FULL PROTOCOL TITLE: CARING FOR CAREGIVERS WITH MIND-BODY EXERCISE

PRINCIPAL INVESTIGATOR:

Pinky Shani, PhD, RN
University of Houston
College of Nursing
(713) 743-7181
pshani@central.uh.edu

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1.0 Objectives

1.1 Using cancer caregivers (CCGs) as a representative population of the larger CG population, our long-term goal is to conduct a large-scale fully powered trial evaluating a widely accessible and previously studied Qigong regimen (Eight Brocades, *Baduanjin Qigong*). The goal of this R34 is to conduct a mixed-methods pilot randomized controlled trial (RCT) to inform the feasibility and design of a future larger definitive trial.

Primary Objectives:

1. To finalize intervention content and delivery of both in-person community-based group and individual internet-based Qigong protocols.
2. To assess the 'learnability' of Qigong delivered in community-based group classes and via an internet-based protocol using a novel proficiency instrument.
3. To evaluate the feasibility of recruiting and retaining cancer caregivers into a 12-week clinical trial, and completing all outcomes testing protocols.

1.2 We hypothesize that participant recruitment, retention, and adherence to intervention and assessment protocols will comply with target goals. Feasibility will be assessed with respect to participant recruitment, retention, intervention adherence, and intervention acceptability. We will assess recruitment feasibility by the number of screened and eligible participants and the number refusing to participate. We will document reasons for refusal. This domain of feasibility will require: a) ≥ 50% screened individuals are study eligible and b) ≥ 5-10% of eligible participants are willing to consent. With a goal of n = 54 enrolled over a one-year period, we will need to screen 14 participants per month. Participant retention will be deemed feasible if loss to follow-up is ≤ 20%. Intervention adherence will require: a) ≥ 70% participation in community or internet-guided classes and > 50% compliance with home practice guidelines. Qualitative interviews with CCGs, including those who drop out and have low adherence, will be used to further inform overall study feasibility, and facilitators and barriers to participation.

2.0 Background

2.1 Longer life expectancies and an aging population mean that an increasing number of adults are likely to develop multiple comorbidities and rely on informal CGs for support.[1] Informal CGs, typically family members or friends, are responsible for caring for individuals with a variety of burdensome conditions including advanced age, dementia, and cancer. The average number of hours spent caregiving is often greater than 21 per week.[2] In addition to providing psychological support, CGs are also commonly responsible for relatively complex medical procedures, despite limited or no formal training, as well as taxing physical support (e.g., weight transfers, increased household chores). Collectively, these responsibilities result in substantial and chronic stress, with negative psychological and physiological effects on CGs' health.[3-5] Informal CCGs provide 70 to 80% of care for those with cancer

and are involved during the cancer care trajectory from diagnosis to death.[6, 7] The burden of caring for someone with cancer can be extremely high; 50% of CCGs report increased levels of stress and depression with 40% indicating that they need help managing their own emotional and physical stress.[2] CG burden has even been identified as an independent predictor of caregiver mortality with a 63% increased risk of death.[8] Additionally, research indicates that decreased CG QOL directly impacts the QOL of care recipients.[9] [10] Moreover, the burden among CCGs often persists for years after patients' initial cancer diagnosis, with evidence of long-term detriments to health and QOL.[11-14] Therefore, there is a pressing need to develop effective and practical interventions to prevent and manage the psychological and physical stressors that reduce QOL in CGs.

2.2 Not applicable.

2.3 Mind-body practices that target both psychological and physical dimensions of distress offer a promising and pragmatic therapeutic strategy for addressing the needs of CGs. [15-17] However, the evidence required to guide such an approach is still limited in multiple ways. First, while a growing body of research supports mind-body practices such as Tai Chi, Qigong, yoga and meditation for a range of symptoms in patients with chronic disease,[18-22] few large scale studies have evaluated impact of these practices in CGs. Of the studies which have evaluated CGs (mostly yoga or MBSR), many have utilized interventions tailored to patient-CG dyads.[21, 23-26] Although this approach has merit, it may limit targeting CGs psychological and physical needs. Additionally, while many MBSR and yoga studies show positive effects on mental health, most do not include physical function and disability measures. Lastly, more widespread access to mind-body interventions targeting CGs has been challenged by economic, geographic, and time barriers.[27] Common barriers to in-person group classes (e.g., issues with CG travel to community-based programs) might be overcome with internet-based delivery of intervention, offering an alternative for some CGs that may significantly increase access and adherence. While internet delivery of individual-based mind-body practices is increasingly studied and shows promise,[1] this approach has not been explored in CG populations.

Qigong is an increasingly popular multi-modal mind-body exercise that shows promise in addressing a broad range of psychosocial and physical factors highly relevant to CGs. Sharing many characteristics with Tai Chi, Qigong incorporates elements of slow gentle movement, breath training, and a number of cognitive skills including heightened body awareness, focused mental attention, and imagery—which collectively may afford greater benefits to health compared to unimodal therapies.[28-30] In contrast with typical Tai Chi choreography, some Qigong regimens focus on simpler repetitive movement phrases, which make them easier to learn both through in-person instruction and especially via video-guided instruction. A robust evidence base supports that across adult populations, Qigong and Tai Chi training in groups can improve multiple domains of physical and emotional health, including those highly relevant to CGs such as depression,[31-33] anxiety,[31, 33] poor sleep,[33-36] musculoskeletal strength,[34, 36] balance during functional activities,[34, 36] pain,[31, 37-40]

and core underlying physiological processes such as inflammation.[41, 42] Reduction of overall distress and improved long-term prognosis is also supported by improvements in broader constructs including overall QOL[31, 33] and self-efficacy.[15, 34, 43] While Qigong is increasingly being used to help manage health and distress in CGs, (including at leading academic medical centers like MD Anderson Cancer Center and Harvard's Dana-Farber Cancer Institute), we are not aware of any studies to date evaluating Qigong for CGs.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion criteria include (1) age ≥35 years; (2) a spouse, partner, family member, or friend providing physical, emotional, and/or financial support for a cancer patient; (3) able to understand, speak, and read English; (4) minimum level of 3 on the National Comprehensive Cancer Network's (NCCN) Distress Thermometer adapted for CGs; and (5) able to provide informed consent. Exclusion criteria include (1) unstable illness (e.g., recent hospitalization, unstable cardiovascular disease, active cancer); (2) psychiatric disorders (e.g., unmanaged depression or psychosis, substance abuse, severe personality disorder); (3) degenerative neuromuscular condition (e.g., Parkinson's disease, multiple sclerosis); (4) inability to walk continuously for 15 minutes; (5) recent history of attending regular Qigong or similar (e.g., yoga or Tai Chi) classes defined as 20 or more classes in the past 6 months; or 6) participation in more than 240 minutes of moderate-intensity exercise per week (as these individuals already exhibit high exercise self-efficacy and are less likely to be otherwise symptomatic).

3.2 Potential subjects will be screened for eligibility based on these criteria over the phone. This call will be based on a script that comprehensively addresses all inclusion and exclusion criteria to ensure that each potential participant is appropriately screened.

3.3 This study will not include adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, prisoners, students for whom the researchers have direct access to/influence over grades, or economically and/or educationally disadvantaged persons.

4.0 Vulnerable Populations

4.1 Not applicable.

5.0 Number of Subjects

LOCAL:

5.1 We expect to consent, enroll, and randomize a total of 54 CCGs.

5.2 The sample size was based on practical/budgetary constraints as well as a preliminary power analysis. A power analysis was conducted to determine the minimum sample

size that is required to find significance with a power set of .80, an alpha level at .05, correlation among the repeated measures of 0.3, and a moderate effect size of .25 using G*Power version 3.1. Based on the primary analysis, to ensure sufficient power on the repeated measure ANOVA (3 time points x 3 groups), a total of 48 participants are required. In consideration of 10-15% of attrition rate, a total of 54 participants will be recruited.

6.0 Recruitment Methods

LOCAL:

6.4 Interested individuals identified through recruitment strategies will be provided contact information to call the study coordinator for an initial phone screen. The coordinator will use a phone screen script to review details of the study with potential participants. To conduct the initial screen, the coordinator asks participants a series of questions related to study inclusion criteria. If the participant meets the inclusion criteria the coordinator will continue the screen with questions about exclusion criteria. If the individual is eligible and interested, they will then be scheduled for an in-person visit to University of Houston, College of Nursing, to complete their baseline visit and receive their group assignment. At this visit, eligibility will again be confirmed by asking the same series of questions about inclusion and exclusion criteria to confirm their eligibility status. After we confirm eligibility, consent is obtained, and baseline assessments made. We will document reasons for refusal.

6.5 Multiple recruitment sites and methods will be used for recruitment. Our primary recruitment site will be MD Anderson Cancer Center (MDACC) facilitated by Dr. Lorenzo Cohen (study consultant). The distribution of how subjects were contacted and participation rate will be systematically tracked using screening logs. Recruitment feasibility will be assessed by the number of screened and eligible participants and the number of CCGs refusing to participate. Participants may also be sourced from churches, other support groups, social media postings, or by word-of-mouth. Recruitment strategies include presenting the study at monthly staff meetings in various cancer subspecialties, providing study brochures to oncologists, nurses, and administrative staff to be passed on to patients and their families, presenting at CG support group events, and posting the study on relevant hospital web sites including those specific to recruiting volunteers into clinical trials. In addition, participants will be recruited through non-hospital online websites such as the Houston Chapter of the Oncology Nursing Society and the Family Caregiver Support Network. Other strategies include targeted advertising in local newspapers and posting of flyers in public places (e.g., library, senior centers).

6.6 Potential subjects may be identified by their attendance at support groups for cancer caregivers. They may also be identified at any of the functions listed above if they mention to a member of the research team that they are currently a caregiver for a cancer patient. Study consultants will also work to identify potential participants and provide them with information about the study if they are interested. Potential

subjects may also be identified if they contact a member of the research team after encountering the study flyer or speaking with a past study participant.

6.7 The materials used for recruitment include a study flier and PowerPoint presentations (when information about the study is presented to a group).

7.0 Study Timelines

7.1 For Cohorts 1 and 2, we will randomize (1:1:1) 24 CCGs to one of three conditions: (1) A community- based Qigong program; (2) an internet-based Qigong program; or (3) a self-care control group. For Cohort 3, we will randomize (2:1) 15 CCGs to one of two conditions: (1) an internet-based Qigong Program, or (2) a self-care control group. For Cohort 4, we will randomize (2:1) 15 CCGs to one of two conditions: (1) a community-based Qigong program, or (2) a self-care control group. Our primary outcomes are feasibility and acceptability.

7.2 Participants in the community-based programs will attend one, 75 minutes class per week supplemented by home practice (guided by printed materials) for 20 minutes on 3 additional days. Participants in the internet-guided program will be asked to follow two online sessions for 40 minutes each, also supplemented by home practice for 20 minutes on 3 additional days. Participants in both Qigong groups will commence training within 2 weeks of baseline visits. Caregivers randomized to either Qigong intervention can expect a total time commitment of 30 hours to complete all study related activities.

Individuals randomized to the self-care control group will be provided with an educational book on caregiving, they will also be provided with a "Self-Care Manual" that includes self-guided activities related to caregiving and caregiver health. Caregivers randomized to this group can expect about a 5-hour total time commitment to study related activities.

7.3 Baseline and 12-week assessments including psychosocial measures and QOL, physical function and cognitive measures will occur in person for all participants at the University of Houston College of Nursing in Sugarland, Brazos Hall, Room 103A. In addition, a short qualitative interview will be conducted with participants in the community-based and internet-based classes. A longer-term 6-month follow-up will assess psychosocial and QOL measures using a mail-in questionnaire packet. Primary analyses should be complete by 08/31/2021.

8.0 Study Endpoints

8.1 This is a minimal risk study. There are no safety endpoints given there are no safety risks associated with the study.

9.1 Procedures Involved

9.1 Using CCGs as a representative population of the larger CG population, our long-term goal is to conduct a large-scale fully powered trial evaluating a widely accessible and previously studied Qigong regimen (Eight Brocades, Baduanjin

Qigong). Interventions will be delivered either in community-based groups led by instructors or via internet to individuals learning thru recorded guided instruction

supplemented with intermittent virtual live feedback from instructors. Outcomes will include QOL, fatigue, sleep disturbances, psychological distress, CG burden, and physical function. The short-term goals of this R34 are to conduct a mixed-methods pilot randomized controlled trial (RCT) to inform the feasibility and design of a definitive trial. We will address these goals by randomizing 54 CCGs to one of three conditions: (1) A community-based Qigong program; (2) an internet-based Qigong program; or (3) a self-care control group.

9.2 At the baseline visit, eligibility will be confirmed, consent will be obtained, and the consent process will be documented. Written informed consent will be obtained by the research assistant or study staff. The subject will be asked to review the study consent form. Investigator or research staff will meet with the subject to review the form, to confirm the subject's understanding of the study, and to answer any questions that the subject might have. Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the investigator or research staff. Informed consent will be obtained and reviewed by the University of Houston Institutional Review Board as appropriate. For the duration of the Covid-19 Pandemic, all participants and research staff will follow the University of Houston Department of Research's Covid-19 precautions. These precautions will be followed during any in-person assessment or in-person Qigong class. All participants and research staff will have a contactless temperature screening prior to any in-person activity. Masks will be worn and social distancing maintained during all in-person assessments and in-person Qigong classes.

At the initial visit at University of Houston, College of Nursing, participants will complete informed consent. This date will be recorded on a case report form as the date of enrollment into the study.

In addition, at this visit initial assessment related to QOL, psychological well-being, caregiver burden, cognitive and physical function will be measured. All outcomes will be assessed at baseline and 12 weeks, following completion of the 12-week intervention. All in-person assessments will be conducted by trained research assistants. Baseline and follow-up assessments are estimated to require 2.0 hours.

At the baseline and 12-week appointments, consented participants will be videotaped performing the Eight Brocades. This video will help assess learnability of the intervention and help with the development of the scoring instrument.

Semi-structured, open-ended interviews lasting approximately 30 minutes will be conducted at the 12-week assessment for participants in all groups. Questions will focus on characterizing participants' perceived effectiveness and enjoyability of the Qigong intervention, both community-based and internet-based, and identifying facilitators and barriers to participation. Questions specific to the mode of intervention delivery may include those related to use of technology, the role of face-to-face instructor feedback, perceived motivators to adherence, and self-efficacy.

In weeks 1, 2, 4 and 6 of the program, participants will participate in a one-to-one call with a Qigong instructor. This call will be audio recorded and will give participants

the opportunity to address any training- related questions or concerns, and to receive personalized feedback and encouragement from the instructor. At the 12-week assessment, participants will be asked to return the computer tablet. Participants will

be asked to keep track of their home Qigong practice on provided logs throughout the study. We will ask participants to send their logs to the study researchers at the end of each week, and we will provide them with stamped envelopes for mailing.

9.3 The Qigong Instrument used is the Eight Brocade Protocol. Qigong is an increasingly popular multi-modal mind-body exercise that shows promise in addressing a broad range of psychosocial and physical factors highly relevant to CGs. Sharing many characteristics with Tai Chi, Qigong incorporates elements of slow gentle movement, breath training, and a number of cognitive skills including heightened body awareness, focused mental attention, and imagery—which collectively may afford greater benefits to health compared to unimodal therapies.[28-30]

Table 1. Template for Group-Taught Eight Brocade Protocol

Week	Activities	Approx. Duration (in minutes)
1-2	Check-in	2
	Qigong Warm-up Exercises	
	Qigong Swinging and Drumming the Body	
	Swinging Up and Down	
	Spiraling the Waist	
	Mindful stretching	
	Lower Extremities (feet, ankles, knees)	20
	Upper Extremities (hands, arms, shoulders)	
	Spinal Cord Breathing	
	Washing with Qi from the Heaven	
	Tan Tien Breathing	
	Introduction to Eight Brocades Movements #1-4	35
	#1 *Holding the Hands High to Regulate Internal Organs*	
	#2 *Posing as an Archer Shooting Both Left- and Right-Handed*	
	#3 *Holding One Arm Aloft to Regulate Spleen and Stomach*	
	#4 *Looking Backwards to Prevent Sickness and Strain*	
	Cool-Down Exercises	3
	Self-massage and meridian tapping	
3–8	Check-in	2
	Qigong Warm-up Exercises	10
	Review/ Practice Eight Brocades Movements #1-4	15
	Learn and practice Eight Brocades Movements #5-8	30
	#1 *Swinging the Head and Lowering the Body to Relieve Stress*	
	#2 *Moving Hands Down Back and Legs, and Touching Feet to Strengthen Kidneys*	
	#3 *Thrusting Fists and Making Eyes Glare to Enhance Strength*	
	#4 *Raising and Lowering the Heels to Cure Diseases*	
	Cool-Down Exercises	3
9–12	Check-in	2
	Qigong Warm-up Exercises	10
	Review/ Practice/ Refine Eight Brocades Movements #1-8	45
	Cool-Down Exercises	3

9.4 In addition to caregiver distress, medical history and demographics, the following outcomes will be assessed at baseline, 12-weeks, and 6-months:

The following will be measured at baseline and 12-weeks:

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- Grip strength of the dominant hand will be measured using a **Jamar hydraulic hand dynamometer** (Patterson Medical – Canada, Mississauga, ON, CAN).[44]
- **Timed Up-and-Go Single and Dual Task** will be completed among participants. For the single task, CGs will be asked to sit in a chair with their back against the back of the chair. When the researcher says, "Go," the participant will walk briskly around a marker on the floor and back to the chair. The stopwatch is stopped when the participant's backside and back are against the chair. For the dual task, the participant completes the steps above in addition to counting backwards by 3s from 100. Both tests will involve two trials.

- **Digit Span**[45] measures verbal short-term memory. Participants will be asked to repeat numbers in a specific order. Performance is indicated by the average number of digits correctly remembered.
- **Trail Making Test** Parts A & B[46] consist of 25 circles distributed over a sheet of paper. Participants are timed as they connect the circles without lifting the pen or pencil from the paper.

The following is a table of study measures:

Measure	Description
QOL	• Promis-29. 29 items consisting of self-reported health measures in the domains of physical health, mental health and social health.
Depression	• Patient Health Questionnaire-9 (PHQ-9). 9 items measuring depression and used to grade severity of symptoms.
Anxiety	• Generalized Anxiety Disorder (GAD-7). 7 item tool used for screening, diagnosis and severity assessment of anxiety disorder.
Fatigue	• Brief Fatigue Inventory (BFI): 9 items measuring the severity of fatigue and the impact of fatigue on daily functioning in the past 24 hours.
Perceived Social Support	• Multidimensional Scale of Perceived Social Support (MSPSS). 12 item scale designed to measure perceived social support from three sources; Family, Friends and a Significant Other.
Sleep Disturbances	• Pittsburgh Sleep Quality Index (PSQI): 19 items measuring patients' sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication use, and daytime dysfunction over the past month.
Perceived Stress	• Perceived Stress Scale (PSS). 10 item psychological instrument measuring the perception of stress.
Caregiver Burden	• Caregiver Burden Scale (CBS): 14 items measuring the impact of caregiving on three dimensions of burden: objective, subjective demand, and subjective stress.

Exercise self-efficacy	• Self-Efficacy Scale: 13 items measuring self-efficacy expectations related to the ability to continue exercising in the face of barriers to exercise.
Physical Activity	• Godin Leisure-Time Exercise Questionnaire: 4 items measuring the frequency of light-intensity, moderate-intensity, and vigorous-intensity leisure-time physical activity.

10.0 Setting

10.1 The baseline assessment and 12-week follow-up assessment components of the research will take place at the University of Houston College of Nursing Campus at 14000 University Blvd., Sugar Land, TX, Brazos Hall Room 103A. The Community-based Intervention group Qigong classes will take place at 3500 Audubon Place, Houston, Texas 77006. Classes will be held every Wednesday at 2pm.

11.0 Risks to Subjects

11.1 There is a potential for minor musculoskeletal aches and pain that might result due to the Qigong exercises in both the community-based and internet-based programs. These are typical in any low intensity physical activity program. Participants will be instructed and regularly reminded to adjust the level of activity based on their individual abilities. Nonetheless, our instructors are BLS-trained, and Dr. Shani will be available by phone in the event of an adverse event. All participants who participate in the study will have the opportunity to withdraw at any time. There are no other known or anticipated risks of physical, mental or social injury to those who will participate in the study.

11.2 When starting an exercise program, individuals may experience temporary muscle soreness or stiffness. Increased physical activity may worsen an underlying pain condition. These unlikely but possible conditions will be monitored closely at each testing visit. If, at any point, an issue is detected, participants will be immediately referred back to their primary provider for routine care.

11.3 We will utilize a multi-pronged approach to monitor safety and track Adverse Events (AEs) throughout the study with formal oversight by a University of Houston, Institutional Review Board. For participants attending community classes, instructors will be trained to track and report any observed or participant-reported AE in an AE log provided by the study. Participants assigned to both community- and internet-based training will also be asked to complete an AE survey as part of the home practice log, which are sent to study staff weekly. Participants in the self-care control group will be called monthly to ask about any adverse events, and more generally, to maintain contact with study staff. Finally, all participants will be queried in person at 12 weeks about AEs experienced over the course of the study. When an adverse event is reported through any of the above tracking mechanisms, the study PI will be

notified. Any adverse events experienced are followed by the PI and reported to the University of Houston IRB according to established guidelines. If the participants have any questions about their rights as a subject or how this research study is being conducted, they are told in the written consent form to contact Dr. Shani.

12.0 Potential Benefits to Subjects

12.1 CGs represent a well-defined, large and growing subset of a larger population of CGs that overlap greatly in the constellations of morbidities that lead to high levels of distress. The multi-modal nature of the Eight Brocades Qigong regimen explicitly targets both psychosocial and physical functional symptoms, thus expanding the scope of mind-body studies for CGs to date, which have largely focused on stress management and psychological wellbeing.

12.2 Our pilot study, and our eventual large-scale comparative effectiveness trial, explores the effectiveness of Qigong training delivered in both community-based group classes and through self-guided internet-based modules supplemented with one-on-one virtual learning support. This design is innovative for multiple reasons. A finding that both methods are effective would lead to multiple options for CGs. Those with flexible schedules and seeking group support and the opportunity for a change of environments might choose community classes. Those with unpredictable and inflexible schedules and an inability to leave the home could develop a self-guided training plan, with one-on-one virtual support scheduled at a convenient time. More generally, the evidence-base for DVD- and internet-based learning of mind-body exercise is essentially non-existent. Studies are desperately needed to evaluate whether the promising evidence of Qigong's effectiveness based on group and instructor lead clinical trials is also observed when instructions are delivered virtually.

12.3 Since risks of the study are minimal, and the benefits are potentially large, the risk-benefit ratio is strongly on the side of benefit.

13.0 Withdrawal of Subjects

13.1 All participants who participate in the study will have the opportunity to withdraw at any time.

14.0 Costs/Payments to Subjects

14.1 The study intervention and all related items (parking costs, iPads, tablets, caregiver helpbook, etc.) will be provided at no cost to participants. Participants will be compensated for participating in the study with $125 in Amazon gift cards. A $50 gift card will be provided after the baseline assessment, another $50 gift card will be provided after the 12-week follow up assessment, and a final $25 gift card will be provided after the completion of the 6-month follow-up survey.

15.0 Confidentiality

15.1 Participant confidentiality will be maintained at all times. Each participant will be given a unique study ID that does not contain personal identifying information and will be used for all research purposes. Names, code numbers and telephone numbers will be kept in locked secure files, separate from the study data. Likewise all physical study data will be kept in locked storage and all electronic study data will be password protected with access restricted to approved personnel. Any document linking the participant name to an identification number will be kept in a locked file separate from data collection files. Study reports will be aggregated so that individual participants are not identified. All data will be stored in databases, identified only by study ID number, behind appropriate firewalls and with institutional backup.

15.2 Only the Principal Investigators and grant coordinator will have access to the names associated with the identifiers, which will be kept locked in separate files.

15.3 Hard copies of identifiable data will be shredded within 5 years from the completion of the study date (08/31/2026) or by the time all data has been published in manuscript format, whichever comes first.

15.4 Electronic identifiable data will be physically destroyed by the services provided by the Iron Mountain Information Management which is AAA certified by the National Association for Information Destruction.

15.5 Recordings will be destroyed after transcription of audiotapes.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 Participants will be assured that personal identifiers will be detached from all data and a random study ID number will be used. Only the PI and research assistant will have access to the study ID code. In-person assessments will be held in a private room. Phone calls concerning the study will be prefaced by the research team asking if the participant is comfortable discussing their study activities at that time, and if they are not, an alternate phone call time will be established.

16.2 At any point that a participant feels uncomfortable with questions or study procedures, we will remind the participant that it is a voluntary study and they do not have to proceed.

17.0 Informed Consent Process

17.1 Informed consent will be obtained from all participants. The consent process will take place upon the participant's arrival for the baseline assessment, prior to any study procedures. The consent form will describe the purpose of the

study, the procedures to be followed, and the risks and benefits of participation. Each page of the consent form will be reviewed with the participant prior to their signing. Approximately 20-30 minutes will be devoted to discussing the consent form, and the participant will have unlimited time to ask any questions. After the consent form has been discussed, a signed copy of the consent form will be obtained from each participant. A copy will also be given to each participant and this fact will be documented in the participant's record. This research will be following "SOP: Informed Consent Process for Research (HRP-090)." Participants who are unable to provide informed consent are ineligible from study participation.

Interested participants will be pre-screened for eligibility over the phone. A waiver of written documentation of consent for prescreening has been requested.

a. The written script of the information to be provided orally can be found within the Phone Screen Template (attached). The written script of the information to be provided and all written information to be provided include all required and appropriate additional elements of consent disclosure.

b. The research presents no more than Minimal Risk of harm to subjects.

- *Qigong is considered a low, impact mind-body exercise program. Stretching will be completed prior to the initiation of our program. Participants will be encouraged to practice at their own pace, and take rests according to their needs. In addition, subjects will be regularly monitored for adverse effects of exercise during visits. Subjects in the community-based and internet-based programs will be instructed to notify their healthcare provider first, and then study staff of any changes in health status. The PI will contact participants by telephone if any reported adverse event suggests clinical deterioration warranting immediate medical attention. During the study, if a subject experiences a medical problem as deemed by the study physician or subject's regular care provider that prevents participation in the Qigong program, he/she will be temporarily suspended from the study and will resume when at baseline clinical status.*

c. The research involves no procedures for which written consent is normally required outside of the research context.

- *The research does not involve any procedure for which additional consent is required. All components of the research have been addressed within the consent.*

d. Written information describing the research is to be provided to the subject, or the subject's legally authorized, representative.

- *This includes the detailed consent form, flyer, and a specific letter addressed to participants based on their randomization to either the community-based, internet-based, or self-care group.*

17.2 ***Non-English Speaking Subjects***

Not applicable.

18.0 Process to Document Consent in Writing

18.1 This study will be following "SOP: Written Documentation of Consent (HRP-091)."

19.0 Data Management

19.1 Data will be managed using the REDCap data management system supported through UH. REDCap is a secure, web-based application for managing online databases. REDCap provides automated export procedures for seamless data downloads to Excel and common statistical packages such as SAS. Case report forms will be produced using built-in features of REDCap.

Feasibility. We will use descriptive statistics to evaluate recruitment and retention rates, attendance at classes, and adherence with online intervention. Retention rate will be reported by group at the end of the study. Attendance will be recorded as the proportion of classes attended for community-based classes; and online video tutorial use, logs of home practice, numbers of logins to the webpage, clicks on education links, downloads and views of videos for the internet-based classes. We will consider study retention successful if the retention rate is at least 80% at 12 weeks, and attendance at in-person classes and home compliance to internet-based lessons is at least 70%. Similar criteria will be set for internet-based compliance as well as home practice compliance in both groups. We will test for non-inferiority of the observed rates relative to the expected rates of retention and attendance assuming that the retention and attendance rates follow a beta-binomial distribution. Non-inferiority margins will be determined as 90% lower confidence bounds on the estimated rate for participants in each group. Maximum likelihood will be used to obtain significance and confidence intervals. Relative risk of non-completion between each Qigong training method and self-care control group will be used to represent study completion rates with inference based on separate Fisher's exact tests.

Estimating variance for future power calculations. We will use linear mixed models with fixed effects of visit and treatment x post-baseline visit interaction and unstructured covariance among repeated measures to analyze efficacy outcomes. This will yield six variance components required for future power calculations. The Wald statistic from the treatment x visit interaction testing 12-week treatment-dependent response will be used to estimate the effect of Qigong and as a criterion for selecting outcomes that are potentially sensitive to Qigong. Selection of the outcomes to include in our future trial, and which to select as the primary outcome, will also be

guided by consideration of clinical relevance, participant burden, and cost. The study will have 80% power to identify the outcome that is truly most responsive to Qigong from among the 14 measures calculated from the 12 assessments completed at 12 weeks if the most responsive measure is associated with an effect size at least 0.43 SD greater than the others.

Inter-rater reliability and validity testing of proficiency instrument. Inter-rater reliability will be evaluated using Cohen's Kappa statistic. Validity testing based on cross-sectional comparisons of proficiency scores and practitioner's years of training will utilize Pearson's correlations. Associations between longitudinal changes in proficiency and clinical outcomes will be evaluated using mixed model approaches described above.

Qualitative analysis. Semi-structured qualitative interviews will be audio recorded and transcribed verbatim. Thematic analysis will be informed by grounded theory methods to guide description of qualitative interviews. Questions will focus on facilitators/barriers to recruitment/participation, and acceptability of the intervention and its specific components. Two investigators will independently code transcripts to identify emergent themes in an iterative process until thematic saturation is reached as in prior studies.[47, 48 49-51] Transcription, coding, and analysis will be conducted in NVivo v11.

19.2 Three documents will have identifiable data: Informed Consent (name), Screening Questionnaire (name, age, ethnicity, phone number, and email address), and Screening Log (name, phone number). At the baseline assessment, each participant will be given a unique study ID that does not contain personal identifying information and will be used for all research purposes. All physical study data will remain locked at all times in a file cabinet in the PI's office, and all electronic study data will be password protected with access restricted to approved personnel. Study reports will be aggregated so that individual participants are not identified. All data will be stored in databases, identified only by study ID number, behind appropriate firewalls and with institutional backup.

19.3 All data sets will be verified for accuracy by the PI, Co-PI, and grant coordinator. Research data and subject files will be audited for accuracy during the initial months of testing/interviewing and subsequently every 6 months. All REDCap data and subject files will be double cross-checked after they have been entered and/or stored.

19.4 Identifiable data will be stored in a locked file cabinet in Dr. Shani's office. Names, code numbers and telephone numbers will be kept in locked secure files, separate from the study data. Any document linking the participant name to an identification number will be kept in a locked file separate from data collection files.

19.5 Data will be stored for up to 5 years from the completion of the study date (08/31/2026) or by the time all data has been published in manuscript format, whichever comes first.

19.6 Only the research team will have access to the data.

19.7 The research team will be responsible for the receipt of data.

19.8 Not applicable.

20.0 Sharing of Results with Subjects

20.1 Study results will be shared with participants via email or physical mailing address if the participant wishes to receive them. Participants who wish to receive study results at the conclusion of the study may provide the research team with their preferred method of receiving these results.

21.0 Resources

21.1 Per UH's IRB policies, prior to being involved in the study, all key personnel will have: successfully completed the NIH or CITI Human Subjects Certificate of training modules; read the research protocols and plans for data and safety monitoring; and are familiar and have practiced with data collection. In addition, the PI and Co-PI have completed the CITI Responsible Conduct in Research training. The PI, Co-PI, grant coordinator will oversee data collection and review the progress of the study.

21.2 The Qigong instructor working for this study has worked with MD Anderson as part of the Integrative Medicine Center team, Baylor College of Medicine, Texas Woman's Hospital and is currently at Rice University, sharing the health benefits of Tai Chi, Qi Gong, Yoga and Meditation with patients, caregivers, students, faculty and staff.

22.0 Additional Approvals

22.1 This study has received agency approval from the MD Anderson Cancer Center. Please find attached the supporting letter from our study consultant, Dr. Lorenzo Cohen.

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