

Protocol for the MATCH study (Mindfulness and Tai Chi for cancer health): A preference-based multi-site randomized comparative effectiveness trial (CET) of Mindfulness-Based Cancer Recovery (MBCR) vs. Tai Chi/Qigong (TCQ) for cancer survivors



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ABSTRACT

Purpose: A growing number of cancer survivors suffer high levels of distress, depression and stress, as well as sleep disturbance, pain and fatigue. Two different mind-body interventions helpful for treating these problems are Mindfulness-Based Cancer Recovery (MBCR) and Tai Chi/Qigong (TCQ). However, while both interventions show efficacy compared to usual care, they have never been evaluated in the same study or directly compared. This study will be the first to incorporate innovative design features including patient choice while evaluating two interventions to treat distressed cancer survivors. It will also allow for secondary analyses of which program best targets specific symptoms in particular groups of survivors, based on preferences and baseline characteristics.

Methods and significance: The design is a preference-based multi-site randomized comparative effectiveness trial. Participants (N = 600) with a preference for either MBCR or TCQ will receive their preferred intervention; while those without a preference will be randomized into either intervention. Further, within the preference and non-preference groups, participants will be randomized into immediate intervention or wait-list control. Total mood disturbance on the Profile of mood states (POMS) post-intervention is the primary outcome. Other measures taken pre- and post-intervention and at 6-month follow-up include quality of life, psychological functioning, cancer-related symptoms and physical functioning. Exploratory analyses investigate biomarkers (cortisol,

Abbreviations: BP, blood pressure; BPI, Brief Pain Inventory; BRS, Baroreceptor Sensitivity; CET, comparative effectiveness trial; C-SOSI, Calgary symptoms of stress inventory; EQ-5D, EuroQol Five Dimensions Questionnaire; FACIT-Sp, Functional Assessment of Chronic Illness Therapy - Spirituality; FACT-F, Functional Assessment of Cancer Therapy - Fatigue; FACT-G, Functional Assessment of Cancer Therapy - General; HRV, Heart Rate Variability; MBCR, Mindfulness-Based Cancer Recovery; MBSR, Mindfulness-Based Stress Reduction; MBT, Mind-body therapy; MINDSET, Mindfulness versus supportive expressive therapy; POMS, Profile of mood states; PSQI, Pittsburgh sleep quality index; PTGI, Post-Traumatic Growth Inventory; RCT, randomized controlled trial; SET, supportive expressive therapy; STS, Sit To Stand; TCQ, Tai Chi/Qigong; TL, telomere length; TUG, Timed Up and Go; QL, quality of life

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cytokines, blood pressure/Heart Rate Variability, telomere length, gene expression), which may uncover potentially important effects on key biological regulatory and antineoplastic functions. Health economic measures will determine potential savings to the health system.

1. Introduction

People diagnosed with cancer face many difficulties, including high levels of distress, anxiety, depression and symptoms such as fatigue, pain and sleep disturbance [1,2] which often persist well into survivorship [3,4]. There is also a limited but growing body of evidence supporting the efficacy of a range of mind-body therapies (MBTs) in alleviating these and other symptoms [5,6]. MBTs are therapies that harness mental practices and processes including breath work and movement to affect both psychological and physical function, often inducing the relaxation response, which is in opposition to the fight-or-flight reaction. These include meditation, yoga, imagery, relaxation, hypnosis, biofeedback, Tai Chi and Qigong, among others. While many MBTs have shown efficacy in helping cancer patients and survivors cope, most have been compared with usual care, not active controls or other viable interventions. There are also very few supportive care studies in cancer which integrate patient choice as a design feature.

One exception is the MINDSET trial in which we compared MBCR to supportive expressive group therapy (SET) and a control group (a one-day stress management seminar) for treating distressed breast cancer survivors [7]. In that large randomized clinical trial we demonstrated that while both active interventions were better than usual care, MBCR was superior to SET over a wide range of outcomes [7,8], and benefits persisted over a full year of follow-up [9]. We also found that treatment preference at baseline had an effect on outcomes, in that those women who were assigned to their chosen intervention (MBCR, SET or the control condition) improved more over time on quality of life (QL) and stress symptoms than those who did not receive their preferred treatment [8]. Similarly, a systematic review on the influence of preference on clinical outcomes in acupuncture trials reported that preference was associated with reduced program attrition, with most studies demonstrating an effect of preference on outcome, though few were clinically significant [10]. Hence, in the current study we will include patient preference in the study design and simultaneously evaluate the most efficacious MINDSET trial treatment compared with Tai Chi/Qigong (TCQ).

We chose these two therapies because both have evidence of efficacy for treating distress and improving QL in cancer care [5,6,11]. Both have also shown potential to affect important biomarkers and clinical outcomes. Both MBCR and TCQ are similarly rooted in meditative practice; however, MBCR places greater emphasis on cognitive/mental practice whereas TCQ is more explicitly a physical movement-based practice. Evidence for the efficacy of both interventions when compared to usual care is growing (see *Methods*), but these and other MBTs are rarely evaluated in the same study, and/or compared against one another.

We will specifically address the overarching question of which MBT works for whom, when, and for treating which symptoms? The first question is whether mental or physical mind-body practices are better than usual care, and secondly if being able to choose a practice makes a difference. Next, we ask how the primary and secondary outcomes are moderated by baseline characteristics. This requires a more sophisticated research approach that includes preference-based group allocation and has the ability to test moderation of effects by baseline characteristics, symptomatology, and treatment credibility. This pragmatic design promotes both internal and external validity.

2. Methods

2.1. Objectives and hypotheses

2.1.1. Objective 1

In the context of a preference trial, to compare the impact of either MBCR or TCQ with a waitlist control condition, on total mood disturbance (primary outcome).

Hypothesis 1. When randomly assigned, both MBCR and TCQ will be superior to wait list control pre-post intervention.

Hypothesis 2. When chosen by participants, both MCCR and TCQ will be superior to wait list control pre-post intervention.

Hypothesis 3. (exploratory): Mean between-group pre-post differences in total mood disturbance for both MBCR and TCQ will be larger in the preference vs. randomized groups.

2.1.2. Objective 2

In the context of a preference trial, to compare the impact of either MBCR or TCQ with a waitlist control condition, on secondary outcomes (psychological function, physical function, quality of life).

Hypothesis 4. When randomly assigned, both MBCR and TCQ will be superior to wait list control on secondary outcomes pre-post intervention.

Hypothesis 5. When chosen by participants, both MCCR and TCQ will be superior to wait list control on secondary outcomes pre-post intervention.

Hypothesis 6. (exploratory). Mean between-group pre-post differences in secondary outcomes for both MBCR and TCQ comparisons will be larger in the preference vs. randomized groups.

Hypothesis 7. (exploratory): MBCR groups will improve more on the psychological outcomes than TCQ; TCQ groups will improve more than MBCR on the physical outcomes.

2.1.3. Objective 3

In the context of a preference trial, to compare the impact of either MBCR or TCQ with a waitlist control condition and each other, on exploratory biomarker outcomes (cortisol, Heart-Rate Variability (HRV) and blood pressure (BP), immune function, telomere length/telomerase, gene expression) pre-post intervention. No specific hypotheses are provided for these exploratory analyses.

2.1.4. Objective 4

To investigate the health economic impact of MBCR and TCQ from pre- to post-intervention and follow-up in terms of total healthcare costs, effectiveness and cost-utility.

Hypothesis 8. There will be a greater decrease in average total costs from baseline to post-intervention in the MBCR and TCQ randomized groups compared to waitlist controls.

Hypothesis 9. The difference in changes in average effectiveness from baseline to post-intervention will not vary in the preference versus no preference groups. We speculate that all active intervention groups will decrease charges similarly over this relatively short period of time.

Hypothesis 10. We have no specific hypotheses for the differential cost-utility of MBCR vs. TCQ.

2.1.5. Objective 5

To investigate whether demographic or disease-related characteristics, treatment credibility or childhood trauma moderate any of the effects seen in previous objectives.

2.1.6. Objective 6

To investigate the longer-term (6 months post-intervention) effect of MBCR and TCQ on all outcomes.

2.2. Study design: preference-based comparative effectiveness trial (Fig. 1)

Preference-based trials are a type of pragmatic clinical trial design that takes into account the real-world scenario wherein patients choose interventions they prefer, rather than accepting random assignment to treatments. In traditional RCTs this element of choice is removed in the desire to create a trial with high internal validity and reduced bias that can isolate the effect of the intervention on outcomes and demonstrate the efficacy of an intervention. This works in drug trials where patients are not aware of which treatment they are receiving (placebo pills or active pills), but in nonpharmacological studies (e.g. exercise and MBTs) blinding to intervention is usually not possible. Hence equipoise might vary with patients' perspectives and these preferences and expectations can bias results. Randomized trials are also based on the theory that the two treatment groups represent random samples from the same population, thus are likely to contain similar people. Choice, preference and expectancy may be important to integrate into study designs, but make it less likely that the samples represent the same population, so this must be taken into consideration in the analysis and interpretation of data.

In some cases investigators simply measure preference, expectation or credibility and use it as a moderator or confounder variable in traditional RCTs, but a direct approach is to incorporate preference into study design. Such a preference-based comparative effectiveness trial balances both internal and external validity, with an RCT embedded in a larger pragmatic trial. Patients with a preference for one of the two treatments of interest receive the preferred therapy; others without a preference are randomized (see Fig. 1 for trial design). The theory that the comparisons represent similar samples from a population is relinquished in favor of a study design more similar to how patients select treatments and benefit in real life.

In addition we have included a waitlist component in each portion of the trial to create a control group for the pre-post assessment phase. It can be argued that this is not necessary for the primary outcomes and many of the secondary analyses, as there is already strong evidence that each intervention is superior to a usual care or waitlist control. However, there are many gaps in the research specific to the population we will be studying and some of the outcomes such as the biomarker data and health economic measures. We also suspect both interventions may be similarly beneficial on some outcomes and hence the primary comparison is between each intervention and usual care, to determine if the effects are robust to patient preferences. The presence of waitlist controls will be valuable as comparison groups which control for repeated measurement, historical and cohort effects, regression towards the mean and natural history of changes over time during cancer recovery.

In the preference arms, patients will get their preferred treatment, but within each of the MBCR and TCQ groups will be randomized to either immediate or wait-listed sub-groups in a 2:1 ratio. In the randomized arms, patients will be randomized to either MBCR or TCQ first, and then either to immediate or waitlist groups. Allocation ratios will be 1:1 (MBCR to TCQ) then within those groups 2:1 (immediate: waitlist).

Hence the resulting 8 study groups are as follows:

Preference arms:

1. P-MBCR immediate: those who choose MBCR, randomized to attend the next group.
2. P-MBCR waitlist: those who choose MBCR, randomized to wait for the group after the next one.
3. P-TCQ immediate: those who choose TCQ, randomized to attend the next group.
4. P-TCQ waitlist: those who choose TCQ, randomized to wait for the group after the next one.

Randomized (no-preference) arms:

5. R-MBCR immediate: those without a preference randomized to MBCR, randomized to attend the next group.
6. R-MBCR waitlist: those without a preference randomized to MBCR, randomized to wait for the group after the next one.
7. R-TCQ immediate: those without a preference randomized to TCQ, randomized to attend the next group.
8. R-TCQ waitlist: those without a preference randomized to TCQ, randomized to wait for the group after the next one.

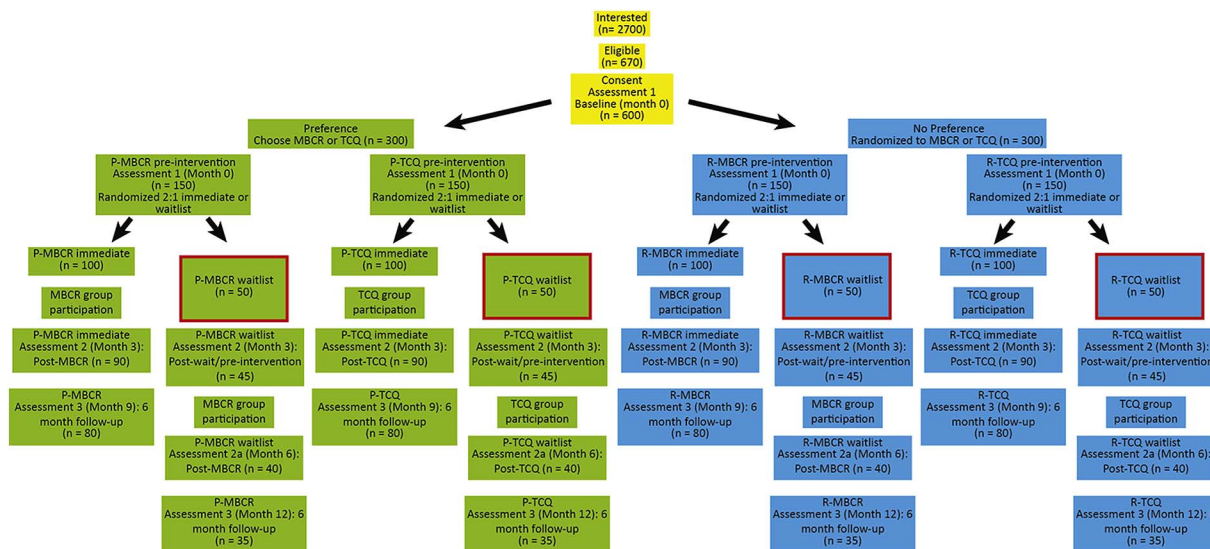


Fig. 1. Study recruitment flowchart.

Assessments will occur either 3 or 4 times, depending on whether participants are assigned to the immediate or waitlist groups, as follows:

Assessment 1. Baseline (after consent and before randomization).

Assessment 2. Post-intervention for immediate groups and post-waiting period for the waitlist groups (3 months following baseline; also serves as “pre-intervention” for waitlist group).

Assessment 2a. Post-intervention for waitlist groups only (6 months following baseline).

Assessment 3. Six-month follow-up for all groups (9 months from baseline for immediate groups and 12 months from baseline for waitlist groups).

See [Table 1](#) for a summary of the assessment timeline.

2.3. Participants

Our intention is to offer this program as widely as possible to cancer survivors over 18 still struggling with significant overall distress post-treatment. Hence, we have used the broadest inclusion criteria deemed feasible by the study team. See [Table 2](#) for a summary of the inclusion and exclusion criteria.

2.3.1. Sample Size

Based on the POMS Total Mood Disturbance as the primary outcome measure, we are aiming to be able to detect a differential effect size of $d = 0.5$ between each of the two randomized intervention arms and randomized waitlist controls, because we typically see medium to large effects sizes on this outcome in trials of MBTs compared to usual care, documented in several recent meta-analyses [12–15]. With beta (power) at 0.8, alpha at $p < 0.05$ and two-sided, this only requires 63 participants in each group (each intervention and control). We also have to take into account the intra-class correlation (ICC) due to the clustering of groups into cohorts. In MINDSET we anticipated an ICC of 0.05 and used a resultant inflation factor of 1.55 for the sample size calculation. However it turned out the actual ICCs in the MINDSET study ranged from 0.00 to 0.04 [7]. The ICCs for the primary outcome (POMS TMD) as well as the C-SOSI total score were both 0.00. In this case the inflation factor is 1.0, indicating the sample does not need to be increased to account for variability across cohorts. The highest ICCs were on the social support measure (which we are not using in this trial) and QL (IF = 0.18), with a corresponding IF of 1.45. Hence with a planned 90 participants at post-intervention/post-wait in each group we will have sufficient power for the analyses even with this level of ICC on some outcomes.

For the direct comparison between MBCR and TCQ, the differences between groups on the POMS TMD will likely be smaller as they are both active interventions, so we need to target a smaller effect size, in this case we have chosen $d = 0.3$, which is also based on the small group \times time interactions on this outcome seen in the MINDSET study comparing MBCR and SET. With beta (power) at 0.8 and alpha at $p < 0.05$ and two-sided, the required sample is 160 participants in each group. After the waitlist control participants have completed their intervention ([Assessment 2a](#)), we will have about 130 randomized to each group for this comparison. With that sample size our power to detect a 0.3 effect will be 0.70. When the other nonrandomized

preference-based groups are added the power will be significantly higher to detect smaller effect sizes and conduct moderator analyses.

Assuming approximately 20% attrition, which is common in MBT trials, and adding in the control group participants, a total of 600 will need to be recruited (about 300 per site) [Table 3](#).

2.4. Recruitment

There are two study sites involved in the trial: The Tom Baker Cancer Centre in Calgary, Alberta, Canada and the Princess Margaret Cancer Centre in Toronto, Ontario, Canada.

Recruitment at both sites will occur through advertising and referrals at area cancer treatment centres. Participants can refer themselves or be referred by a healthcare professional. A study website is currently online (theMATCHstudy.ca) and will be updated and continually available for recruitment and information purposes. Social media (primarily Facebook and Twitter) will be used to disseminate information to cancer advocacy and survivor groups online. Based on past recruitment successes (e.g. In the MINDSET study [7]), we will use cancer registries from both sites to send invitation letters to potentially eligible cancer survivors. Interventions will be delivered in person at cancer centres in Calgary and Toronto.

When interested participants call into one of the study telephone lines, they will be told about the study and screened for eligibility using pre-determined scripts and an online screening protocol. If potentially eligible, an in-person visit will be scheduled at which point eligibility will be confirmed, consent provided and the initial assessment completed.

2.5. Randomization

Following completion of baseline assessments, participants with no intervention preference will undergo block randomization (the proportion of each cohort choosing randomization constitutes each block) into either the MBCR or TCQ program. The exact size of each cohort will depend on participant recruitment rates, but the planned size for each cohort is 40 subjects. All participants (preference and non-preference groups) will be further randomized to receive their intervention either immediately (beginning within the next month) or after a three-four month wait in a 2:1 ratio favouring assignment to the immediate intervention condition. Randomization will be performed using software which allows replication. Permuted blocks will be used to help conceal the allocation. In an attempt to address imbalances, cohorts will be stratified for age, sex, cancer diagnosis and stage. Because the distribution of strata within and across cohorts will not always be consistent, we will use an adaptive approach and adjust the sampling probability to help maintain balance over the course of the trial. Randomization results will be concealed from everyone except the study coordinator who will inform patients of their group assignments after the baseline assessment.

Once everyone in the cohort has completed the baseline assessment, randomization will occur at the latest by two weeks before the group sessions are set to begin. At that point participants will be informed of their specific group assignments. In case there is a large imbalance between those with and without preferences, to ensure strong randomized arms, we will continue recruitment until at least 300 participants without a preference have been allocated to the randomized groups.

Table 1
Assessment times.

Timeline	Baseline	Post-intervention immediate (3-months)	Post-intervention waitlist (6 months)	6-month follow-up immediate (9-months)	6-month follow up waitlist (12-months)
Immediate groups	Assessment 1	Assessment 2		Assessment 3	
Waitlist groups	Assessment 1	Assessment 2	Assessment 2a		Assessment 3

Table 2
Inclusion and Exclusion criteria.

Inclusion criteria	Rationale	Exclusion criteria	Rationale
1) Men and women over the age of 18	Both men and women are included to broaden the generalizability of results and allow sex comparisons. All participants must be adults	1) Metastatic patients and those with ongoing chemotherapy or radiation therapy	Ongoing therapy may impair biomarker profiles, and metastatic patients may not be stable enough to participate in the interventions and follow-up assessments.
2) Diagnosed with any type of cancer (stage I-III) excluding brain	Metastatic disease and brain cancers were recommended to be excluded by the study oncologists as unlikely to be able to fully participate or complete the interventions and follow-up assessments	2) Suffering from current major depressive disorder, Bipolar Disorder or other psychiatric disorder (self-report) that would interfere with the ability to participate.	Participants with active psychological disorders should be treated for these problems individually before engaging in group programs of this nature.
3) Completed primary treatment (i.e. surgery, chemotherapy, radiation therapy) at least 4 months previously (ongoing hormonal therapies including AIs, tamoxifen, as well as herceptin are not exclusionary).	Current primary therapies can impact the ability to complete the programs and also interfere with biological measurements such as immune function and telomere length. A period of at least 3 months is needed for these to normalize after treatment.	3) Currently engaging in meditation or TCQ one or more times per week, or having done so within the previous year.	We want to include people who are NOT currently practicing the two therapies, but don't want to exclude everyone who may have dabbled with them in the past.
4) Experiencing significant distress (4 or greater) on the Distress Thermometer.	People with low distress are not likely to benefit significantly from the interventions. To see improvements we need to target people who are symptomatic to begin with.	4) Participation in an MBCR or MBSR program in the last five years.	Because this program has been widely offered in Calgary and Toronto many people may have already been exposed to it recently, which could confound results.
5) Able to attend MBCR or TCQ classes at scheduled times	People must have transportation and time to attend the groups as scheduled	5) Cognitive impairment that would interfere with completing questionnaires or the intervention (< 25 on the Mini Mental Status Exam).	People require enough cognitive capacity to complete the questionnaires, attend the groups and complete homework independently. The MMSE only rules out those with significant cognitive impairment and won't exclude those with the more mild cognitive impairment associated with cancer-related "brain fog"
6) Sufficient functional capacity to participate in intervention groups (as judged by the Physical Activity Readiness Questionnaire (PAR-Q))	The interventions require gentle physical activity so participants must have enough functional capacity to be able to participate		
7) Ability to speak and write English sufficiently to complete questionnaires and participate in groups.	The groups and assessments will be conducted in English so participants must be able to understand the instructors and fill out the questionnaires.		

2.6. Blinding

At the baseline assessments everyone (patients, study co-ordinator, RAs, statistician) will be blinded to condition as this occurs before randomization and before each participant states whether they have a preference or not. Once patients are randomized or choose their group, the study co-ordinator will inform them of their group assignments and become unblinded to condition, as will participants. The secondary RAs who conduct assessments will remain blind to condition throughout, as will the study statistician (databases will be created with groups labeled G1-G8 by the study co-ordinator without labels so the statistician who runs the analyses will not know which intervention groups are which).

2.7. Group formation

The randomized participants will join those with a preference in the MBCR and TCQ group sessions. Group numbers should not exceed a maximum of 25 per group, which will allow a larger number of participants with a preference to join each cohort if necessary. As the study progresses, participants coming off the waitlists will also be added to ongoing groups. We will begin with one group each of MBCR and TCQ running at each site, but add additional groups as numbers require.

2.8. Assessment procedures

First, potential participants will be screened for eligibility by the study coordinator and RAs on the telephone using a computer-assisted screening protocol. If eligible and interested, an in-person 90 min visit to the study centre will be scheduled, up to 2 months before the intervention groups are scheduled to begin (to allow testing of 40/cohort). When participants arrive they will first be fully screened for eligibility, and if eligible provide informed consent (20 min). Once consented, they will complete the baseline questionnaires on a laptop, tablet or by paper (their preference; 30 min). Researchers will then assess blood pressure (BP), Heart Rate Variability (HRV), Baroreceptor Sensitivity (BRS) (20 min), and complete the physical function testing

(10 min). Before leaving participants will choose which intervention they prefer from standard descriptions, or indicate equal interest in both interventions. Researchers will provide salivettes for the cortisol collection along with instructions that will be reviewed, and they will also provide a laboratory requisition form and instructions on where and when participants can attend the lab that will take blood samples in a morning after overnight fasting (10 min).

Participants will collect saliva samples at home over three consecutive weekdays the following week, and bring the collected samples with them to their blood draw the next week to be picked up by an RA. They will go to the blood lab at their respective Cancer Centre to provide 30 mL of blood after the collection of saliva samples. RAs will assure that cortisol and blood samples are collected as directed by contacting participants by telephone.

2.9. Interventions

2.9.1. MBCR

Through an ongoing program of research we adapted a group intervention based on intensive training in mindfulness meditation (Mindfulness-Based Stress Reduction; MBSR [16]) specifically for people with cancer. The program is called Mindfulness-Based Cancer Recovery (MBCR [17]), acknowledging its roots but also that its form and content is somewhat different, and focused primarily on the challenges faced by people living with cancer. It is a 9-week program consisting of weekly group meetings of 1 h 45 min, shortened from traditional MBSR based on practical logistical concerns and the needs of our population. Home practice of 45 min per day (15 min yoga; 30 min meditation) is prescribed. A 6-hour weekend retreat is offered on a Saturday between weeks 6 and 7. As the weeks progress, different forms of meditation are introduced, beginning with a body scan sensory awareness experience, progressing to sitting and walking meditations. Gentle Hatha yoga is incorporated throughout, as a form of moving meditation. Didactic instruction as well as group discussion and reflection, problem solving and skillful inquiry are commonly applied teaching tools during group meetings.

Table 3
Measures.

Construct	Measure	Description
<i>Screening measures</i>		
Distress	Distress thermometer [46] [41]	0–10 visual analogue scale using the metaphor of a usual thermometer. ROC analyses show that a DT cut-off score of 4 has optimal sensitivity and specificity relative to both the Hospital Anxiety and Depression Scale and the Brief Symptom Inventory-18 cut-off scores for detecting significant distress
Physical Fitness	Physical Activity Readiness Questionnaire - Plus [48]	A two-part questionnaire screening suitability for beginning physical activity. If any of the responses to the 7-item first section are positive, the participant will complete a second longer section so any restrictions to physical activity can be identified.
<i>Baseline measures - moderators</i>		
Treatment Acceptability/Preference	The Treatment Acceptability & Preference Measure [51]	4-item scale assessing preference and expectations specific to each intervention.
Childhood Trauma	Childhood Trauma Questionnaire [50]	28-item questionnaire which assesses the impacts of childhood traumatic experiences.
<i>Outcome measures: quality of life</i>		
Health-related quality of life	Functional Assessment of Cancer Therapy – General [55]	27-item questionnaire which assesses QL in five domains: Physical, social/family, emotional, and functional well-being. Broadly used and validated in oncology.
<i>Psychological function</i>		
Mood	Profile of mood states [53]	65-item scale assessing six affective dimensions: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The POMS measures state (vs. trait) attributes and therefore previous administrations do not influence subsequent administrations.
Stress	Calgary symptoms of stress inventory [56]	56 items and 8 subscales tapping into multiple domains of stress reactivity: Depression, Anger, Muscle Tension, Cardiopulmonary Arousal, Sympathetic Arousal, Neurological/GI, Cognitive Disorganization, and Upper Respiratory Symptoms.
Spirituality	Functional Assessment of Chronic Illness Therapy - Spirituality (FACIT-SP) [57]	12-item scale. Subscales include Meaning, Peace and Faith, summed to a Total Score. Measures one's connection to something larger than oneself. Distinct from religiosity.
Post-Traumatic Growth	Post-Traumatic Growth Inventory (PTGI) [61]	21-item questionnaire. Subscales include relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. Measures the occurrence of positive outcomes following a traumatic event. Validated in cancer patient samples.
<i>Cancer-related symptoms</i>		
Sleep quality	Pittsburgh sleep quality index [62]	Includes 19 questions with 7 subscales and a global score: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.
Pain	Brief Pain Inventory [71]	Includes 10 questions about pain that load onto 3 factors: pain intensity, activity interference, and affective interference.
Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) [75]	13-question add-on to the FACT-G that measures overall fatigue with a global score. Often used in cancer research.
<i>Physical function</i>		
Agility	Timed Up and Go Test [77,78]	Subjects are given verbal instruction to stand up from a chair, walk 3 m, turn around, walk back, and sit down. The average time (s) of 3 trials will be recorded
Speed	Maximal walking speed [79]	Participants walk in a straight line as fast as possible, without running, on a premeasured 11 m course. The time taken to walk 5 m, from the 3 m to 8 m mark is used to calculate maximal walking speed (m/s).
Strength	Sit-to-Stand (STS) [76]	Participants will be asked to sit in a chair, cross their arms of their chest and attempt to stand without the assistance of their arms.
	Maximum grip strength [80]	The dominant hand will be measured using a handgrip dynamometer Grip D (Takei Scientific Instruments, Tokyo, Japan). Measurements are recorded to the nearest 0.5 Kg, repeated three times and averaged
Balance	Single leg standing [81]	Three 30 s trials are completed for eyes-open and eyes-closed conditions, and the greatest duration (s) for each condition is used for analysis.
<i>Biomarkers</i>		
Telomere length and telomerase	TL is analyzed from DNA isolated from blood buffy coat via quantitative real-time polymerase chain reaction (qPCR) in triplicate. Telomerase is also measured with qPCR by determining mRNA transcript levels of hTERT from RNA isolated from buffy coat	A T/S ratio is calculated that compares the TL in cells to both a pooled reference sample and control cell lines.
Cytokine production	Luminex multiplex assays, basic 48 cytokines (includes inflammatory and regulatory cytokines and chemokines)	The mRNA transcript levels of hTERT (the catalytic component of the telomerase enzyme) strongly correlate to telomerase activity. A range of different cytokines including TNF-alpha, IFN-gamma, IL-1, IL-4, IL-6, IL-10, IL-12, which have a variety of important inflammatory and anti-inflammatory functions in cancer.
Salivary cortisol	Salivary samples are taken at four timepoints during the day (waking, noon,	Slopes are calculated by averaging the cort value at each timepoint

(continued on next page)

Table 3 (continued)

Construct	Measure	Description
	5 pm and bedtime) over 3 days	over the 3-day period, then determining the slope of the averaged line using linear regression. Cort distribution values are typically skewed so logarithmic transformations are applied.
Gene expression	Genome-wide transcriptional profiles are assessed in blood samples using microarrays or RNA sequencing.	Analyses test for intervention effects on 1) reduced activity of the “conserved transcriptional response to adversity” profile (marked by an a priori-specified set of 19 pro-inflammatory gene transcripts and 34 interferon- and antibody-related transcripts) and 2) reduced activity of pro-inflammatory transcription factors (e.g., NF-kappaB, AP-1), increased activity of interferon-related factors (e.g., IRF), and decreased activity of stress-related signaling pathways (e.g., CREB). Data will be analyzed using Nevrokard advanced Heart Rate Variability (aHRV) software. High frequency HRV will be calculated using the spectral decomposition method and examined. Baroreflex sensitivity will also be assessed by examining high frequency HRV response to a posture challenge.
HR/Heart Rate Variability	A Biopac MP36 data acquisition device running Biopac Student Lab software will record inter-beat intervals during 10 min of sitting and 5 min of a postural (supine to standing) challenge.	The BpTRU device obtains six 1-minute measurements spaced by 1-minute intervals. The first measurement is discarded and the average of the last 5 measurements is recorded.
Blood pressure	Automated office BP will be measured automatically using a BpTRU device.	
<i>Health economics</i>		
Health care utilization	CCHS survey subset are standardized questions that will be used to ask participants about formal and informal health care utilization	These questions will assess utilization of physician services, hospital services, allied health providers and how health care needs were met.
Health utility	EQ-5D-5L is a preference based measure of HRQoL so that we are able to calculate QALYs for subsequent application in our cost utility analysis.	The EQ-5D-5L descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension defines 5 levels from no problems to extreme problems. The classifier system can be used for descriptive purposes as well as to derive an index of overall health represented by a single preference-based summary score. This instrument also allows for comparison of HRQoL across different conditions.

Since 1998, we have tested the efficacy of MBCR in a wide range of studies and groups of people with cancer. Our work has spanned the spectrum of research from basic mechanistic research to clinical trials and implementation science, beginning with psychological outcomes including stress symptoms, mood disturbance including anxiety, anger and depression [18,19], then expanding in scope and scale to assess effects on sleep disturbance and fatigue [20–22]. We also examined positive outcomes including Post-Traumatic Growth, spirituality and benefit finding [23–25]. To assess potential biological mechanisms of change, we investigated the effects of the program on biomarkers including BP [26], inflammatory cytokines [20,27], stress hormones [7,21] and most recently telomere length [28] using increasingly sophisticated study designs, showing benefit across all of these measures. Other researchers have also studied MBSR with cancer patients, and several reviews and meta-analyses have been conducted that summarize its benefits across outcomes of anxiety, stress, mood disturbance and QL [12–14,29,30].

2.10. TCQ

The intervention follows the structure and content of multiple mind-body exercise protocols employed in studies based at the Harvard Medical School [31–39], and incorporates simple training elements common to both Tai Chi and Qigong [36,40,41]. For this reason, we call it Tai Chi/Qigong (TCQ), following nomenclature of Klein and colleagues [11]. Tai Chi and Qigong are both multi-component mind–body exercises that are grounded in the holistic model of traditional Chinese medicine. Both integrate meditative postures and flowing rhythmic movements, along with breath awareness and variety of cognitive skills including focused attention, heightened body awareness, and imagery. Tai Chi has its roots in the martial arts, but it is more commonly practiced for health and wellness. Both practices target multiple physiological, motor, and cognitive processes which makes them particularly well-suited for cancer patients with complex constellations of comorbidities [11]. Our TCQ intervention has equal contact time as MBCR but is structured somewhat differently; it is an 11-week program

consisting of a 1.5 h weekly group meeting and a 4 h weekend retreat, as the instructors felt longer sessions would not be practical. Group meetings are supplemented with daily home practice. We piloted a program with shorter (45 min) twice weekly sessions but participants found it difficult to attend more than once weekly, so the format to more closely parallel the MBCR program was adopted.

Evidence for the efficacy of Tai Chi and Qigong programs in cancer care has also amassed over the years, and reviews are now available for both [11,15,42–44]. A recent review of eleven randomized controlled trials concluded that TCQ had positive effects on cancer-specific QL, fatigue, immune function and cortisol levels in individuals with cancer [11]. However, methodological limitations including small sample sizes and heterogeneity in protocols delivered and populations studied necessitate the need for additional well designed larger trials to inform TCQ integration into cancer care.

2.11. Measures

In the text below we provide rationale for choice of measures and measure descriptions; Table 1 includes details of the specific number of items, scoring methods and questionnaire subscales.

2.11.1. Screening measures

2.11.1.1. Distress thermometer (DT) [45]. The DT is a 10 point visual scale for perceived distress. A clinically significant cut-off level of 4 (moderate distress) will be used as an inclusion criterion for participation in the study [46]. Only people at least moderately distressed will be included in the study. Reasons for this are two-fold. First, psychosocial intervention studies that include all interested patients without screening for a minimal level of distress or depression often fail to find significant improvements in these outcomes, likely due to floor effects. Second, resources are limited so ethically we should offer services to those who are most in need and most likely to benefit. We have done this screening in two previous clinical trials and it has proven feasible and successful [7,47].

2.11.1.2. Physical Activity Readiness Questionnaire-Plus (PAR-Q+) [48]. The PAR-Q+ is a two part questionnaire that screens for contraindications prior to beginning a program of physical activity. The purpose of the use of the PAR-Q+ is to ensure that [1] it is safe for patients to participate in the intervention and [2] to ensure that all participants are capable of performing the program. The first section is a 7-item screen for various cardiovascular, bone and joint, ambulatory, or chronic medical conditions. If the patient positively identifies any of these, the second section, which includes 9 additional domains, is included to ensure that the individual will be able to participate safely.

2.11.2. Baseline measures

2.11.2.1. Demographic characteristics. We will assess age, socioeconomic status, medical history, psychiatric history and current medications, and previous experience with yoga, tai chi, qigong or meditation. Participants will also report recent health behavior, such as alcohol and nicotine intake, and quality of sleep and diet. Disease parameters including stage and type of disease and date of diagnosis at the time of study enrollment will be collected through chart reviews.

2.11.2.2. Credibility scale [49]. The Treatment Acceptability and Preference Measure was adapted for each of the interventions and used to describe preferences and expectations for the assigned treatments. This is included to determine the influence of not only initial preference (which is taken into account in treatment allocation) but also of the perceived credibility of each treatment and how likely an individual feels they personally will benefit. Credibility will be measured both before and after participation in the groups to see whether direct experience of a program affects the ratings of credibility either for the program experienced or the one not taken.

2.11.2.3. Childhood Trauma Questionnaire (CTQ) [50]. The CTQ assesses the experience of childhood traumatic events using a sliding scale of the severity for each traumatic occurrence. This is included because previous literature has associated treatment response within psychotherapy [51] and psychosocial oncology studies to childhood adversity [52], and it may be an important treatment moderating factor.

2.11.3. Adherence and contamination measures

Home practice logs will be used to track program adherence among participants in both groups. Participants will be asked to provide daily estimates of practice and practice focus each week for the duration of the study. Automated emails will be sent weekly with a link to a personalized online homework log.

2.11.4. Outcome measures

2.11.4.1. Primary outcome

2.11.4.1.1. Profile of mood states (POMS) [53]. The POMS assesses various dimensions of mood which can be summed to generate a Total Mood Disturbance (TMD) score, and six subscale scores: tension-anxiety, depression, anger-hostility, vigor-activity, fatigue and confusion. The POMS has been widely used in clinical populations, including cancer patients [54]. The TMD will be the primary outcome, as in our previous trials and much other psychosocial oncology research [7,9,54]. Previous studies provides a good deal of data to allow accurate sample size calculations. We will also examine each of the subscales to determine the relative magnitude of changes across domains.

2.11.4.2. Secondary outcomes

2.11.4.2.1. Quality of life

2.11.4.2.1.1. Functional Assessment of Cancer Therapy-General (FACT-G)

 [55]

The FACT-G is a commonly used general cancer-related QL measure with four well-being subscales, used to assess overall QL. This will provide a global picture of overall health-related QL across groups and

over time.

2.11.4.2.2. Psychological measures

2.11.4.2.2.1. Symptoms of stress inventory (C-SOSI)

 [56]

The C-SOSI will be used to measure physical, psychological and behavioural responses to stressful situations. This measure is included because it taps into subjective stress across a range of domains and systems in the body. We have used it extensively and it has shown good responsiveness to treatment-related changes in our previous studies [7,9].

2.11.4.2.2.2. Functional assessment of chronic illness therapy-spiritual well-being (FACIT-sp)

 [57]

Spirituality will be measured with the FACIT-Sp, a questionnaire designed for people with cancer or other chronic illnesses. It taps into the domain of spirituality, which is distinct from religiosity and refers to having a connection with something larger than oneself. This connection may be faith-based or focus on community and relationships. It includes elements of feeling calm and at peace. In the cancer literature higher levels of spirituality are associated with better overall well-being [58,59] and we have shown improvements in spirituality in previous mindfulness studies [9,60].

2.11.4.2.2.3. Post-Traumatic Growth Inventory-Revised (PTGI-R)

 [61]

The PTGI-R measures the construct of Post-Traumatic growth (PTG), which describes the observation that people who experience trauma often benefit from the experience by re-evaluating and re-prioritizing their life values and goals. PTG is associated with finding a greater sense of meaning and purpose in life, discovering an untapped well of personal strength in the face of adversity, re-evaluating one's relationships and increasing overall appreciation for life. In previous research we found increased PTG following participation in MBCR programs [13].

2.11.4.2.3. Cancer-related symptom measures

2.11.4.2.3.1. Pittsburgh sleep quality index (PSQI)

 [62]

The PSQI measures several components of sleep quality including total sleep time, sleep efficiency and overall satisfaction with sleep quality. It is a widely used measure of sleep disturbance. Sleep problems are ubiquitous in people with cancer, with approximately 40% of cancer patients meeting the diagnostic criteria for clinical insomnia [63,64]. In previous work team members showed that cancer survivors with insomnia benefited from MBCR programs as well as traditional cognitive-behavioural therapy for insomnia [63,65], and that better sleep efficiency was related to higher Heart-Rate Variability [66] and longer survival [67] in metastatic breast cancer. Studies of Tai Chi in cancer patients also support enhanced sleep quality [68–70].

2.11.4.2.3.2. Brief Pain Inventory (BPI)

 [71]

The BPI allows participants to rate their pain along dimensions of pain severity and how much their pain interferes with daily experiences and functioning, which is recommended by the IMMPACT group on pain assessment [72]. Pain is also common in cancer survivors and while we have not routinely measured it in clinical intervention studies, other studies show improvements in pain from both MBIs [73] and TCQ programs [74].

2.11.4.2.3.3. Functional assessment of chronic illness therapy-fatigue (FACIT-F)

 [75]

The FACIT-F is an add-on to the FACT-G which specifically assesses the level of fatigue symptoms and degree to which it interferes with overall function. Fatigue is the most commonly reported lingering and bothersome symptom of cancer treatment [4], and amenable to improvement from MBCR [22].

2.11.4.2.4. Physical functioning measures. We will assess a short battery of physical function outcomes commonly used in conventional exercise and TCQ clinical trials, including in studies of cancer patients.

2.11.4.2.4.1. Sit-to-Stand (STS)

 [76]

The ability to stand safely without assistance requires functional strength, balance, and accurate sensation. The STS will be incorporated to assess lower body strength and capability. Participants will be asked to sit in a chair, cross their arms over their chest and attempt to stand without the assistance of their arms.

2.11.4.2.4.2. Timed Up-and-Go Test (TUG)

 [77]

Side effects of cancer and cancer treatment (e.g., neuropathic pain) can influence the person's capacity for tasks of daily living such as rising from seated. The TUG is a validated test of mobility in which the participant must rise from a chair, walk 3 m, and return to a seated position [77,78]. The test will be repeated twice and the average of the two scores will be used for analysis.2.11.4.2.4.3. Maximum walking speed [79]

Walking speed has been put forward as a “vital sign” because it is a useful measure of functional health status [79], and it may change as a consequence of study participation. Participants walk in a straight line as quickly as possible, on a premeasured 11 m course. The time taken to walk 5 m, from the 3 m to 8 m mark is used to calculate maximal walking speed (m/s). This test will also be repeated twice and the average score used for analysis.2.11.4.2.4.4. Grip strength

Poor grip strength is associated with increased mortality from all causes [80]. The strength of the dominant hand will be measured using a Jamar hydraulic handgrip dynamometer (Patterson Medical – Canada, Mississauga, ON, CAN). Participants are seated and asked to hold the dynamometer in their dominant hand. The elbow is bent at 90° and the shoulder is relaxed. Participants are encouraged to squeeze the dynamometer as hard as possible three times. The best score will be used for data analysis.2.11.4.2.4.5. Balance

The ability to maintain balance provides important information regarding physical functional capacity in daily living, frailty, and risk of falling [81]. Participants will perform a static single-leg postural control balance test twice, once with eyes open and once with eyes closed. The maximum time for both will be limited to 30 s.

2.11.4.2.5. Exploratory outcome2.11.4.2.5.1. Biomarkers

Another innovative aspect of our work has been to assess biological mechanisms of change. While our focus is primarily on clinical outcomes, we remain interested in some of the basic biological mechanisms of action of MBTs and effects on biomarkers that may be important for disease progression and mortality. These may also be helpful in individualizing therapies and optimizing dose. Most of these outcomes have been studied in MBTs, but this research is in its nascence and there is much more to be learned about how these therapies affect the body at a biological level while interacting with different disease states. By assessing these parameters over time in two active MBTs and having a control comparison group we will be able to learn much about intervention impacts on potentially important biomarkers.2.11.4.2.5.1.1. Salivary cortisol

Cortisol is a hormone secreted by the adrenal gland in response to physical and psychological stress. It typically follows a daily pattern of secretion with a burst of production after waking followed by a gradual decrease over the course of the day, with the nadir after bedtime. Hence, the slope of the change across a day is a good measure of the steepness of this descending curve from waking to bedtime, which may be clinically meaningful [82]. Previous research has shown steeper cortisol slopes to be associated with better survival outcomes than flatter slopes in lung, breast and ovarian cancers [82–84] and our previous work showed steeper slopes after participation in MBCR or support groups [7,9].2.11.4.2.5.1.2. Immune function

A number of measures of immune system functioning are important markers of health in people with cancer, in part because immune cells such as cytokines and natural killer (NK) cells have the ability to destroy cancer cells through apoptosis or antiangiogenic activities [85]. Psychosocial oncology interventions, including both MBIs and TCQ, have shown the ability to affect immune system parameters including NK cell numbers and cytotoxic function, lymphocyte numbers (CD4, CD8) inflammatory cytokine production including IL-6, IFN-gamma, TNF-alpha and NK-Beta [86]. Hence, measurement of cell counts and both pro-and anti-inflammatory cytokines has precedence and is promising in this context.2.11.4.2.5.1.3. Telomere length (TL) and Telomerase

Telomeres are specialized nucleoprotein complexes that form the protective ends of linear chromosomes [87] and provide genomic stability through a number of mechanisms. Telomere dysfunction and the loss of telomere integrity may result in DNA damage or cell death [87].

Shorter TL has been implicated in a number of disease states including cardiovascular disease and diabetes [78,88,89] and shorter TL also predicted earlier mortality in leukemia [90], and in breast cancer patients [91,92]. In order to maintain telomeres, most cells use Telomerase, a specialized cellular reverse transcriptase that elongates telomeric DNA, thereby counteracting the telomere shortening that occurs with successive rounds of cell division [87]. TL and telomerase activity may be susceptible to psychosocial influences, particularly stress [93,94]. In previous exploratory work we found that participants in MBCR and a support group showed no change in TL over 4 months pre-post intervention, but control women had shorter TL over the same period of time [28].2.11.4.2.5.1.4. Gene expression

In the field of social genomics, research has uncovered associations between adverse life events and prolonged exposure to stress with alterations in genome-wide transcriptional profiles in circulating leukocytes. The common pattern shows increased expression of pro-inflammatory genes accompanied by suppression of genes involved in interferon-mediated innate antiviral responses and immunoglobulin G production [95,96]. Within oncology, a trial of a cognitive-behavioural stress management intervention randomized breast cancer patients to treatment or control and found reduced expression of pro-inflammatory and metastasis-related genes and increased expression of interferon-related genes in leukocytes from women in the intervention [97]. Similarly, Bower and colleagues found significant reductions in pro-inflammatory gene expression and inflammatory signaling at post-intervention in a group mindfulness program for breast cancer survivors [98], and Irwin and colleague review a large literature supporting altered inflammation related gene expression following TCQ [69,99,100]. Collectively, these observations further justifying an exploration of this outcome in response to MBCR and TCQ.2.11.4.2.5.1.5. Heart Rate Variability (HRV)/Baroreflex sensitivity (BRS)/blood pressure (BP)

HRV is a measure of the degree of variability between heartbeats which reflects parasympathetic influence on the cardiac pacemaker by way of the tenth cranial nerve. Both low HRV and higher heart rate are predictors of shorter survival in metastatic breast cancer and are risk factors for cardiovascular disease [101–103]. BRS reflects the ability of the baroreflex to regulate acute changes in BP by adjusting heart rate. BRS and HRV are associated but are independent predictors of mortality after a cardiac event [101]. Elevated BP is a risk factor for cardiovascular disease [104]; many forms of chemotherapy and radiation therapy to the chest wall can damage the heart muscle and make cancer patients more vulnerable to heart disease after cancer treatment [105]. Our previous work showed decreases in BP over the course of an 8-week MBCR program [26], and studies in non-cancer patients also support the notion that TCQ can help manage BP [31,106].2.11.4.2.5.2. Health economics

In this era of managed health care delivery, the cost of interventions and their potential to save future healthcare spending becomes an important factor in determining uptake and sustainability. Health economic impacts can be assessed by tracking how much it costs to deliver an intervention and the effects of the intervention on downstream costs to the healthcare system. Participation in a 6-week psychosocial group intervention targeting depression and social support resulted in cost offsets of 25% less healthcare billing over the subsequent two years in breast cancer survivors compared to randomized controls receiving usual care [107]. Cost-utility assessment can be implemented in order to determine if the intervention is efficient at improving health outcomes and a cost-effectiveness analysis to assess the impact of the intervention on public health care utilization.2.11.4.2.5.2.1. Canadian Community Health Survey (CCHS) subset

CCHS is a cross-sectional survey that collects information related to health status, health care utilization and health determinants for the Canadian population. It relies upon a large sample of respondents and is designed to provide reliable estimates at the health region level [108]. The questions regarding health care utilization from the CCHS will be used in this study to collect information about the utilization and cost

effectiveness of the intervention relative to the avoidance of health care costs. The CCHS questions are standardized and the information collected will be comparable to national healthcare utilization data collected through the CCHS.2.11.4.2.5.2.2. EQ-5D-5L

The EQ-5D-5L is a preference based measure of QL which will enable us to calculate Quality Adjusted Life Years (QALYs) for application in our cost utility analysis. This instrument also allows for comparison of QL across different conditions. The EQ-5D is the generic preference based instrument of choice in cancer studies [109], and it has the benefit of being widely used and simple to administer. The EQ-5D-5L has been validated for use in cancer studies [110].

2.12. Data analysis

Data analyses will use linear mixed models (LMM) and an intent-to-treat principle to assess several planned comparisons across the groups based on identified aims and hypotheses. Data will be cleaned and descriptive statistics of the sample assessed. All variables will be checked for normality and meeting assumptions for the LMM analyses.

2.12.1. Objective 1

Comparing MBCR and TCQ to waitlist on primary outcome.

Hypothesis 1. To assess group differences in change scores on the POMS TMD from baseline to post-intervention (assessment times 1 and 2) in the randomized groups only, separate LMMs will be conducted comparing R-MBCR immediate to R-MBCR waitlist groups, and R-TCQ immediate to R-TCQ waitlist. Group will be a fixed effect and participants a random effect. To account for dependencies in the data introduced by the design of the study we will include random intercepts for each cohort to assess and if necessary account for correlations of observations within cohorts.

Hypothesis 2. To assess group differences in change scores on the POMS TMD from baseline to post-intervention (assessment times 1 and 2) in the preference groups only, separate LMMs will be conducted comparing P-MBCR immediate to P-MBCR waitlist groups, and P-TCQ immediate to P-TCQ waitlist. As above, group will be a fixed effect and participants a random effect, with cohorts a random intercept in the model.

Hypothesis 3. To assess the impact of preference on POMS TMD within each intervention modality, LMM will be conducted comparing the P-MBCR immediate group directly to the R-MBCR immediate group pre-post intervention, and the P-TCQ immediate group to the R-TCQ immediate group, using similar parameters as above.

There may be two sources of confounding in the data. 1) Factors that we haven't included in the randomization strata may be imbalanced due to chance, and 2) Participant preference for treatment type may be related to confounding factors. For each treatment type, we'll present tables of potential confounders within the preference and no-preference groups. Because the design does not ensure that covariate imbalances will only occur due to chance, we will use covariate adjustment within our primary analyses to include potential confounders.

2.12.2. Objective 2

Secondary outcomes (Hypotheses 4–7). Corresponding analyses as in Objective 1 will be utilized for the secondary outcomes as for the primary outcome. To account for multiple tests we will use a false discovery rate (FDR) approach for our secondary outcome measures. We will use this approach to ensure that the FDRs are < 5% within each of our groups of secondary outcome measures (quality of life, Psychological Measures, and Cancer Related Symptom Measures).

2.12.3. Objective 3

Exploratory outcomes: The same analyses will be utilized for the exploratory outcomes as detailed for the primary and secondary

outcomes.

2.12.4. Objective 4

Health economic outcomes:

Hypothesis 8. To assess the group differences in change in average total costs from baseline to post-intervention in the MBCR and TCQ randomized groups. First, a separate comparative analysis will be conducted within each group compared to its corresponding waitlist group (i.e. R-MBCR immediate vs. R-MBCR waitlist and R-TCQ immediate vs R-TCQ waitlist). Then, a comparative analysis will be carried out between the two intervention groups i.e. R-MBCR and R-TCQ. We shall use difference-in-difference methodology to control the difference in characteristics of two group. Costs will be measured using data on health care utilization from Canadian Community Health Survey. Costing information will be collected from the government reports, peer-reviewed articles and participating agencies.

Hypothesis 9. To assess the differences in changes in average effectiveness from baseline to post-intervention in the preference and no preference group. The EQ-5D-5L generic preference-weighted questionnaire will be used to derive utility from the cohort. The Canadian population tariff will be used to obtain QALYs. The same analyses methods will be applied for comparative analysis in the Preference arms as in the Randomized arms described in Hypothesis 8.

Hypothesis 10. To perform a cost-utility analysis of MBCR and TCQ. Two cost-utility analysis will be undertaken-1) Cost-utility analysis for the preference group and 2) Cost-utility analysis for the no-preference group within each of the interventions. The incremental cost will be calculated by subtracting the average total costs in TCQ group from the average total costs in MBCR group from baseline to follow-up. Similar methods will be used to calculate the incremental effectiveness. The incremental cost-effectiveness ratio will be derived by dividing the incremental costs by the incremental effectiveness. A one-way and probabilistic sensitivity analysis will be conducted to check uncertainties of parameters used in the model and to establish the 95% confidence interval around the calculated ICER.

2.12.5. Objective 5

Moderator analyses: In order to compare everyone who had MBCR to everyone who had TCQ and all controls pre-post intervention we will combine preference and randomized groups and evaluate moderating effects of individual differences, baseline symptomatology, childhood trauma, disease characteristics and treatment-related variables on outcomes using multiple linear regression and mediation/moderation analyses.

2.12.6. Objective 6

Follow-up: Six month follow-up data analysis between the two groups (MBCR and TCQ) adding in the waitlist controls from each group will be analyzed using Hierarchical Linear Modeling to look at changes in growth curves over time between participants in the two groups. This will be done separately for each of the randomized and preference groups within each intervention, and together to see if patterns are different.

2.13. Study timeline

Three cohorts will commence interventions each year at each site (a group in fall, winter and spring) beginning in Fall 2016; therefore, with a maximum of 80 in each cohort (40 at each site), over three years of recruitment we will deliver interventions for up to 9 cohorts, which will allow us to reach recruitment targets of 600 participants (allowing for some cohorts smaller than 40). It will take a full year for each cohort to complete their involvement with the study from the time of enrollment through follow-up assessments, so the entire data collection period will

take four years. Another year will be required for ethics approval, recruitment contingencies, data analysis, manuscript preparation, presentations and publications.

3. Discussion

This is the first study of its kind to use a preference-based non-randomized effectiveness design alongside a fully randomized efficacy trial of two interventions, and include randomized waitlists in each case. This unique design offers certain advantages, and also poses potential challenges. Advantages include: 1) Patients who have a strong preference will get the intervention they want, maximizing recruitment and also allowing exploration of the effects of preference on outcomes by comparing outcomes between those who choose an intervention and those randomized to the same treatment without a preference for it. However, a drawback of allowing preference-based assignment is that groups may also differ by demographic and disease characteristics, and the design could introduce other biases caused by preference for certain days/times classes are offered, etc. 2) A full standard comparative efficacy RCT with two active interventions and a waitlist control is embedded in the design, which will allow testing the efficacy of both interventions compared with each other and control. 3) Randomized control groups will allow us to see the natural course of changes over time, which will be especially valuable if there are no differences between the active intervention groups on any of the outcomes. Without controls interpretation of main effects of time across MBCR and TCQ would be confounded and we could not know whether improvements were due to the interventions or just the natural history of change over time due to any number of factors such as repeated measures, regression to the mean, time since cancer treatment completion or even seasonal variations.

Risks and challenges are inherent in trying a new design for the first time. The largest unknown is exactly what proportion of people will have preferences for each of the interventions, and how many will have no preference. If there are very few participants willing to be randomized into either intervention (i.e. with no clear preference at baseline), the RCT arms may be difficult to populate. To manage this we will shift recruitment strategies if the preference arms meet recruitment targets first and focus on recruitment of people willing to be randomized into either intervention.

Recruitment in general is always a challenge for large clinical trials with cancer survivors, but we have faced this challenge previously and have developed effective strategies for recruitment. We are also using the Princess Margaret Cancer Centre as a recruitment and treatment delivery site for the first time, so while they are an experienced team, methods will still need to be tested and refined in that locality. Having fairly broad inclusion criteria should help with recruitment, and these may also be adjusted over time if low recruitment rates are found. Another barrier to recruitment is going to be the requirement of randomization into immediate or delayed groups within both preference and non-preference arms. As such, participants will have to make themselves available for program dates over a period of 6 months, in case they are randomized to the waitlist groups. Logistically managing simultaneous baseline and follow-up assessments with limited resources as cohorts progress is an additional difficulty.

In our previous studies retention has also been a challenge. In MINDSET we used a full year of follow-up and lost almost half of the sample by that point. In this study we will focus on a shorter follow-up time, due partly to this factor and also due to financial constraints. We will apply more aggressive retention strategies in this study, including regular newsletters to participants, calls from RAs, social media discussion groups, a study website and regular email communication listing relevant and interesting resources. Questionnaires will also be available to complete easily and securely online at home. We are not able to pay participants a stipend for completing assessments, but if budgetary constraints allow we will pay for their parking expenses and

provide them with coffee cards or similar as compensation after each assessment.

In summary, the MATCH trial is a large, ambitious and innovative study attempting to understand on a more nuanced level what type of mind-body therapies may be beneficial for a wide range of cancer survivors troubled by a myriad of problems and symptoms. We will gain new understanding about the importance of patient preference and beliefs about treatments, and how personal and disease-related characteristics may be combined to predict who will benefit most from what type of intervention. Excitingly, we will also begin to understand more about the mind-body connection and how psychosocial interventions can potentially “get in the body” and affect a range of important cancer-related biomarkers. Health economic data will also help us to understand potential fiscal benefits of these complementary therapies, which in turn may help to accelerate implementation efforts.

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