.66, 10.29) and between EG vs. UC was −2.13, CI (−13.70, 9.43), adjusted for baseline. These contrasts showed a small positive signal for PTSD Coach, with an eta squared of 0.013. At 6 months on the PCL-S, the signal appeared to strengthen, with a medium to large eta squared of 0.105. See Fig. 2 for a plot of the mean differences on PCL-S between EG vs. UC groups at each time point adjusted for baseline, as well as a plot of the mean differences between EG vs. AC groups.

Mean differences in the secondary outcomes of quality of life and HADS showed a positive signal for the PTSD Coach group. Focusing on the 3-month outcomes, the EG showed potential contrasts in the expected direction against both AC and UC groups on FACT Functional Wellbeing subscale, with a medium to large eta squared of 0.09, HADS Total, with a small eta squared of 0.015, and HADS Anxiety, with a small to medium eta squared of 0.028 (see Table 2).

There was a signal for the EG group to receive fewer treatments than the AC group, for psychotropic medications at 1 month, psychotherapy at 3 months, and

Table 1 Sociodemographic, medical, and clinical characteristics of patients newly diagnosed with head and neck cancer participating in the PTSD Coach trial

Variables	Total ($n=39$) M (SD)/n (%)	EG ($n=11$) M (SD)/n (%)	AC ($n=13$) M (SD)/n (%)	UC ($n=15$) M (SD)/n (%)
Sociodemographic				
- Age	56.4 (11.1)	57.5 (9.00)	55.1 (12.0)	56.8 (12.0)
- Sex (male)	32/39 (82.1)	8/11 (72.7)	12/13 (92.3)	12/15 (80.0)
- University education attainment	20/39 (51.3)	8/11 (72.7)	5/13 (38.5)	7/15 (46.7)
-Born in Canada	25/39 (64.1)	7/10 (70.0)	10/13 (76.9)	8/15 (53.3)
- Living alone	16/39 (41.0)	3/11 (27.2)	5/13 (38.5)	8/15 (53.3)
Medical Variables				
- Advanced stage (III/IV)	23/39 (59.0)	7/11 (63.6)	7/13 (53.8)	9/15 (60.0)
- Tumour site				
Oropharynx	24/39 (61.2)	7/11 (63.6)	9/13 (69.2)	8/15 (53.3)
Oral	3/39 (7.7)	1/11 (9.1)	1/13 (7.7)	1/15 (6.7)
Larynx/ hypopharynx	2/39 (5.1)	2/11 (18.2)	-	-
Nasopharynx	3/39 (7.7)	-	2/13 (15.4)	1/15 (6.7)
Nasal/ paranasal	3/39 (7.7)	-	1/13 (7.7)	3/15 (20.0)
Salivary	2/39 (5.1)	1/11 (9.1)	-	1/15 (6.7)
Other	1/39 (2.6)	-	1/13 (7.7)	-
Unknown	1/39 (2.6)	-	-	1/15 (6.7)
Physical function—Eastern Cooperative Oncology Group (ECOG 2+)				
Oncology Group (ECOG 2+)	5/38 (13.2)	1/11 (9.1)	3/13 (23.1)	1/15 (6.7)
Primary outcome				
Cancer-Related Anxiety (PCL-S)				
PCL-S baseline	32.0 (14.0)	26.8 (12.0)	39.6 (16.1)	29.1 (10.9)
PCL-S 1 month	29.6 (12.4)	25.5 (9.2)	31.8 (12.9)	30.4 (13.7)
PCL-S 3 months	31.4 (14.1)	27.1 (15.0)	37.3 (15.3)	30.6 (13.0)
PCL-S 6 months	27.2 (9.5)	21.7 (5.4)	29.9 (9.1)	28.5 (10.8)
Secondary outcomes				
Rates of psychosocial oncology program uptake				
Psychotherapy baseline	14/39 (35.9)	4/11 (36.4)	6/13 (46.2)	4/15 (26.7)
Psychotherapy 1 month	13/33 (39.4)	2/8 (0.25)	6/10 (60.0)	5/15 (33.3)
Psychotherapy 3 months	10/28 (35.7)	1/7 (14.3)	5/7 (71.4)	4/14 (28.6)
Psychotherapy 6 months	8/24 (33.3)	0/6 (0.0)	4/7 (57.1)	4/11 (36.4)
Psychotherapy total 1 to 6 months	12/23 (52.2)	1/6 (16.7)	6/6 (100.0)	5/11 (45.5)
Psychotropic baseline	10/39 (25.6)	3/11 (27.3)	3/13 (23.1)	4/15 (26.7)
Psychotropic 1 month	8/33 (24.2)	1/8 (12.5)	5/10 (50.0)	2/15 (13.3)
Psychotropic 3 months	10/28 (35.7)	1/7 (14.3)	5/7 (71.4)	4/14 (28.6)
Psychotropic 6 months	6/24 (0.25)	0/6 (0.0)	3/7 (42.9)	3/11 (27.3)
Psychotropic total 1 to 6 months	9/23 (39.1)	2/6 (33.3)	3/6 (50.0)	4/11 (36.4)
Functional Assessment of Cancer Therapy (FACT)				
FACT-General (FACT-G) baseline	2.73 (0.6)	3.0 (0.6)	2.4 (0.5)	2.8 (0.7)
FACT-G 1 month	2.8 (0.7)	2.9 (0.7)	2.7 (0.7)	2.7 (0.7)
FACT-G 3 months	2.7 (0.6)	2.9 (0.7)	2.4 (0.5)	2.7 (0.6)
FACT-G 6 months	2.9 (0.5)	2.9 (0.6)	2.6 (0.3)	3.0 (0.5)
FACT-G + Head and Neck (HN) baseline	2.4 (0.5)	2.6 (0.4)	2.2 (0.3)	2.5 (0.5)
FACT-G + HN 1 month	2.4 (0.5)	2.5 (0.5)	2.4 (0.5)	2.4 (0.6)
FACT-G + HN 3 months	2.40 (0.4)	2.5 (0.5)	2.2 (0.4)	2.4 (0.4)
FACT-G + HN 6 months	2.54 (0.3)	2.6 (0.2)	2.4 (0.3)	2.6 (0.4)
FACT Physical Wellbeing (PW) baseline	2.78 (1.0)	3.1 (1.1)	2.3 (0.8)	3.0 (1.1)
FACT PW 1 month	2.94 (1.0)	3.2 (1.2)	2.7 (0.7)	2.9 (0.9)

Table 1 (continued)

Variables	Total (*n* = 39) M (SD)/n (%)	EG (*n* = 11) M (SD)/n (%)	AC (*n* = 13) M (SD)/n (%)	UC (*n* = 15) M (SD)/n (%)
FACT PW 3 months	2.85 (0.7)	3.1 (0.9)	2.6 (0.8)	2.9 (0.6)
FACT PW 6 months	3.16 (0.6)	3.4 (0.7)	2.9 (1.1)	3.2 (0.4)
FACT Functional Wellbeing (FW) baseline	2.45 (0.9)	2.7 (0.9)	2.1 (0.6)	2.6 (0.8)
FACT FW 1 month	2.35 (1.0)	2.6 (1.0)	2.4 (0.5)	2.2 (1.0)
FACT FW 3 months	2.22 (0.8)	2.6 (0.7)	1.7 (2.2)	2.3 (0.9)
FACT FW 6 months	2.5 (0.9)	2.8 (1.0)	2.0 (3.4)	2.6 (0.9)
Hospital Anxiety and Depression Scale (HADS)				
HADS Total baseline	21.2 (2.4)	20.6 (2.8)	21.7 (3.2)	21.2 (2.2)
HADS Total 1 month	21.2 (3.5)	20.6 (2.8)	21.4 (2.1)	21.4 (4.0)
HADS Total 3 months	19.6 (3.5)	18.6 (2.4)	20.3 (3.7)	19.7 (4.1)
HADS Total 6 months	20.5 (3.2)	20.8 (3.1)	20.3 (4.2)	20.4 (4.0)
HADS Anxiety baseline	7.5 (3.5)	6.5 (3.7)	8.1 (3.0)	7.8 (3.3)
HADS Anxiety 1 month	7.4 (3.7)	6.5 (3.3)	7.9 (3.2)	7.6 (3.6)
HADS Anxiety 3 months	6.4 (3.3)	4.7 (3.7)	7.4 (2.3)	6.7 (3.2)
HADS Anxiety 6 months	6.6 (3.1)	5.7 (3.7)	7.1 (2.8)	6.7 (2.8)
HADS Depression baseline	13.7 (2.1)	14.1 (2.1)	13.6 (2.3)	13.4 (2.0)
HADS Depression 1 month	13.8 (2.4)	14.1 (1.1)	13.3 (2.8)	13.8 (2.8)
HADS Depression 3 months	13.4 (2.9)	13.9 (2.5)	13.7 (2.3)	13.0 (3.4)
HADS Depression 6 months	13.9 (2.4)	15.2 (1.3)	13.1 (3.0)	13.6 (2.3)
Self-Stigma of Seeking Help (SSOSH)				
SSOHS Baseline	17.1 (2.4)	16.8 (2.8)	16.8 (0.8)	17.6 (2.8)
SSOHS 1 month	18.3 (5.3)	16.3 (2.5)	16.0 (2.0)	20.1 (6.6)
SSOHS 3 months	17.9 (2.1)	16.8 (1.1)	18.5 (2.1)	18.5 (2.6)
SSOHS 6 months	17.6 (2.7)	17.5 (1.7)	20.0 (1.4)	16.6 (3.3)

psychotherapy at 6 months; with large eta squared values ranging from 0.07 to 0.26. More people seemed to have received psychotherapy from 1-6 months in the UC (45.5%) compared to the EG (16.7%), as well as potentially more people taking psychotropic medication in the UC (28.6%) compared to the EG (14.3%) at 3 months (see Table 1, cf. Table 3).

The 80% upper confidence limit for the baseline s.d. on the PCL-S was used to inform the sample size calculation for the full study [41]. The baseline s.d. was 14 and the 80% upper CL $= \sqrt{[(n-1)^{*}s^2/\chi^2_{0.10,df}]} = \sqrt{[(39\text{-}1) \times 14^2/27.34]} = \sqrt{38 \times 196/27.34} = \sqrt{272.42} = 16.51$. A 6.5-point difference between the two independent groups would be close to an effect size of 0.40 (i.e., 6.5/16.51). Using G*Power, [42] the ability to detect an effect size of 0.40 with 80% power would require a sample size of 100 per group. Factoring in 15% to 35% attrition, we would need to recruit a baseline sample size of 118 to 154 per group.

Discussion

To our knowledge, this is the first study to examine the feasibility and acceptability of an early intervention with PTSD Coach in patients newly diagnosed with head and neck cancer. The intervention was deemed acceptable to patients. Fewer patients were eligible and recruitment was slower than expected, i.e., a recruitment rate of 2.4 participants per month compared to the anticipated 8 per month set as the stop/go cut-off for progression, representing an observed recruitment of 30% of the required level for progression. Our overall participation rate was 40%, with an increase in participation to 65% once we implemented changes such a shortening the questionnaire, including more relevant games in the AC group, pacing study components introduction (questionnaire and biological samples), and enlarging eligibility to 4 weeks post-diagnosis instead of 2. The 1-month timepoint had a good retention rate (85%; EG 73%, AC 77%, UC 100%) followed by 72% at 3 months and 62% at 6-month post-randomization; below the anticipated 85%. Seventy-three percent of participants allocated to PTSD

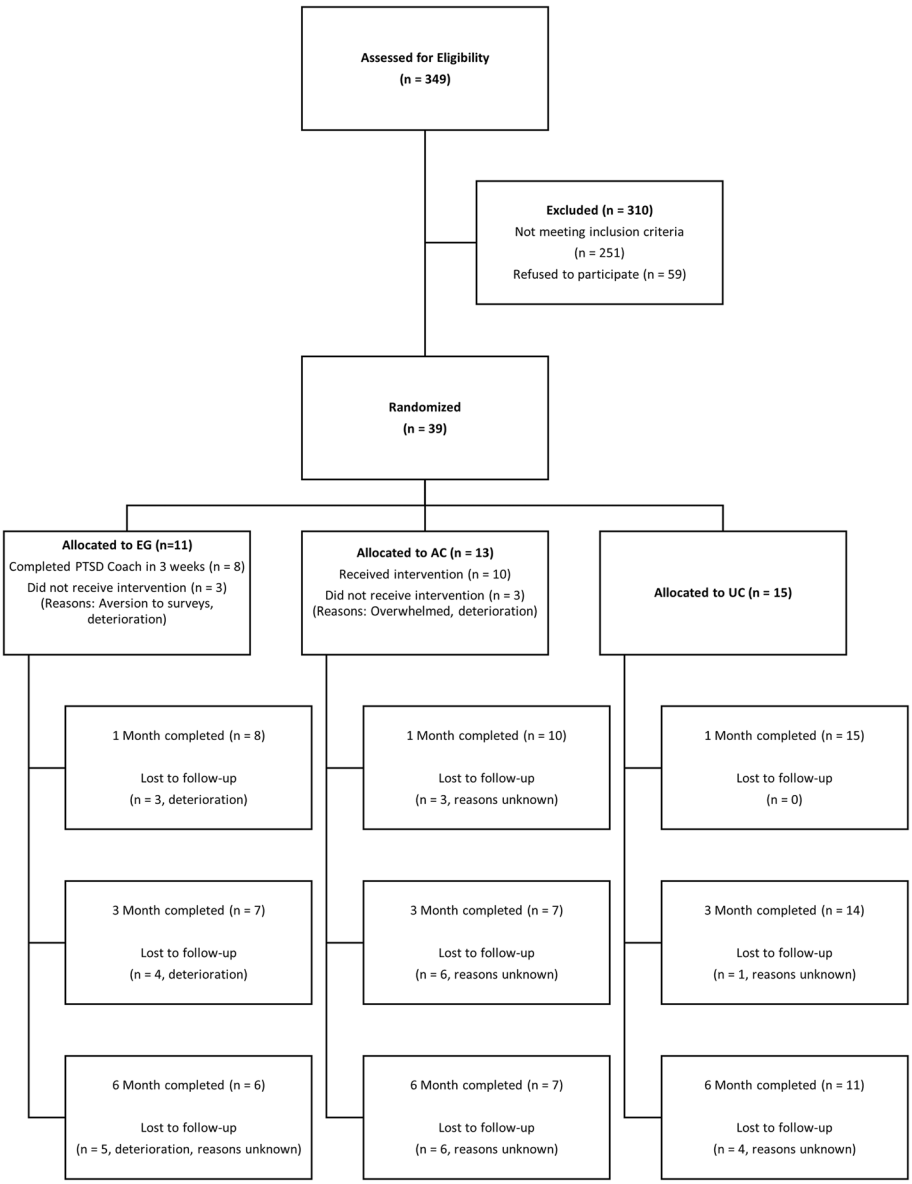

Fig. 1 Flow diagram

Coach started the intervention; once started 100% completed it within 3 weeks from randomization, in higher proportion than the 90% criterion, with more than 85% of the content completed for each module. Seventy-seven percent of AC participants started the attention-control tasks and 100% of the individuals who started, completed their assignments (i.e., time corrected to 20 min/week to correspond to EG exposure). Considering the slower pace of recruitment than originally planned, we would need to enlarge our study population to include either additional HNC clinics or additional cancer sites with other cancer types of newly diagnosed patients to demonstrate feasibility. Feasibility could also be improved with design alterations that may include running a two-arm trial for greater power, changes in eligibility criteria, adding remuneration of participants, or the choice of comparison conditions, such as integrating PTSD Coach to therapy versus therapy alone [47].

We found what appeared to be a medium to large effect size of an early intervention with PTSD Coach on cancer-related anxiety at 6 months, and a moderate effect size on general anxiety at 3 months. This is in line with previous studies in the general population [13] and general oncology patients [14], which all found associations

Table 2 Mean differences adjusted for baseline for quality of life and affective outcomes

Outcome	EG-UC M diff	Lower 95% CL	Upper 95% CL	EG-AC M diff	Lower 95% CL	Upper 95% CL	Eta squared
PCL-S 1 month	-4.38	-13.56	4.80	0.56	-9.99	11.11	0.053
PCL-S 3 months	-2.13	-13.70	9.43	-3.69	-17.66	10.29	0.013
PCL-S 6 months	-6.04	-14.45	2.36	-5.10	-14.54	4.33	0.105
FACT-G 1 month	0.02	-0.51	0.55	-0.14	-0.73	0.45	0.017
FACT-G 3 months	-0.18	-0.63	0.26	0.14	-0.36	0.63	0.111
FACT-G 6 months	-0.32	-0.77	0.13	-0.08	-0.57	0.41	0.151
FACT-G + HN 1 month	-0.07	-0.44	0.31	-0.18	-0.60	0.24	0.029
FACT-G + HN 3 months	-0.18	-0.46	0.10	-0.03	-0.36	0.30	0.107
FACT-G + HN 6 months	-0.19	-0.41	0.04	0.01	-0.23	0.25	0.279
FACT PW 1 month	0.15	-0.67	0.97	0.31	-0.57	1.18	0.019
FACT PW 3 months	-0.03	-0.64	0.59	0.35	-0.34	1.04	0.077
FACT PW 6 months	-0.03	-0.70	0.64	0.27	-0.45	0.99	0.061
FACT FW 1 month	0.33	-0.48	1.13	-0.19	-1.09	0.72	0.063
FACT FW 3 months	0.25	-0.42	0.93	0.61	-0.19	1.41	0.094
FACT FW 6 months	-0.02	-0.80	0.76	0.45	-0.44	1.34	0.088
HADS Total 1 month	-0.55	-3.64	2.54	-0.19	-3.68	3.30	0.005
HADS Total 3 months	-0.67	-4.22	2.87	-1.21	-5.46	3.03	0.015
HADS Total 6 months	1.58	-1.92	5.08	1.88	-2.00	5.76	0.055
HADS Anxiety 1 month	-0.62	-3.59	2.34	-0.77	-4.00	2.45	0.009
HADS Anxiety 3 months	-0.74	-3.54	2.06	-1.29	-4.52	1.93	0.028
HADS Anxiety 6 months	0.35	-2.72	3.42	-0.39	-3.66	2.88	0.015
HADS Depression 1 month	0.09	-1.93	2.11	0.80	-1.43	3.03	0.025
HADS Depression 3 months	0.49	-2.39	3.37	0.27	-3.13	3.68	0.005
HADS Depression 6 months	1.18	-1.06	3.42	2.11	-0.32	4.55	0.141

CL confidence limit, *PCL* PTSD Checklist–Specific, *FACT-G* Functional Assessment of Cancer Therapy–General, *FACT-PW* Functional Assessment of Cancer Therapy–Physical wellbeing subscale, *FACT-FW* Functional Assessment of Cancer Therapy–Functional wellbeing subscale, *HADS* Hospital Anxiety and Depression Scale

Insufficient follow-up sample sizes for Self-Stigma of Seeking Help (SSOHS) scale for analysis

between PTSD Coach and reduced PTSD symptoms. The AC seemed to present with higher psychosocial oncology consultations. This contrast would merit further exploration and may be an artifact of the study design, with AC participants being potentially sensitized to psychosocial resources and services through participation in this study and more motivated to consult.

There are important clinical implications of addressing anxiety and barriers to psychosocial oncology service access early on in the cancer trajectory of patients with HNC. First, this population is known to experience particularly high levels of distress, as well as has been identified as being at risk for suicide. An early identification of distress within this context can help buffer the stress of treatments. The built-in retroaction on levels of distress provided to patients through PTSD Coach, together with de-stigmatization of mental health and the provision of self-management tools, can increase awareness, motivation, and capability towards optimizing one's coping. The locus of control can then shift from being focused on cancer and treatment effects on the body to one's reactions to this stress, thus helping people achieve an increased sense of mastery and control in the face of adversity. Second, research has shown that early levels of anxiety predict physical symptom burden and function in the immediate post-treatment. One may want to further study the mechanisms of this association through well-designed intervention studies combining functional neuroimaging, psychiatric genetics, and immunological processes, which could lead to the tailoring of supportive approaches in line with personalized medicine.

A recent meta-analysis of 16 primary studies supported that PTSD Coach is a feasible and acceptable intervention in populations who have experienced trauma (such as a recent diagnosis and treatment of HNC) [47]. More specifically in the HNC population, early intervention with PTSD Coach should be viewed in the context of a stepped-care approach. By doing so, we aim to harness technology as a means for the provision of psychoeducation and first-level resources on which to build to optimize PSO care. Much is to be learned about the barriers to PSO support within the context of a stepped-care

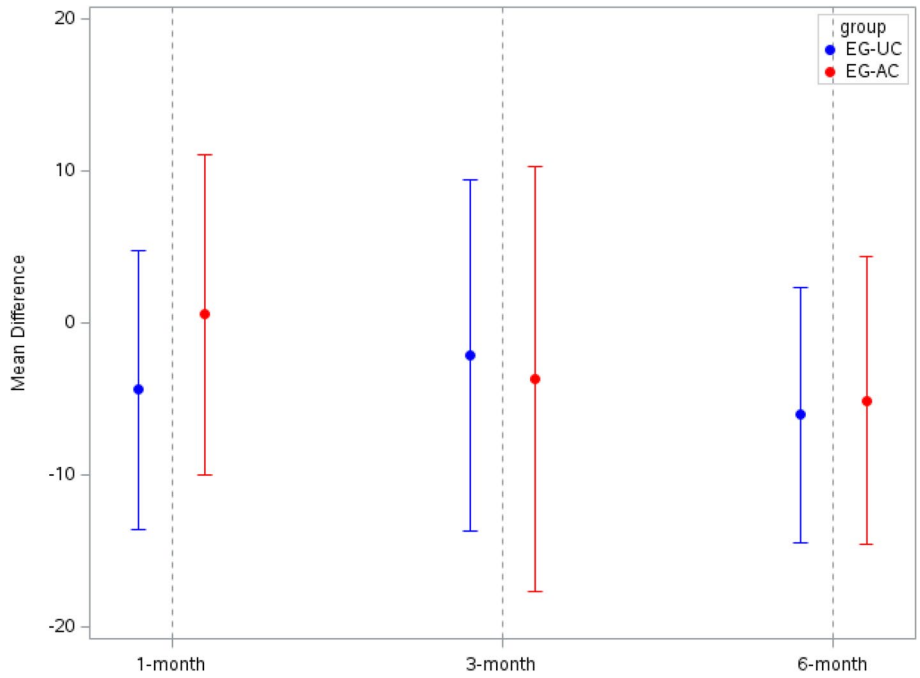

Fig. 2 Plot of mean differences on PCL-S between EG vs. UC and EG vs. AC groups with 95% confidence intervals, adjusted for baseline

Table 3 Mean differences adjusted for baseline for psychotropic and psychotherapy count outcomes

Outcome	EG-UC M diff	Lower 95% CL	Upper 95% CL	EG-AC M diff	Lower 95% CL	Upper 95% CL	Eta squared
Psychotherapy count 1 month	-0.11	-0.54	0.32	-0.32	-0.79	0.15	0.066
Psychotherapy count 3 months	-0.36	-1.15	0.44	-0.93[a]	-1.85	-0.01	0.156
Psychotherapy count 6 months	-0.43	-1.52	0.66	-1.50[a]	-2.78	-0.22	0.256
Psychotropic count 1 month	0.001	-0.29	0.29	-0.35[a]	-0.66	-0.03	0.219
Psychotropic count 3 months	0.05	-0.41	0.52	-0.43	-0.96	0.11	0.167
Psychotropic count 6 months	-0.08	-0.71	0.54	-0.50	-1.20	0.20	0.123

CL confidence limit

[a] Statistically significant

approach in oncology, and the components that are necessary to include as part of the first level of intervention. Notably, one may want to consider additionally targeting depression and tobacco/alcohol/substance abuse/dependency, considering their high prevalence [3] and how they are involved in negatively influencing outcomes [47].

Our study presents some limitations. First, our pilot study was limited by the initially low participation rate, which may have introduced a selection bias. Even if participation rates are higher in our study than those of previous trials in patients with HNC and were increased by the introduction of strategies during the trial, a future enlarged study would need to track characteristics of patients refusing participation to monitor any potential bias. Second, at 6 months, more than one-third of participants had dropped out of the study (the most common reason being health deterioration). It may be important to add certain study modifications to limit this attrition over time, such as introducing new eligibility criteria or limiting questionnaire completion to the primary outcome only for patients experiencing health deterioration. Third, there were low baseline levels of cancer-related anxiety in the sample, which may impact the ability to observe significant improvements. One would need to ensure that people with high levels of distress are represented in our sample and that responses to the questionnaire are not impacted by social desirability or gender norms. While our intention was to provide PTSD Coach as a first-level intervention as part of a stepped-care approach, one may want to consider including only patients with clinically elevated stress for the purpose of a trial.

In conclusion, our pilot study has demonstrated acceptability but design changes are needed to improve study feasibility. While early intervention with PTSD Coach seemed to present a signal for reduced anxiety, depressive symptoms appeared to be higher, possibly in the context of the intervention targeting anxiety alone or of decreased psychotropic medications and psychotherapy. A repeat pilot study is warranted with either additional HNC clinics, an enlarged patient population to general oncology, or a different design to demonstrate feasibility for an eventual phase III RCT. Multi-site efforts are key if we are to have what would appear to be a potential preventive impact on levels of distress and positive impact on quality of life in this known to be vulnerable oncologic population.

Abbreviations

AC	Attention-control
ANCOVA	Analysis of covariance
CL	Confidence limit
CIHR	Canadian Institutes of Health Research
CRS	Central randomization system
ECOG	Eastern Cooperative Oncology Group
EG	Experimental group
FACT	Functional Assessment of Cancer Therapy–General
FRQS	Fonds de recherche Québec-Santé
HADS	Hospital Anxiety and Depression Scale
HNC	Head and neck cancer
KPS	Karnofsky Performance Status
MDD	Major depressive disorder
OHNS	Otolaryngology–Head and Neck Surgery
PCL-S	Post-traumatic Stress Disorder Checklist–Specific
PSO	Psycho-oncological support
PSQ	Pilot Study Questionnaire
PTSD	Post-traumatic stress disorder
QoL	Quality of life
RC	Research coordinator
RCT	Randomized controlled trial
SD	Standard deviation
SSOSH	Self-Stigma of Seeking Help
UC	Usual care

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Authors' contributions
All authors (LD, CL, MH (Michael Hier), AZ, KK, AM, MA, EK, JO, DH, RP, FF, NS, ZR, SF, KS, GS, FC, and MH (Melissa Henry)) provided scientific input, helped recruit patients, helped interpret the data and write up the manuscript. All authors provided substantial revisions to the work and approved the final manuscript. More specifically, LD led the drafting of the paper; CL analyzed and interpreted the data regarding various test scores among the participants in the study; MA helped interpret the data and provided scientific input on immunological aspects; EK provided us with the PTSD Coach code and permissions; DH and RP provided scientific input on methodological aspects of the RCT, operational challenges, and subsequent interpretation of analyses; NS provided scientific input, helped recruit patients, helped interpret the data and write up results; ZR and SF provided ongoing guidance, scientific input and supervision throughout the study and the writing of the manuscript; MH (Melissa Henry) oversaw the day-to-day running of the project, planned recruitment, supervised data collection and entry, analyzed data, and wrote up results.

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Data availability
All de-identified data (SPSS format) generated or analyzed during this study is available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The study received full ethics approval from McGill University Faculty of Medicine's Institutional Review Board #MM-CODIM-M-17-085. Informed consent to participate in the study has been obtained from all participants.

Consent for publication
The present study does not include details, images, or videos related to an individual person.

Competing interests
The authors declare that they have no competing interests.

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