MSK PROTOCOL COVER SHEET

Integrative Medicine for Patient-reported Outcomes, Values and Experience (IMPROVE)

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Table of Contents

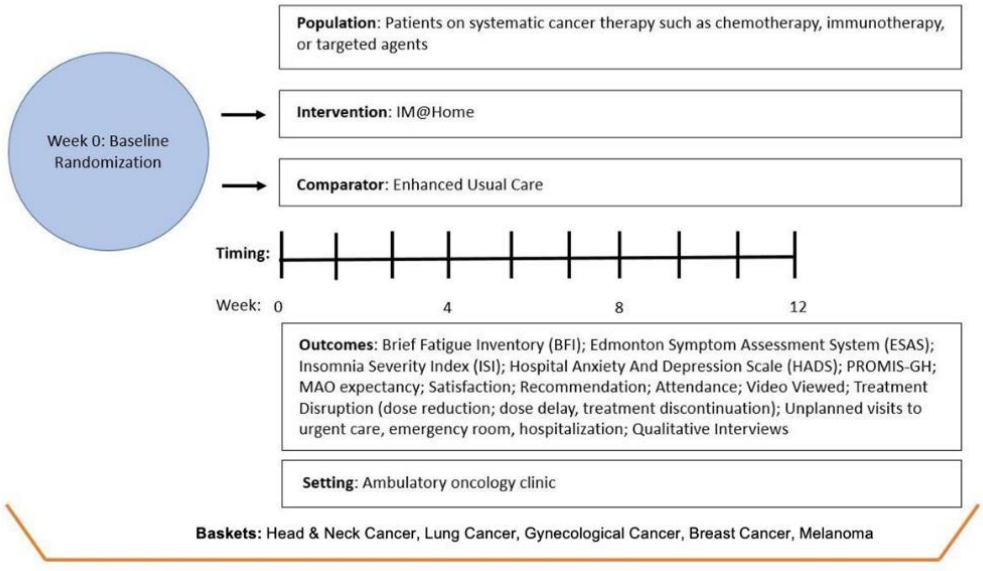
1.0 PROTOCOL SUMMARY AND/OR SCHEMA 3
2.0 OBJECTIVES AND SCIENTIFIC AIMS 4
3.0 BACKGROUND AND RATIONALE 4
4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION 9
4.1 Design 9
4.2 Intervention 9
5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS 11
6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY 11
6.1 Participant Inclusion Criteria 11
6.2 Participant Exclusion Criteria 12
7.0 RECRUITMENT PLAN 12
7.1 Research Participant Registration 13
7.2 Randomization 13
8.0 INFORMED CONSENT PROCEDURES 14
9.0 PRE-TREATMENT/INTERVENTION 14
10.0 TREATMENT/INTERVENTION PLAN 16
11.0 EVALUATION DURING TREATMENT/INTERVENTION 16
12.0 CRITERIA FOR REMOVAL FROM STUDY 18
13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY 19
14.0 BIOSTATISTICS 19
15.0 TOXICITIES/RISKS/SIDE EFFECTS 22
15.1 Serious Adverse Event (SAE) Reporting 23
15.2. External SAE Reporting 24
16.0 PROTECTION OF HUMAN PARTICIPANTS 24
16.1 Privacy 26
16.2 Data Management 26
16.3 Quality Assurance 28
16.4 Data and Safety Monitoring 28
17.0 REFERENCES 28
18.0 APPENDICES 37

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Table 1. Protocol Summary	
Study Title	**I**ntegrative **M**edicine for **P**atient-**r**eported **O**utcomes **V**alues and **E**xperience (**IMPROVE**)
Primary Aim	To evaluate the effect of IM@Home intervention on symptoms, oncology treatment adherence, and health care utilization among oncology patients undergoing active systemic treatment.
Secondary Aim	To identify the specific factors (e.g., socio-demographic, clinical, or symptom) associated with IM@Home engagement and satisfaction among oncology patients undergoing active systemic treatment.
Tertiary Aim	To understand patients' experiences and identify opportunities for refinement of IM@Home program in specific tumor groups to be further developed and tested.
Exploratory Aim	To evaluate the effect of active radiation treatment vs. finishing radiation treatment on trial enrollment and participation in the IM@Home program among women with breast cancer.
Patient Population	Patients on any systemic cancer therapy such as chemotherapy, immunotherapy, radiotherapy or targeted agents used alone or in combination or up to 4 weeks of radiation treatment completion.
Total Enrollment	200 patients
Study Design	Randomized Controlled Trial (PRO-Basket Design)
Treatment	Participants will receive 12 weeks of enhanced usual care, or virtual mind- body program (IM@Home)
Time to Completion	Participants will be on the study for 12 weeks.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Figure 1 IMPROVE Study Schema



The overarching long-term goal of the **I**ntegrative **M**edicine for **P**atient-**r**eported **O**utcomes **V**alues and **E**xperience (**IMPROVE**) research program is to evaluate whether integrating a virtual mind-body programming, Integrative Medicine at Home (IM@Home), will improve patient perceived values, outcomes, and experiences as they undergo systemic cancer treatment such as chemotherapy, immunotherapy, radiotherapy or targeted agents. IM@Home is a virtual mind-body live programming that we have developed in response to COVID-19. The 7-day a week program has registered over 30,000 class participants (mostly cancer patients) since April 1st, 2020. Our ongoing qualitative research has shown that participants valued IM@Home to improve their physical activities, reduce anxiety and promote social connectedness with other cancer patients. Building on both prior scientific literature and our preliminary experience, our overarching hypothesis is that IM@Home can be integrated into oncological treatment to improve symptom control, quality of life, functions, and adherence to cancer therapies. The specific aims are as followed and will be stratified by 5 cancer types: head and neck cancer, lung cancer, gynecological cancer, melanoma, and breast cancer:

1. **Primary Aim:** To evaluate the effect of IM@Home intervention on symptoms, oncology treatment adherence, and health care utilization among oncology patients undergoing active systemic treatment.

   Hypothesis 1(a): Compared with enhanced usual care group, participants in the IM@Home group will have lower fatigue severity (**Primary Outcome**) and co-morbid symptoms (e.g., pain, insomnia, anxiety) while experiencing higher quality of life during the 12 weeks from randomization.
   Exploratory hypothesis 1(b): Compared with enhanced usual care group, participants in the IM@Home group will have less oncology treatment disruptions (e.g., dose reduction, dose delay, treatment premature discontinuation) during 12 weeks from randomization.
   Exploratory hypothesis 1(c): Compared with enhanced usual care group, participants in the IM@Home group will have less unplanned emergency room utilization and hospitalization during the 12 weeks from randomization.

2. **Secondary Aim**: To identify the specific factors (e.g., socio-demographic, clinical, or symptom) associated with IM@Home engagement and satisfaction among oncology patients undergoing active systemic treatment.

   Exploratory Hypothesis 2(a): Specific socio-demographic (i.e., age, sex, race/ethnicity, education) and clinical factors (e.g., tumor type, stage, cancer therapy, presence of anemia), and baseline symptoms (e.g., fatigue, pain, anxiety), and outcome expectancy may be associated with the overall engagement of IM@Home program.
   Exploratory Hypothesis 2(b): Specific socio-demographic (i.e., age, sex, race/ethnicity, education) and clinical factors (e.g., tumor type, stage, cancer therapy, presence of anemia), and baseline symptoms (e.g., fatigue, pain, anxiety), and outcome expectancy may be associated with the overall satisfaction of IM@Home program.

3. **Tertiary Aim:** To understand patients' experiences, perceived values, and identify opportunities for further refinement of IM@Home program in specific tumor groups for further development and testing.

   Exploratory Hypothesis 3: Participants may experience unique benefits, perceived values, and challenges with participation in IM@Home and can provide important insight to further develop specific treatment pathways to enable future program refinement.

4. **Exploratory Aim (Breast Basket only):** To evaluate if timing of patient recruitment, during active treatment vs. within four weeks of finishing radiation treatment, impacts the rate of trial enrollment and participation in the IM@Home program among women with breast cancer.

   Exploratory Hypothesis 4(a): Recruitment of patients within four weeks of finishing radiation treatment will result in higher enrollment rates than those on active radiation treatment.
   Exploratory Hypothesis 4(b): Patients enrolled within four weeks of radiation treatment stop date will attend more classes than those on active treatment.

3.0 BACKGROUND AND RATIONALE

3.1 Symptom Burden During Active Cancer Treatment: An Unmet Need. Patients with cancer experience substantial physical and psychological symptom burden during oncological treatment.[1] In a systematic review of symptom burden during active cancer treatment (n = 4067), symptoms such as fatigue (59%), pain (48%), insomnia (49%), irritability (52%), and depression (34%) are among the most common.[2] Apart from their cancers, patients may have to cope with symptom toxicity from their treatment.[3-5] In fact, symptom burden increases with more aggressive treatment. In an observational study (n = 2596), relative treatment toxicities double or quadruple when patients receive radiation (23.8%), chemotherapy (30.4%), or chemoradiation (39.2%), compared to no treatment (10.1%).[6] The cumulative symptom burden can further impair physical functioning, leading to reduced physical activities, which further impedes recovery.[7] At MSK, there were 9,424 UCC visits among patients who were on active therapy of which 68% were for CMS-defined potentially preventable conditions. Pain was the most frequent cause of UCC presentation (n=3,368) followed by fever (n=2,152) and nausea/emesis (n=1,376). Despite growing recognition of the importance of symptom control, symptom management is often viewed secondary to the active cancer treatment; symptoms may be under-managed or overlooked as reflected by the discordance of clinician- and patient-reported symptom burden.[8] For patients undergoing radiation for primary breast cancer, MSK implemented an electronic patient-reported outcomes tool (ePRO) to collect side effects of radiation weekly during and for 6 weeks immediately after finishing treatment. [82] Among 678 patients completing 5,787 PROCTCAE questionnaires, fatigue was identified as one of the most common symptoms with up to 60% of patients experiencing moderate or greater fatigue at some point during or immediately after treatment. A separate study of patients underoing radiation recently found that patient-reported fatigue correlated with quality of life more than other disease-specific symptoms. [83] Furthermore, the coronavirus disease 2019 (COVID-19) pandemic unprecedentedly disrupted the delivery of necessary cancer and supportive care, as well as patients' coping routine;[9, 10] thus, there is a critical need to test novel virtual interventions that enhance engagement, personalize treatment, and expand access to evidence-based symptom management services.

3.2 Non-Pharmacological Interventions for Symptom Management: The Challenge in Research & Integration. Evidence for non-pharmacological interventions have been increasing over the last two decades to improve the quality of life and symptom burden for patients with cancer.[11-13] For example, high-quality metanalyses and systematic reviews have shown that aerobic exercise enhances physical functioning and decreases fatigue;[14, 15] yoga improves health-related quality of life and reduces fatigue, insomnia, anxiety, and depression;[16] and meditation lessen patients' fear of recurrence and other psychological distress.[17] Among men undergoing prostate radiation, resistance and aerobic exercise has been shown to reduce fatigue in a randomized. [84] With growing evidence in today's era of

patient-centered care, the question now becomes how we can best tailor specific treatment at the specific setting to the specific patient needs. Historically, research on non-pharmacological interventions in oncology has mostly been conducted by controlling for a single cancer population, primarily in breast or prostate cancer; for a single symptom such as fatigue or insomnia; and for a single intervention like yoga or exercise. Optimal symptom management for patients during active treatment is unlikely to benefit from a one-size-fits-all approach. Given several evidence-based interventions available, there is a need to see whether packaging these approaches together and providing patients with choices depending on the patients' unique physical and emotional needs. Further, despite the growing evidence of these non-pharmacological interventions for symptom control, they are rarely integrated into oncological care delivery. Therefore, we propose a novel study design, a PRO-basket trial, to advance patient-centered research by investigating IM@Home as a multimodality program among patients across different cancer types, and to leverage technology to deliver a choice of integrated non-pharmacological services for patients during active cancer treatment.

3.3 IM@Home: A Potential Solution for Scalable Symptom Care Delivery. Telemedicine has the potential to increase the access and reach of symptom management services.[18] Initially developed for rural populations, telemedicine uses telecommunication technologies to deliver remote health care services to patients with limited access to care.[18-20] In oncology, telemedicine has been tested in multiple clinical settings, including remote chemotherapy supervision,[21, 22] symptom management,[23-25] and cancer clinical trials.[26-29] Early experience of tele-oncology services demonstrated promising outcomes of feasibility, satisfaction, and cost-effectiveness.[18] Despite the potential, telemedicine has not been widely adopted until the COVID-19 pandemic, and its role in delivering non-pharmacological services remains undefined. At Memorial Sloan Kettering Cancer Center (MSK), we deployed one of the nation's first cancer-specific virtual mind-body medicine platforms – IM@Home. An early attendance record of 5,948 unique visits demonstrates high engagement and satisfaction, suggesting that remote mind-body service is acceptable and can improve symptom outcomes.[29] Our ongoing qualitative research shows that IM@Home improves physical activities, reduces anxiety, and promotes social engagement. Thus, building on the feasibility and perceived values from patients, we bring a multidisciplinary group of investigators in integrative medicine, medical oncology, radiation oncology, implementation science, psycho-oncology, patient-reported outcomes, and biostatistics and propose a novel research program, IMPROVE, to evaluate whether IM@Home will improve patients' perceived values, outcomes and experiences as they undergo active systemic cancer treatment.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The overall design of the IMPROVE research program is a randomized controlled trial using a novel PRO-basket study design that we have conceptualized to identify study participants based on a targeted patient-reported outcome (PRO). Traditionally, a basket trial is a type of "master" protocol designed to improve the efficiency of developing promising therapies for different diseases that share a similar therapeutic target (e.g., BRAF V600E mutation).[30] Master protocols, classified as basket trials, umbrella trials, and platform trials, are novel designs that investigate multiple hypotheses through concurrent sub-studies (e.g., multiple treatments or populations or that allow adding/removing arms during the trial). However, therapeutic target as defined in a traditional basket trial is less suitable in symptom oncology research when targeted outcomes are often measured by PRO. Therefore, we conceptualize the PRO-basket trial study design to define the therapeutic target as a specific PRO (e.g., fatigue). With a PRO-basket trial, our goal is to

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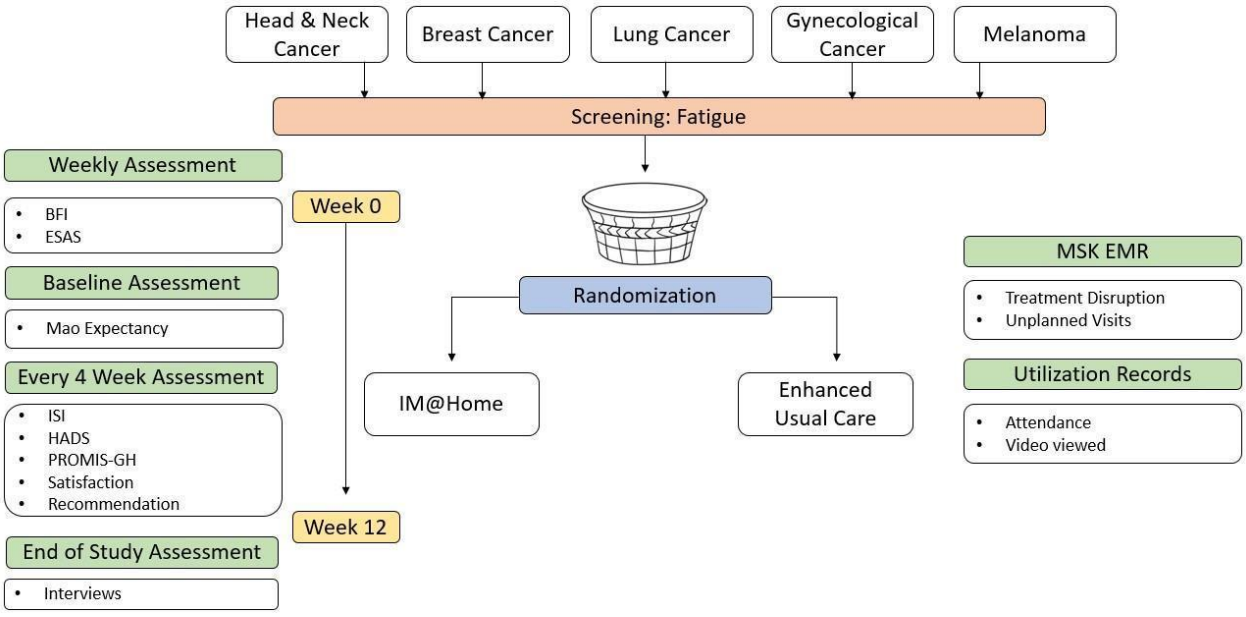
adapt the similar master-protocol concept to accelerate the development of symptom and quality of life research in oncology. In addition, basket trial design usually may not include a control group given the expected response rate is reasonably characterized for a specific tumor; however, in symptom research, the variability of symptom outcomes is not clearly known; therefore, including both randomization and a control group will allow us to detect signals that we can power for future clinical trials. In summary, our trial design represents an innovation for increasing the efficiency of developing effective supportive care interventions that can be more quickly implemented into specific oncology settings to improve patient-reported and clinical outcomes.

Based on qualitative research we have conducted so far, IM@Home improved patients' engagement in physical activities, reduced psychological distress, and fostered social connectedness among a community of cancer patients and survivors. We hypothesize that these are desirable targets that can then improve symptoms such as fatigue and other co-morbid symptoms, increase the adherence to oncological treatment (prevent dose reduction or treatment delay), and prevent unplanned health care utilization (e.g., emergency room visit and hospitalization). However, we are also mindful that the testing of virtual supportive interventions is also in its infancy; therefore, we choose not to design a large definitive trial as we do not clearly know that this intervention in the current format will optimally address patients' experience, values, and outcomes in specific disease settings. Further, the specific outcome measures may differ in the disease groups. Therefore, the choice of the randomized PRO-basket trial design will allow us to examine the overall effects of the intervention in patients undergoing active treatment as well as provide a focused examination within the disease setting so we can estimate effect size for specific outcomes and inform the development of precision IM@Home for specific disease groups.

Figure 2 IMPROVE Study Design



4.2 Interventions

IM@Home: Patients will be enrolled into either IM@Home or enhanced usual care for the study duration of 12 weeks. IM@Home is an online mind-body program consisted of a series of

virtual, synchronous classes that offer a variety of rigorously tested mind-body therapies led by an Integrative Medicine Service (IMS) clinical therapist. The virtual mind-body group therapy sessions will be conducted using Zoom video conferencing platform. Once enrolled in IM@home, a message will be sent to the patients, through the MSK's patient messaging portal, with detailed information regarding the schedule of the classes offered and how to register for individual classes in Zoom. *(Figure 3)* Patients will then register for each class they wish to attend. Patients can choose to register and participate in as many classes as they prefer. Once registered, patients will receive a confirmation email with Zoom link, password, and instructions to join their chosen classes. Patients choose from a variety of weekly classes, occurring one to four times per week. A licensed IMS clinician (e.g., licensed dance therapist, certified yoga instructor, nurse specialist/physical trainer) with specific expertise in the oncology setting will lead each session. Activities can range from more movement-based (fitness, yoga, dance therapy, or tai chi) to meditative (meditation, guided meditation, or music therapy). All clinicians will provide an overview of the session, 25 to 40 minutes of content, and five minutes for feedback and discussion. Each class lasts 30 to 45 minutes with optional audio or video participant participation and group chat.

Figure 3 IM@Home Class Schedule

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
8:30 to 9:15 AM: **Fitness for Everyone**						8:30 to 9:15 AM: **Core Strength**
9:30 to 10:00 AM: **Morning Meditation**	9:30 to 10:15 AM: **Tai Chi**	9:30 to 10:30 AM: **Fitness for Everyone**	9:30 to 10:00 AM: **Morning Meditation**	9:30 to 10:30 AM: **Fitness for Everyone**	9:30 to 10:15 AM: **Tai Chi**	9:30 to 10:30 AM: **Chair Yoga**
			10:30 to 11:00 AM: **Fitness for Everyone**	1:00 to 2:00 PM: **Dance Therapy**	1:00 to 1:45 PM: **Dance Cardio**	
5:00 to 5:45 PM: **Dance Cardio**	4:00 to 5:00 PM: **Chair Yoga**	4:00 to 4:30 PM: **Tai Chi**		4:00 to 4:45 PM: **Music Therapy**		5:00 to 5:30 PM: **Evening Meditation**
	7:00 to 7:45 PM: **Core Strength**	7:00 to 7:45 PM: **Music Therapy**	7:00 to 7:45 PM: **Mat Yoga**			

Virtual Classes, available to the patients, with brief description are listed below:

4.2a *Physical Fitness Group Sessions*

Fitness for Everyone
Description: This class includes cardio fitness; resistance training; and breathing, balancing,

and stretching exercises.

Dance Cardio
Description: This faster-paced, cardio-focused dance class is designed to boost energy. This class is low impact but will keep the body moving with basic dance moves while keeping the heart rate elevated.

Core Strength
Description: This low-impact, moderate-intensity floor mat class aims to increase spinal flexibility and mobility. Inspired by Pilates, Barre, and yoga, this class focuses on mindful movement to build core strength and improve posture.

Benefits of exercise: Studies have shown that exercise enhances physical functioning and decreases fatigue;[14, 15] NCCN clinical guidelines recommend exercise for management of cancer-related pain, fatigue, and anxiety/depression, among other symptoms.[31, 32]

Tai Chi
Description: Tai chi is a traditional Chinese self-defense practice and gentle form of exercise based on a series of graceful movements. It can increase balance, steady breathing, and improve mental function and outlook. This class is for people with or without tai chi experience. Exercises can be done seated or standing.

Benefits: Preliminary studies in cancer patients suggest that tai chi improves QoL[33, 34] and neuropsychological functioning.[35] In addition, meta-analyses found significant improvements in cancer-related fatigue, sleep difficulty, depression, and QoL[36] as well as cortisol levels and limb function.[37]

Chair Yoga
Description: This class consists of gentle and purposeful movements of chair yoga to bring awareness to the body. The class focuses on the spine and practice breath work (pranayama) to calm the nervous system.

Mat Yoga
Description: This mat yoga class aims to ease side effects of cancer treatment such as lymphedema, neuropathy, and bone density loss through sequenced movements (vinyasa), supported balances, and breathing exercises.

Benefits of yoga: Studies show that yoga can help promote stress reduction, a sense of well-being, restful sleep, and better quality of life. [38-41] [42-44] in recently diagnosed cancer patients as well as survivors. Additionally, it decreases fatigue in patients with various cancer types.[45] Further studies have shown yoga's benefit in social functioning, mood, stress reduction[46], and management of psychological symptoms.[47] Guidelines from SIO[48] and ASCO[49] also indicate yoga for cancer patients to help manage depression, anxiety, and mood disturbances, as well as to decrease stress and enhance overall quality of life.

4.2b *Mind-Body Group Sessions*

Morning Meditation
Description: This is a group meditation session designed to connect participants with their community and inner self. This class is for people with or without meditation experience.

Evening Meditation
Description: This meditation at the end of the day is designed to transition into a relaxed mindset. This class is for people with or without meditation experience.

Benefits of meditation: Studies show that meditation is effective for reducing anxiety, depression, fear of recurrence, and fatigue[50, 51] as well as improve sleep quality in cancer patients. Current SIO[48, 52] and ASCO[49] cancer care guidelines suggest meditation for improving quality of life, mood disturbance, reducing anxiety and stress, fatigue, and depression in cancer patients. NCCN cancer guidelines for supportive cancer care also recommends meditation for fatigue.[53]

Music Therapy
Description: This is a relaxing and interactive musical session with an MSK music therapist. Soothing and stimulating music and guided relaxation accompanied by classical guitar are designed to increase well-being, regulate emotions, balance energy, and connect with inner peace and resilience.

Benefits: Preliminary studies have shown music therapy to reduce cancer-related fatigue,[54] pain,[55] and anxiety.[54, 56, 57] Current oncology societies recommend music therapy for anxiety, stress reduction, depression and mood disorders.[58] Music therapy is also indicated in the NCCN guidelines for anxiety/depression and nausea/vomiting.[53]

Dance Therapy
Description: This gentle body workout engages the mind and body by opening a playful space for stretching, movement, and dancing.

4.2c *Fidelity of Delivery of Interventions:* Licensed and oncology-experienced physical fitness specialists and mind-body therapists will deliver all interventions. Our clinical lead and senior clinical coordinator (who is also a yoga instructor) will audit a class each week.

4.2d Enhanced Usual Care: Patients in the enhanced usual care will receive usual care. In addition, once enrolling into the trial, they will be given a handout to encourage them to visit the MSK's multimedia page on the Integrative Medicine website to access pre-recorded, on-demand meditation videos/audios. Patients will be provided the following link to the website, also known as Meditation Station, to access any of the videos/audios: https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/multimedia/meditations

The website has 17 audio or video recordings of meditation, guided imagery, music guided relaxation. The enhanced usual care seeks to provide participants with something that can help them but without the key active ingredient of live class programming available in IM@Home. After the primary outcome assessment at 12 weeks, participants in the Enhanced usual care group will be given a 3-month access to IM@Home.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

All IM@Home sessions will be held virtually. An IMS staff member will initiate and troubleshoot any technical issue related to Zoom prior to the start of each IM@Home session. After each session, participants will be asked to provide feedback on the virtual session.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

We have established broad eligibility criteria to be consistent with our study design, while ensuring the safety of participants and the rigor of clinical research. To be eligible for the study, patients will be 18 years or older; have a diagnosis of head and neck cancer, thoracic cancer, gynecological cancer, melanoma or breast cancer; are actively receiving systemic or locoregional oncological treatment including chemotherapy, immunotherapy, targeted agents, or radiotherapy; has Karnofsky score 60 or greater (ambulatory); have a life expectancy greater than six months; and speak English. We selected these criteria to ensure that: 1) the study is safe for the research participants; 2) the population is relevant to the eventual dissemination of the information with as wide as possible inclusion criteria; 3) the population is relatively well-defined so that the change in outcomes among intervention groups can be appropriately measured and detected. No individuals will be excluded on the basis of race, ethnicity, or sex.

6.1 Participant Inclusion Criteria

- Age ≥ 18 years or older
- Patients with a diagnosis of head and neck tumors, thoracic tumors, gynecological tumors, melanoma, or breast cancer
- Actively receiving systemic oncological treatment or radiotherapy, or within 4 weeks of radiotherapy completion
- Worst fatigue over the last 7 days rated 4 or greater on (0-10 scale)
- Karnoffsky score 60 or greater
- Life expectancy greater than six months
- English speaking

6.2 Participant Exclusion Criteria

- Cognitive impairment that would preclude response to study assessments or require the use of Legally Authorized Representatives
- Unwilling to accept random assignment
- Concurrently enroll onto ongoing competing trials of integrative medicine interventions with symptom/toxicity as primary outcome. Note, however, patient will be allowed to enroll on other therapeutic protocols

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited waiver of Authorization)
Potential participants can be identified and referred to the study clinical research coordinator (CRC) for accrual and consent by protocol investigators. The study PI and Co-I of the research team will reach out to colleagues about the study and present at Service meetings, including Head and Neck Oncology, Thoracic Oncology, GYN Med Oncology, Breast Radiation Oncology, and Melanoma. In addition to Integrative Medicine physicians, other Integrative Medicine therapists can also refer patients to the study. Participants will also be recruited at the Regional Care Network sites. Study investigators and interested colleagues will be provided with study flyers (Electronic or paper format) to provide to potential participants (approved by IRB). We will also work with health informatics to develop digital recruitment strategy during the life of this proposal to increase the efficiency of providing potential eligible patients the opportunity to learn and participate in this study.

For Breast Radiation Oncology specifically, we will have informatics conduct a weekly query of the ePRO for “Acute Breast Symptoms” with fatigue scored moderate or greater to provide to the CRC. We will then create a list of all radiation oncologists treating breast cancer patients (approximately 23, excluding the two breast basket leads that already enrolled more than one patient to this trial) and randomize them to recruit their patients using either standard of care (in which we rely on the clinical team identify patients and notify the CRC) or a direct portal message to the patient inviting them to meet with the CRC to discuss the study. This randomization will be stratified by physician caseload (high/low) and physicians will be assigned to the two groups with 1:1 ratio. We will utilize this system to message patients that are either on treatment or post-radiation treatment for less than or equal to four weeks. The goal of this approach is to assess if using ePROs to automatically prompt patients for an intervention invitation increases the likelihood of them taking the next step. Specifically, for the patients who are post-radiation treatment, the goal is to evaluate if recruiting patients during the post-treatment period increases the rate of trial enrollment and/or impacts participation in the IM@Home. Additionally, for those within the ePRO prompt group and actively on treatment, we will assign every other patient to one of two versions of the portal message, in which the message comes from either a) the primary treating radiation oncologist and clinical team or b) the Integrative Medicine Service.

Information about the protocol will appear in lay language on MSK’s website and on clinicaltrials.gov. Materials will also be distributed to potential referral sources who we have worked with on other research studies. All study recruitment materials will be submitted to and approved by the Institutional Review Board. We have used these recruitment strategies successfully to recruit participants to similar studies.

Potential research subjects will be identified by a member of the patient’s treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient’s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator and study team may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, initial contact with prospective subject will be conducted either by the treatment team, or the research staff working in consultation with the treatment team. The recruitment process presents no more than minimal risk to patient privacy, and minimal PHI will be

maintained on screening logs. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained in those records and provided by potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Once a patient is deemed eligible, they may be enrolled through an in-person consent appointment, econsent, or by a verbal consent conducted over the phone. Patients who do not have a desktop or laptop computer capable of a remote econsent and who cannot travel to Manhattan may be consented using a verbal consent. Patients recruited at the Regional Care Network sites will be consented remotely through telemedicine by Integrative Medicine CRCs.

We estimated an overall accrual rate of 15 to 20 patients per month, with 3 to 5 patients per month from each of the disease groups. Given our broad eligibility criteria, majority of patients within each disease group would be eligible for our study. Because our basket (PRO) target of fatigue is common, we anticipate the accrual rate to be fairly distributed among groups. Additionally, our co-investigators will facilitate patient enrollment from each subspecialty. In the event of delayed accrual from a specific disease group, we will work closely with the disease-specific investigators to do targeted recruitment in that specific disease group.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

Participants will be randomized to IM@Home or enhanced usual care (allocation ratio 1:1) using MSK's Clinical Research Database (CRDB), a secure computer system that ensures full allocation concealment. After eligibility is established and consent is obtained, patients will be registered through the Clinical Trials Management System (CTMS) and then randomized using the Randomization Module in the CRDB. Randomization will be accomplished by the method of random permuted block stratified by each tumor type (head and neck cancer, lung cancer, gynecological cancer, melanoma, breast cancer). For each of these 5 tumor types, we will randomize 40 patients. Information on group assignments will be communicated to the CRCs. The study statisticians and the outcome assessment CRC will remain blinded. The CRC will inform the subject whether s/he is randomized to the IM@Home or enhanced usual care control group, after which the CRC will virtually enroll the subject to the randomization assignment.

8.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals including the PI, Co-PI, and research staff will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign or verbally agree to an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants. The participant will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant and consenting professional will sign and date the consent form. The participant must receive a copy of the signed informed consent form.

If a verbal consent is being conducted, the consenting professional will use the IRB/PB-approved verbal informed consent script when calling patients. A verbal consent would be used in cases where individuals do not have access to a computer and those who are unable to travel to Manhattan for an in-person consent appointment. In following the Code of Federal Regulations Title 45, Part 46, Subpart A, the IRB is waiving the requirement for an investigator to obtain a signed consent form from the participant as the research:

1. This research involves no more than minimal risk to participants and
2. Use of a verbal consent would not adversely affect the rights and welfare of the research participants.

The verbal informed consent/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent/research authorization script will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.
2. The length of study, what it entails, and the likely follow-up required.
3. Alternatives to the proposed study.
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
6. How the participants' data will be protected, who will have access to their PHI, and what

data will be disclosed for research purposes.

The consenting professional must sign an IRB/PB-approved consent /research authorization script to document the consent discussion and the participant's agreement.
In following the Code of Federal Regulations Title 45, Part 164, Subpart E, IRB/PB is waiving the requirement for the investigator to obtain signed research authorization from the participant as:

- The use or disclosure of the PHI involves no more than minimal risk to the privacy of the individuals, based on the following elements:
  - An adequate plan to protect identifiers from improper use and disclosure;
  - An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and
  - Adequate written assurances that the PHI will not be reused or re-disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.
- The research could not be practicably conducted without access to and use of the PHI.
- The research could not practicably be conducted without the waiver.

A member of the research staff will notify the primary oncologist of the patient's enrollment in the study and will be informed if the patient will be participating in the study.

9.0 PRE-TREATMENT/INTERVENTION

9.1 Initial Screening: All potential participants will undergo an initial screening with a CRC in person or over the telephone. At this initial contact, the CRC will explain the study goals and procedures and ensure that participants meet basic eligibility criteria.

9.2 Clinician Screening, Informed Consent, and Baseline Assessment: Interested and potentially eligible patients will complete screening form found online using MSK Engage or over the phone by a member of the research staff. If deemed eligible, the study staff will explain the study procedures and review the written informed consent with the patient. After patients sign the informed consent, they will complete a set of baseline questionnaires. Please see Table 1 below for questionnaires collected throughout the study period. All questionnaires and diaries have a window of plus or minus ten days.

9.3 Covariates: We will collect specific demographic (e.g., age, sex, race/ethnicity, education) and other relevant historical medical data on each subject (e.g., tumor type, stage, cancer therapy, presence of anemia). As symptoms often result in increased health care utilization and treatment disruption, we will track unplanned visits to the urgent care, emergency department, and hospitalizations, as well as any treatment disruption such as dose reduction, dose delay and treatment discontinuation by patient self-report and in the EMR. Additionally, we will collect the patient's reasons for either stopping participation of virtual intervention or dropping out of the clinical trial, such as treatment adverse events or disease complications.

Table 1. Schedule of data collection		
	BL†	Active Intervention

Outcome	Week 0	1	2	3	4	5	6	7	8	9	10	11	12
Primary Outcome													
Brief Fatigue Inventory*	x	x	X	x	x	x	x	x	x	x	x	x	x
Secondary Outcomes													
Edmonton Symptom Assessment System (ESAS)	x	x	X	x	x	x	x	x	x	x	x	x	x
PROMIS-10 Global Health	x				x				x				x
Insomnia Severity Index (ISI)	x				x				x				x
Hospital Anxiety and Depression Scale (HADS)	x				x				x				x
Satisfaction/Recommendation of Intervention					x				x				x
Treatment Disruption (e.g., dose reduction, dose delay, treatment discontinuation)													x
Unplanned visits (e.g., urgent care, emergency room, hospitalization)					x				x				x
Attendance to IM@Home Sessions	x	x	x	x	x	x	x	x	x	x	x	x	x
Covariates													
Demographics (e.g., age, sex, race/ethnicity, education)	x												
Clinical Characteristics (e.g., tumor type, stage, cancer therapy, presence of anemia)	x												
Predictive Variables													
Mao Expectancy of Treatment Effects	x												
* Average fatigue severity is the primary outcome													

†BL: Baseline

10.0 TREATMENT/INTERVENTION PLAN

IM@Home is a monthly membership program of online lifestyle and mind-body classes. Developed and delivered by our expert team of integrative cancer care specialists, Integrative Medicine at Home offers daily online group classes plus discounts for immersive small-group workshops. Group classes include cardio-strength fitness training, yoga, Tai Chi, mindfulness meditation, music therapy, and dance therapy.

Patients recruited in the intervention arm will be enrolled at no cost to the IM@Home membership for 12 weeks through the study duration. Once enrolled, a message will be sent to the patients, through the MSK's patient messaging portal, with detailed information about how to register for individual classes in Zoom and schedule of the classes offered. Patients will then register once for each class they wish to attend. Patients can choose to register and participate in as many classes as they prefer. Once registered, they will receive a confirmation email with a Zoom link, password and instructions to join their chosen classes. More information can be found on the web: https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/therapies/membership

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Patients assigned to the enhanced usual care control group will be enrolled in our "meditation station" as well as subscription to the on-demand video to encourage them to keep physically active during treatment.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

The study schema and study schedule were presented in Section 1.0, Figure 1, and Section 9.0, Table 1, respectively. The following questionnaires will be collected according to the study schedule table. All patient-reported outcomes (PROs) have been previously validated and shown to be reliable, valid, and responsive to change in our prior studies. The average time to complete the PROs is 30 minutes, which has been judged to be acceptable by our prior study participants with minimal missing data. Patients will complete PROs online using MSK Engage or over the phone with the outcome assessment CRC, who is blinded to treatment group *(*see descriptive of MSK Engage below*). To minimize missing data, the CRC will check surveys after completion. For patients who miss a study assessment, the CRC will email/call patients to complete the assessment. Additionally, for patients who are unable to complete all PROs (due to sickness, time constraints, etc.), we will ask them to complete only the Brief Fatigue Inventory (primary outcome). This approach, of collecting PROs online has been validated in our prior research with less than 10% missing data. Online data collection through MSK Engage has been well received by our patient population. The data collection schema can be seen in Section 9.0, Table 1.

*All surveys will be developed and distributed under the MSK Engage platform. MSK Engage is the MSK's electronic questionnaire tool. It is a robust, user-friendly and secured platform that enable the collection and visualization of patient generated health data for clinical and research purposes. Built within the patient portal, MyMSK, and available for use in CIS, MSK Engage is seamlessly integrated into the patient and clinician experience.

11.1 Primary Outcome: Average Fatigue Severity from the Brief Fatigue Inventory (BFI)
Primary outcome will be measured by the **average fatigue severity** measured by the Brief Fatigue Inventory (BFI). The BFI is a 9-item instrument designed to assess one construct of fatigue severity in cancer and non-cancer populations. Three items ask patients to rate the severity of their fatigue at its "worst," "usual," and "now" during normal waking hours, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine." Six items assess the amount that fatigue has interfered with different aspects of the patient's life during the past 24 hours. The interference items are measured on a 0–10 scale, with 0 being "does not interfere" and 10 being "completely interferes."[59] A composite fatigue severity score can be found by averaging the 9 item scores. The score was found to be reliable and valid in multiple languages and diverse populations.[59, 60] In our study, we will use the **average fatigue severity** as the **primary outcome** and the worst fatigue rating in the past week and the fatigue interference subscale as secondary fatigue outcomes.

11.2 Secondary Outcomes:

Edmonton Symptom Assessment Scale (ESAS): The ESAS is a brief self-report tool of symptom intensity, initially developed for patients with advanced cancer.[61] It includes nine common symptoms of advanced cancer (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath), with the option of adding a tenth patient-specific symptom. It is designed to capture multidimensional symptom profiles over

time by obtaining repeated quantitative measurements of symptom intensity with minimal patient burden. The original ESAS used visual analogue scales (VAS) to rate symptom intensity. A subsequent revised version replaced the VAS with 11-point numerical rating scales.[62, 63]

Insomnia Severity Index (ISI) will be used to measure subjective insomnia severity.[64] The ISI has 7 items rated on a 5-point Likert response scale (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28 with higher scores representing more severe insomnia symptoms. The usual recall period is the "last month." The ISI authors suggest the following guidelines for interpreting the ISI total score: < 8, no clinically significant insomnia; 8-14, subthreshold insomnia; 15-21, clinical insomnia (moderate severity); > 21, clinical insomnia (severe). [64] The ISI has demonstrated internal consistency, reliability, construct validity, specificity and sensitivity in a representative sample of 1670 cancer patients.[65] The ISI has established minimally important change values to ensure that the change is not only statistically, but also clinically, meaningful to patients.[66] A reduction of eight points has been deemed to be clinically significant improvement.[66]

Hospital Anxiety and Depression Scale (HADS) will be used to explore the effect of treatments on psychological distress. HADS is a 14-item scale with 7 items measuring depression and 7 items measuring anxiety. Each item is answered by the patient on a four-point (0-3) response category, so possible scores range from 0-21 for anxiety and depression, with higher scores indicating higher symptomatology. Established cutoffs are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.[67] Factor analysis showed two distinct but correlated factors of anxiety and depression.[68] The scale scores have been shown to be both reliable and valid.[69]

Patient Reported Outcomes Measurement Information System (PROMIS®) Scale v1.2 - Global Health is a brief instrument composed of 10 items that demonstrates adequate reliability and validity[70, 71] as a measure of health-related QOL in general and clinical populations.[72, 73] Patients are asked to respond to questions 1-8 and 10 on a scale of 1-5. Question 9 is on a 0-10 scale (average pain rating). The measure yields two scores, Physical Health and Mental Health, that will be used as secondary outcomes to evaluate the effect of our interventions on QOL.[70] These scores will be calculated using item-level calibrations based on item response theory (IRT) scaling and then transformed to T-Scores, which are standardized such that 50 represents the mean for the US general population, and the standard deviation around that mean is 10 points. Higher scores indicate better Physical and Mental Health.

Mao Expectancy of Treatment Effects (METE): is a four-item instrument originally developed as the Acupuncture Expectancy Scale (AES) by Mao (PI) et al.[74] Outcome expectancy has long been considered an important predictor of treatment outcomes and has gained increasing recognition in clinical trials.[75, 76] It has demonstrated reliability (Cronbach's α of 0.82) and validity and is positively correlated with patient self-reported efficacy and satisfaction.[74] The score ranges from 4 to 20, with higher scores indicating greater expectancy. We will use this measure to explore whether expectancy predicts treatment outcomes and may impact the observed differences between groups.

Satisfaction of Intervention
Satisfaction will be measured through a five-point Likert scale assessing overall approval and recommendations for improvement. Trevino et al. (2020) demonstrated high engagement and satisfaction with IMS remotely delivered mind-body services, including fitness, meditation,

yoga.[77] Furthermore, qualitative interviews will be conducted using thematic content analysis to determine program satisfaction and triangulate quantitative data.

Recommendation of Intervention to Others
Willingness to recommend the intervention will be measured by a one-item assessment. Participants will be asked their willingness to recommend the intervention to a friend, family member, or fellow cancer patient/survivor.

Treatment Disruption
Record on treatment disruption will be extracted from MSK EMR via DataLine. This includes records on dose reduction, dose delay, and treatment discontinuation. Participants will also self-report and comment on treatment disruption in log. Dose reduction is defined as any dosage decrease or adjustment relative to dosage at the start of intended systemic regimen. Dose delay is defined as any delay or temporary stoppage in administration of systemic regimen relative to the intended schedule. Treatment discontinuation is defined as permanent discontinuation of the intended systemic regimen that does not include treatment completion during intervention. The treatment variables will be abstracted by the clinical research coordinators and adjudicated with guidance from the collaborating medical oncologists in the specific services.

Unplanned medical visits
Record on unplanned medical visits to the urgent care, emergency room, and hospitalization will be patient-reported and extracted from MSK EMR via DataLine. For each unplanned medical visit, CPT code, ICD-10 code, chief complaints, and the length of stay will be collected. Unplanned medical visit data will also be tracked at partner hospitals in collaboration with ambulatory care. Participants will also self-report and comment on unplanned medical visits in log.

Attendance to IM@Home Sessions
Participants will self-report attendance in a weekly log of the number and type of classes attended. Once randomized, participants will be instructed to record their attendance in the mind-body classes throughout the week. A log will be sent out through the MSK Engage, where participants can fill out their attendance at the end of each week.

11.3 Qualitative Interviews:
Interviews will be conducted over the phone or via the Zoom conferencing platform and will last between 10-20 minutes. We will interview 10 participants within each tumor type between week 4 and week 8 of participation in the study. Participant level of engagement will be defined. We will purposely sample patients with high engagement and those with low engagement to understand the variations in patient-perceived experience, values, and challenges of participating in the program. Such information will be useful for further refinement of the program and inform future research. Using an interview guide developed by the research team (Appendix 2). Interviews will cover topics such as participants' reflections on their experience, their perception of the benefit and perceived values of these therapies, as well as areas of unmet need and recommendations for how to enhance the program. Consistent with the practice of semi-structured interviewing, the guide will also include subsidiary prompts to enable participants to elaborate on aspects of their experience. As interviews will be conducted and analyzed iteratively, themes from observational data will inform the formulation of questions for the interview guide. Interviews will be administered by a research staff member trained in qualitative interviewing and analysis. Interviews will be audio-recorded, and transcribed for qualitative analysis.

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

12.0 CRITERIA FOR REMOVAL FROM STUDY

Any subjects experiencing a serious adverse event (SAE) felt to be related to the study intervention will be removed from receiving further treatment. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study.

Subjects will be informed during the consent discussion that treatment may be discontinued due to Intolerable side effects (side effects felt by the patient, therapist, or physician to be of greater severity than the potential benefit from treatment).

Reasons for subject discontinuation from the clinical trial will be documented on the Study Termination Form, along with any referrals that are made. We will make every effort to continue to collect data on every subject for the entire study duration regardless of whether or not the subject continues to adhere to the study interventions, assuming the subject has not withdrawn his/her authorization to obtain such information.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

Our primary hypothesis is that over 12 weeks from randomization, participants in IM@Home will have in greater overall improvements in fatigue (primary outcome), co-morbid symptoms (e.g., pain, insomnia, anxiety), quality of life, oncology treatment adherence, and health care utilization compared to participants in the enhanced usual care. Our primary outcome measure is BFI average fatigue severity, which will be assessed at baseline and weekly up to 12 weeks post-randomization. Our secondary and exploratory outcome measures include ESAS, PROMIS-10 Global Health, ISI, and HADS, which will be assessed at baseline and at 4-, 8- and 12-weeks post-randomization. Additionally, we will track on a weekly basis individual patients' treatment disruption (e.g., dose reduction, dose delay, treatment discontinuation), unplanned visits (e.g., urgent care, emergency room, hospitalization), and attendance to IM@Home sessions or video viewed on enhanced usual care. At the end of interventions, we will conduct satisfaction survey and qualitative Interviews to 1) Understand patient perceived benefit and harm of the interventions: 2) Identify experiences that are not captured by our quantitative measures; and 3) Provide recommendations for further refinement of the program.

13.2 Criteria for Study Endpoint Evaluability

All patients who are randomized will be considered evaluable for the study primary endpoint of change in BFI average fatigue severity. No patient will be replaced after randomization. We will, at the minimum, have the baseline BFI average fatigue severity for all randomized patients, since patients will complete the BFI as part of eligibility screening. All randomized patients will be included in the analyses using the intention-to-treat (ITT) principle (i.e., participants will be analyzed according to the treatment group to which they will be randomly allocated regardless of drop-out or treatment adherence status).

14.0 BIOSTATISTICS

This is a single institution, investigator-initiated study evaluating the Integrative Medicine program @ Home (IM@HOME) against enhanced usual care. Two hundred patients initiating anti-neoplastic treatment will be randomized (allocation ratio 1:1) to one of the two arms and will be enrolled in the program for a 12-week period (n=100 in IM@HOME, n=100 in enhanced usual care arms). IM@Home is an online mind-body program consisted of a series of virtual, synchronous classes that offer a variety of rigorously tested mind-body therapies. Patients can choose to register and participate in as many classes (fitness or meditative) as they prefer. Patients in the enhanced usual care will receive usual care and access to pre-recorded, on-demand meditation video/audios.

We describe the analysis for the primary objective below using the intention-to-treat (ITT) principle (i.e., participants will be analyzed according to the treatment group to which they will be randomly allocated regardless of drop-out or treatment adherence status). We will also perform a per-protocol sensitivity analysis among assessment completers, but study conclusions will be based upon the ITT analysis results.

This is a two-arm PRO-basket trial to compare the effectiveness of IM@HOME versus enhanced usual care for fatigue severity (primary outcome) and co-morbid symptoms (e.g., insomnia, anxiety) while experiencing higher quality of life during the 12 weeks from randomization. Patients will be randomized to either IM@HOME or enhanced usual care. Target cancers include head and neck cancer, melanoma, lung and gynecologic cancer. Patients will complete validated patient-reported outcome (PRO) measures: Brief Fatigue Inventory (BFI) at baseline and weekly for 12 weeks (primary outcome), Edmonton Symptom Assessment (ESAS) at baseline and weekly for 12 weeks. The PROMIS-10 Global Health, Insomnia Severity Index (ISI) and HADS will be measured at baseline, week 4, 8 and 12.

For the added recruitment strategy randomization (ePRO prompt vs standard of care) in Breast Radiation Oncology, we will use a negative binomial (NB) regression model to compare the enrollment rates (defined as enrollments divided by total number screening eligible based on ePRO survey responses) between patients recruited using the ePRO prompt vs standard of care. We will attempt to incorporate clustering of patients within physicians by either adding a random effect to the NB model (preferred) or by using a GEE version of the NB model, depending on the data distributions within and across physicians. Sample size permitting, we will also incorporate a variable in the model for race/ethnicity (defined as binary white/non-Hispanic vs other), with an interaction term for recruitment strategy (ePRO vs standard of care) to determine the potential impact of the recruitment strategy on enrolled population diversity. We will also report the number of patients referred and the reasons for non-enrollment. Of note, the two physicians leading the breast basket (that have already enrolled patients at the time of ePRO prompt initiation) will be excluded from this analysis. Additionally, to evaluate potential differences in patient response based on the source of the ePRO screening-based portal message (Rad Onc vs IMS), we will analyze the proportion of patients responding to the initial ePRO-prompted portal messages using a two-sample, two-sided proportion test. Secondarily, we will compare and report the proportion of patients enrolling.

14.1 Primary Aim: To evaluate the effect of IM@Home intervention on symptoms, oncology treatment adherence, and health care utilization among oncology patients undergoing active systemic treatment. We will plot the outcome measure trajectories by randomization arm over time and summarize each outcome measure at each assessment time by treatment arm using descriptive statistics. We expect patients who are participating in IM@Home will have lower level of fatigue severity relative to those in the control group. Accordingly, we will test for differences between the two study arms in change in BFI severity between baseline and the

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1275 York Avenue
New York, New York 10065

post-baseline follow-up period using a generalized estimating equations model (GEE) with identity link function and exchangeable correlation structure predicting BFI severity as a function of treatment arm, assessment period (baseline versus all post-baseline), and the arm-by-period interaction, controlling for disease type. Tests of ITT differences between randomization arms will be based on the coefficient for the arm-by-period interaction in the general GEE linear regression template described above. Secondary outcomes (e.g. ESAS, PROMIS-Global Health, ISI and HADS) will be analyzed using the same methods described above. The frequencies of treatment/dose delays, health services utilization and emergency department visits will be captured over the 12-week period and the frequencies will be compared across the two treatment arms using chi-square tests. Any visit as well as the number of visits will be analyzed by a variant of the GEE model described above. Since these endpoints are not continuous, we will use a model with the canonical link functions (logit link for the binary outcome of any visit and log link for the number of visits) and will also conduct covariate-adjusted analyses.

Sample Size and Power: Our sample size will provide sufficient statistical power to detect clinically relevant effect sizes for our primary outcome as well as for analyses for the secondary endpoints QOL measures, health services utilization. Our primary Aim 1 hypothesis is that IM@HOME will result in lowered average fatigue severity score compared to enhanced usual care across the 12-week period from randomization. Our GEE model will allow us to compare these average post-randomization change scores (taken over all post-randomization timepoints) while accounting for within-patient variation in these scores at repeated assessments. Although we will use a GEE model to compare the mean change in fatigue severity from baseline to post-baseline between arms, we conservatively estimated our power/sample size using a two-sample t-test. Power will be increased in our GEE analysis due to accounting for the within-patient correlation among repeated assessments and controlling for stratification factors. If we enroll n=100 in IM@HOME and n=100 patients in enhanced usual care (200 total) we will have 80% power to detect an effect size (standardized mean difference, or Cohen's d) of 0.40 in the average fatigue severity across the follow-up period between arms using a two-sided two-sample t-test at significance threshold $p < 0.05$. Note that the effect size assumes all randomized patients will be evaluable for analysis, which is defined as having at least baseline assessment per ITT principle. This is considered a moderate effect size by convention and comparable to other published literatures on structured exercise program.[79, 80] This effect size is also smaller than 0.50, which is considered a minimum clinically meaningful effect size by convention.[81]
The PRO-basket design allows for estimation of effect sizes in each of the five disease types. This will allow for future studies of disease-specific interventions. Within each disease type, assuming 40 patients will be enrolled in each disease type (20 patients in IM@HOME and 20 patients in enhanced usual care) we will estimate effect sizes along with 95% confidence intervals. These will be used for the design of future studies.

14.2 Secondary Aim: To identify the specific factors (e.g., socio-demographic, clinical, or symptom) associated with IM@Home engagement and satisfaction.

Engagement with IM@Home will be measured by the total number of sessions attended by each patient in the IM@Home arm during the 12-week intervention period. Patients will report their attendance weekly, and these reports will be summed to calculate the total number of sessions attended. We will treat this as a continuous variable, and use uni- and multi-variable linear regression to assess associations between IM@Home engagement and specific socio-demographic factors (i.e., age, sex, race/ethnicity, education), clinical factors (e.g., tumor type, stage, cancer therapy, presence of anemia), baseline symptoms (e.g., fatigue, pain, anxiety),

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

and outcome expectancy.

Satisfaction with the IM@Home program will be assessed by the satisfaction item described in Section 11.2, which asks patients to rate their satisfaction on a 5-point Likert-type response scale with 1 = “Not at all satisfied” and 5 = “Extremely satisfied”. We will dichotomize these responses as 1-3 = “Not Satisfied” and 4-5 = “Satisfied”. We will use uni- and multi-variable logistic regression to assess associations between IM@Home engagement and specific socio-demographic factors (i.e., age, sex, race/ethnicity, education), clinical factors (e.g., tumor type, stage, cancer therapy, presence of anemia), baseline symptoms (e.g., fatigue, pain, anxiety), and outcome expectancy.

14.3 Tertiary Aim: To understand patients’ experiences, perceived values, and identify opportunities for further refinement of IM@Home program in specific tumor groups for further development and testing.

Exploratory Hypothesis 3: Participants may experience unique benefit, perceived values, and challenges with participation in IM@Home and can provide important insight to further develop specific treatment pathways to enable future program refinement.

Thematic content analysis (TCA) will be conducted by two trained qualitative researchers. Analysis will place emphasis on identifying areas of improvement to IM@Home. The study team will review and code the interview transcripts in two phases, using the qualitative software NVivo v. 12.0. The first stage of TCA will involve independently reading each transcript to identify key narrative content through a process of “open coding” in order to develop a set of descriptive and interpretive codes. The team will meet to reach consensus on code name and definition, and then use this codebook to independently code all transcripts. The team will then engage in a secondary analysis, grouping all codes into categories of interest. Each team member will independently review the statements within each category and identify key findings. The team will then meet to reach consensus on the most commonly recurring themes across the dataset. Prominent themes will include those observed across the majority of interviews as well as key divergences between sub-groups (e.g. divergences in class preference by cancer type).

14.4 Exploratory Aim (Breast Basket only): To evaluate the effect of active radiation treatment vs. within four weeks of finishing radiation treatment on trial enrollment and participation in the IM@Home program among women with breast cancer.

Exploratory Hypothesis 4(a): Recruitment of patients within four weeks of finishing radiation treatment will result in higher enrollments rates than those on active treatment.

To evaluate if timing of patient recruitment, active treatment vs. survivorship (within four weeks of finishing radiation treatment), impacts the rate of trial enrollment we will use chi-square analyses to evaluate whether proportion of those enrolled into the study from the portal message sent differ by active or post-radiation treatment.

Exploratory Hypothesis 4(b): Patients enrolled within four weeks of finishing radiation treatment will have higher rates of participation than those on active treatment.

To evaluate if timing of trial enrollment, active treatment vs. survivorship (within four weeks of finishing radiation treatment), impacts participation in the IM@Home study group, we will perform independent T-test to compare the average number of classes attended during the

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

12 weeks by active vs. post-radiation treatment.

14.5 Missing Data: Missing data can be resulted from variety of reasons that including loss to follow up, incomplete report of PRO or lack of capturing of data in electronic medical record. Loss to follow up is defined as patient who cannot be reached for evaluation of outcomes (e.g., death, refusal to be contacted). To minimize missing data, CRC will work closely with the treating investigator to follow each patient to avoid deviations from the intervention and missing data due to reasons unrelated to the study. As the only certain way to avoid biases from missing data is to collect complete data, we will minimize the occurrence of missing observations by using a well- piloted clinical trial design and protocol, well-trained research staff, and an acceptable participant burden. By using weekly data collection time points throughout the trial, we will be able to collect patient-reported outcomes and engage patients on a regular basis to help retain patients throughout the 12-week study. We will also have evening and weekend sessions available on IM@Home for patients to enroll in the IMPROVE study and schedule treatments around their work schedules to prevent missing treatments or data collection. Lastly, for those who voluntarily withdraw from the study, we will record their reasons for withdrawing. Because missing data is inevitable in a prospective study like this (due to hospitalization and potential death), our second line of defense is to perform sensitivity analyses (e.g., assess impact on results of adjusting for patient disease progression or death) and apply data analysis strategies that are as robust as possible to data losses. We will first explore whether missingness is associated with observed variables (particularly randomization arm and the baseline outcome measures) by comparing patients with complete and incomplete data.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Potential Risks: Patients will be monitored for side effects at each visit. Adverse effects related to either IM@Home or enhanced usual care will be collected each week before and after each session by the CRC. CTCAE Version 5 will be utilized for toxicity evaluation. The proposed research study is considered to be low risk. All potential risks that might occur as a result of participation will be detailed in an informed consent form and will also be fully discussed with each patient prior to enrollment. We will also explain to each patient that while some risks are not predictable, every precaution consistent with the best medical practice to protect the health and safety of subjects will be taken. We will document all adverse events and report any related serious adverse events promptly to the IRB.

Psychological Risks: It is possible that subjects may be upset to find out that they are randomized to their non-preferred arm of the study. With appropriate consent and the debriefing process, such risks are minimized. Subjects will be informed that they are participating in an experimental study to determine the effectiveness of IM@Home versus enhanced usual care for chronic pain. They have the chance to be randomized to either the IM@Home or enhanced usual care group. At the end of the study, subjects will be offered the opportunity to discuss the findings with the PI. Additionally, some of the questions in the questionnaire may elicit distress among subjects. If a subject demonstrates clinically significant distress, s/he will be referred to the appropriate clinical and psychosocial services at MSK. Dr. Mao, the PI, has extensive clinical experience in treating physical and psychological distress. During the study period, if the research staff identifies any patients who are psychologically distressed, they will notify Drs. Mao or staffs from Integrative Medicine Services immediately to facilitate appropriate evaluation and treatment.

Financial and Legal Risks: There are no financial or legal risks to the study participants. All

research interventions and evaluations are provided free of charge to study participants.

Privacy and/or Confidentiality Risks: There is a small risk of loss of privacy or confidentiality as someone could get access to the personal information in the study participants' study records.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting will include all SAEs that are related to the intervention. SAEs that are unrelated to the protocol intervention will not be reported, although we will keep track of unrelated SAE in a note to file. If a participant does experience an SAE related to intervention, reporting guidelines will be followed. SAE reporting is required for 30-days after the participant's last investigational treatment/ intervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition

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1275 York Avenue
New York, New York 10065

- Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

16.0 PROTECTION OF HUMAN PARTICIPANTS

Risks/Benefits Assessment: Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. We will also explain to each subject that in the unlikely event of physical injury directly resulting from the research procedures, every effort will be made to make available the facilities and professional skills of MSK. While some risks are unpredictable, every precaution consistent with the best medical practices to protect the health and safety of study participants will be taken. We will document all AEs and report any SAEs promptly to the IRB. The principal investigator and co-investigators will be responsible for judging the nature, severity, and attribution of any adverse events.

Protection Against Psychological Distress Risks. Throughout the study period, if the research staff identifies any subjects who are psychologically distressed, they will notify Dr. Mao or staffs from Integrative Medicine Center immediately to facilitate appropriate evaluation and treatment. If a subject demonstrates clinically significant distress, s/he will be referred to the appropriate clinical and psychosocial services at MSK.

Financial and Legal Risks: All research interventions and evaluations are provided free of charge to study participants.

Protection Against Privacy and/or Confidentiality Risks. Information about study participants will be kept confidential and managed according to HIPAA requirements. MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. Confidentiality of the participants will be maintained.. Original data source (including name and MRN) will be kept in a separate and password-protected database. The paper data files will be kept in locked cabinets and electronic files will be kept in password-protected databases. The patient's name or any other personally identifying information will not be used in reports or publications resulting from the study. Only authorized representatives of MSK, the Food and Drug Administration, or other authorized agencies may inspect the patient's records.

Risk management and emergency response: All patients will be instructed to contact the CRC immediately if they experience any troubling side effects, or worsening of symptoms, or have unplanned emergency room care or hospitalizations. Any patient who experiences an AE that, in the opinion of the PI, would warrant discontinuing treatment, will be discontinued from the trial. Given this level of safety monitoring, we anticipate that potentially dangerous AEs resulting from the study intervention will be detected and treated in a timely manner. We will follow up on all related AEs until they have been resolved. All SAEs, regardless of whether or not they are unrelated to the study treatment, will be reported to the IRB.
Potential Benefits: Study participants may experience an improvement in their fatigue and/or other cancer-related co-morbidities (e.g., fatigue, pain, anxiety). Improving fatigue and other problematic symptoms often leads to an improvement in overall physical and emotional well-

being. This research can help the medical community understand which treatment is more effective for managing symptoms during active cancer treatment. The risks to study participants are small in comparison to the potential benefit to patients with advanced cancer that will result from the conduct of this study.

Alternative to Participation: The alternative to participating in the study is to receive usual care without IM@Home or enhanced usual care or receive these therapies outside of this study. During the informed consent process, potential study participants will be informed of this alternative, that their participation in the study is entirely voluntary, and that their care will not be affected in any way if they decide not to participate in the study.

Risk/Benefit Ratio: The potential benefits of this study far outweigh the potential risks. Symptom burden is substantial during active cancer treatment and experienced by many individuals with cancer. The results of the proposed study will have an immediate impact to help patients with cancer suffering from symptoms during active cancer therapy. Thus, this study has the potential to improve symptom burden and wellbeing for thousands of individuals whose life is impacted by chronic pain. This research also has the potential to generalize to population at large. We will carefully monitor any adverse events related to our interventions and minimize the risks for research subjects.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

The CRC(s) assigned to this study will be responsible for project compliance, data collection, abstraction and entry, data reporting, regulatory and quality control monitoring, problem identification, and prioritization. Coordination of the study team activities will be the responsibility of our Clinical Research Supervisor (CRS) and/or Clinical Research Manager (CRM). The CRS and CRM will work with the CRC on problem resolution, organization, and quality control. We hold regular meetings attended by the research staff and the Principal Investigator to review study progress and to manage any difficulties encountered. For any communication with participants, all security precautions will be taken, including making sure to activate MSKSecure in e-mail correspondences.

The data collected for this study will be entered into MSK Engage.

MSK Engage is the MSK's electronic questionnaire tool. It is a robust, user-friendly and secured platform that enable the collection and visualization of patient generated health data for clinical and research purposes. Built within the patient portal, MyMSK, and

available for use in CIS, MSK Engage is seamlessly integrated into the patient and clinician experience. Members of the CRA will work closely with the MSK Information System teams to ensure proper functioning, development, and distribution of the MSK Engage surveys.

If the patient does not complete the surveys in MSK Engage then the research staff may follow up with a phone call and this data will be entered into RedCap.
Data collected for this study will be entered into and managed via a secure REDCap Database. REDCap, Research Electronic Data Capture, is an open source platform that allows for the collection of research data in a secure manner over a web based interface. Usage of the platform is contingent on an open source license. The platform was developed by Vanderbilt University which MSK has a standing agreement with to allow the usage of REDCap for academic/research purposes.
For this protocol, electronic data entry forms may be completed online by study staff. Electronic participant responses will also be collected either by sending participants a direct link or having the participants fill out the electronic survey on site.
The RedCap database will consist of all patient reported outcomes so that we are able to reduce missed questionnaires and store them outside of MSK Engage.
Data will be housed in the Memorial Sloan Kettering Cancer Center's (MSKCC) New Jersey data center. REDCap has been approved by MSKCC's Information Security to store PHI. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections to ensure data is protected. The server is backed up nightly in the event that disaster recovery would be necessary and system would need to be rolled back. Members of the Clinical Research Administration supporting the REDCap software will have access to REDCap projects for the purpose to ensuring the proper functioning of the database and the overall software system.
Permissions to the database for internal will be managed by the REDCap project manager or study staff. User access to the data is contingent on those a part of the study team and data sharing agreements in place with third party entities if applicable. Project managers are responsible for regularly auditing these permissions to ensure changes in staff are reflected appropriately.
REDCap has the ability maintain an audit trail of changes to the database providing a timestamp as well as the user making the update. In addition, a data resolution module offers the ability of opening and closing queries optionally requiring justification when data is being updated. Permission roles for data resolution are integrated in REDCap. Comprehensive system logs are also maintained of user activity and when changes to the database are made.

A minimal dataset and a study tracker will be entered into Excel. Participants will be asked to complete patient reported outcomes assessments online using MSK Engage, as described below. If they prefer, patients will have the option to complete the measures via pencil and paper or over the phone with a CRC to reduce participant burden and ensure timely completion.

Source documentation will be available to support the computerized patient data. The confidentiality of patient information will be carefully protected. Following data entry by Integrative Medicine Service research staff, data will be maintained in a secure location in the Integrative Medicine offices. All data will be stored in a fashion consistent with FDA guidelines (21CFR11 compliant) and HIPAA security rules. Final data sets for publication will be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

Appendix 1: Patient-reported Outcomes (PRO)
Appendix 2: Qualitative Interview Guide

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