

RESEARCH ARTICLE

Barriers to Participation in a Randomized Controlled Trial of Qigong Exercises Amongst Cancer Survivors: Lessons LearntSiew Yim Loh^{1*}, Shing Yee Lee², Kia Fatt Quek³, Liam Murray⁴**Abstract**

Background: Clinical trials on cancer subjects have one of the highest dropout rates. Barriers to recruitment range from patient-related, through institutional-related to staff-related factors. This paper highlights the low response rate and the recruitment barriers faced in our Qigong exercises trial. **Materials and Method:** The Qigong trial is a three-arm trial with a priori power size of 114 patients for 80% power. The University Malaya Medical Centre database showed a total of 1,933 patients from 2006-2010 and 751 patients met our inclusion criteria. These patients were approached via telephone interview. 131 out of 197 patients attended the trial and the final response rate was 48% (n=95/197). **Results:** Multiple barriers were identified, and were regrouped as patient-related, clinician-related and/or institutional related. A major consistent barrier was logistic difficulty related to transportation and car parking at the Medical Centre. **Conclusions:** All clinical trials must pay considerable attention to the recruitment process and it should even be piloted to identify potential barriers and facilitators to reduce attrition rate in trials.

Keywords: Randomized controlled trials - barriers - retention - recruitment exercise - qigong - complex interventions

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Introduction

Randomized controlled trials (RCT) are widely regarded as the gold standard for evaluation of health care programs. However, barriers and challenges experienced during recruitment into trials and factors influencing adherence continue to be substantial drawbacks of clinical trials (Mills et al., 2006; Spaar et al., 2009). Selection bias and differential attrition rates impact both the internal and external validity of trial results. Internal validity is the validity of inferences drawn from an earlier study (Last, 2001) whilst, external validity is the extent to which the findings from the study can be generalized. In ensuring internal and external validity, selection of a study sample representative of the target population is essential (Gordis, 2004). Inability to achieve calculated sample size is a key factor in premature termination of trials leading to low statistical power to detect significant effects (Courneya et al., 2005; Ford et al., 2008; Spaar, et al., 2009).

Qigong is a favourable form of physical activity amongst Asian cancer survivors. Qigong has been reported as a safe and effective means for improving QoL, fatigue, mood status, whilst reducing symptoms, side-effects and inflammation in cancer patients (Oh et al., 2010). There are some studies reporting immediate improvement without side effects, and some with complete remission in patients

who engaged in ongoing practice (Chen and Yeung, 2002; Lee, 2007). However, there is still limited strong evidence supporting the efficacy of Qigong in cancer patients.

Participants' adherence to behavioral interventions like Qigong trial is often challenging, particularly in trials of complex interventions, or interventions which involve multiple visits (Courneya et al., 2005), require behavioral changes (Oh et al., 2010), or the involvement of engagement of multilingual, multicultural groups with varying educational level (Ford et al., 2008; Loh, 2009). Therefore, 'multiple difficulties in recruitment, retention of trials patients, and recruitment of cancer patients to trials have been reported (Melinda et al., 2008). However, little is known about the characteristics of these non-participants or dropouts. The data on those who refuse to participate or drop out are seldom available due to human subject research guidelines, and/or a lack of published reports about barriers to recruitment and adherence in trials. Although these issues are more widely recognized in developed countries since they are crucial to the success of RCTs (Ross et al., 1999; Avis, 2006; Fayter, 2007) but this issue is often not highlighted in developing countries.

This paper highlights the barriers to participation and high attrition rate encountered during a recent trial of Qigong, to examine its efficacy in a multiethnic breast cancer survivor in Malaysia.

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Materials and Methods

The KL (Kuala Lumpur) Qigong study is a three-arm RCT conducted on breast cancer survivors from 2010-2011 at the University Malaya Medical Centre, Malaysia. Ethical approval was obtained from University Malaya Medical Centre (UMMC).

Subjects

An initial total of 1933 potentially-eligible patients were identified from the UMMC breast cancer database (2006-2010). Out this total, we excluded 1182 women. [10 percent (118/1182) were already physically active, 40.2 percent (475/1182) had carcinoma in situ or late stage diseases (stage III or IV), 22.3 percent (263/1182) were outside the desired age range, 1.3 percent (15/1182) died prior to contact, and 26.3 percent (311/1182) could not be contacted via telephone, despite at least two attempts made at different times of the day]. An a priori sample size calculation estimated that 114 participants were required calculated to obtain 80% power and 5% significance level for a between-group mean difference of 10 units SD on the Functional Assessment of Cancer Therapy-General (FACT-G) (Daley et al., 2007). Inclusion criteria were, having a primary diagnosis of early stage breast cancer (stage I-II), completed primary cancer treatment, at least one year post-diagnosis without evidence of metastasis, and aged between 18-65 years. Women who had medical contraindications for exercise, with a major medical condition (epilepsy, uncontrolled hypertension, significant orthopaedic problem or acute cardiovascular disease), were currently practicing Qigong or participating in line dancing or were already physically active on more than four days of per week, were excluded.

The KL qigong trial interventions

Participants were randomized into one of the three groups (Qigong, Line-dancing or Usual care). During the 8-week trial, participants in Qigong group were required to attend 90 minutes face-to-face session conducted by qualified Qigong master once a week over 8 weeks. For exercise control (line dancing) group, participants were also given weekly 90 minutes face-to-face line dance session by an instructor. Both interventions were conducted at UMMC on different days. In wait-list usual care group, participants needed to follow usual standard medical care and they were assured that physical activity intervention would be given after the 8-week trial.

Data analysis

Descriptive statistic and χ^2 -test or Fisher's exact test were used to determine the social demographic characteristics and the equal distributions among groups.

Results

Numerous reasons were offered by the 554 non-participants who were followed up via telephone. 234 patients were not residents close to the trial location in Klang Valley, and as such, it was impractical for them to participate in the KL Qigong trial which involves at least

6 sessions. Lack of transportation was a key problem for 91 patients, whilst 55 were unable to join due to job-commitments, and a further 170 subjects were just not interested or unmotivated to participate in the study. The final total of 197 consented patients, were randomized into three groups: the Qigong intervention group, line dancing exercise control group and a wait-list usual care group (Figure 1).

The overall response rate was a mere 26%. Out of these 197 participants, 95 patients persevered through the eight-week trial. The attrition rate on the KL qigong trial was 52%. 66 patients, who initially gave consent, did not participate from the start (15 randomised women from the Qigong group, 17 women from exercise control group and 34 women from usual care group). This contributed to 65% (66/102) of the total drop-out. The reasons for refusal were not given by these 66 women, who obviously had second thoughts and perhaps this is possibly contributed by a lack of follow up to ensure adequate information at the initial stages.

Table 1 showed that the majority of the participants are within the age range of 40-59 years (73.6%), Chinese (64%) and with stage II cancer (63%) and are within three years since diagnosis (83.7%). The largest drop-outs or those unable to complete at least 6 out of 8 sessions (75% participation) are made up of the 40-59 years old, Chinese and stage II and survivors of breast cancer of 2-3 years post diagnosis. Table 2 showed the breakdowns of the dropouts

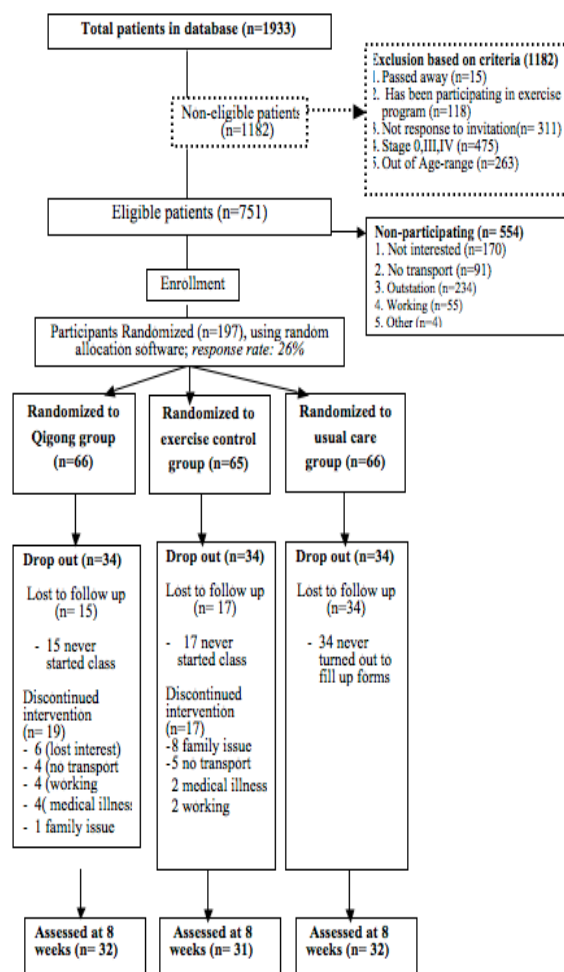


Figure 1. Flow Chart of the Qigong Trial

Table 1. Demographic of the Participants

		All (n=197)		Completed trial (n=95)		Withdrawn from trial (n=102)	
		n	%	n	%	n	%
Age group	21-29	1	0.5	1	1.1	0	0
	30-39	19	9.6	6	6.3	13	12.7
	40-49	61	31.0	29	30.5	32	31.4
	50-59	84	42.6	43	45.3	41	40.2
	60-65	32	16.2	16	16.8	16	15.7
Ethnicity	Chinese	126	64.0	61	64.2	65	63.7
	Malay	38	19.3	24	10.6	14	13.7
	Indian	33	16.7	10	25.3	23	22.5
Cancer Stage	Stage I	73	37.0	36	37.9	37	36.3
	Stage II	124	63.0	59	62.1	65	63.7
Years post-diagnosis	1	26	13.2	14	14.7	12	11.8
	2	83	42.1	37	38.9	46	45.1
	3	56	28.4	24	25.3	32	31.4
	4	13	6.6	10	10.5	3	2.9
	5	19	9.6	10	10.5	9	8.8

Table 2. Number of Drop-out* on Each Session

Session	Qigong (n=19)		Exercise control (n=17)	
	n	%	n	%
1 75% attendance	0	0	0	0
2 75% attendance	3	16	4	23
3 75% attendance	4	21	2	12
4 75% attendance	8	42	7	41
5 75% attendance	2	11	2	12
6 75% attendance	1	5	1	6
7 75% attendance	1	5	1	6
Cumulative total	19	100	17	100

*Drop-out from trial = started but unable to attend at least 6 out of 8 sessions (based on predetermined criteria of at least 75% attendance) from the two arms, where the numbers of drop-outs were slightly higher in QiGong (around the 3rd and 4th sessions where more complex routines were taught). There was no dropout on the first session. These subjects who attended the interventions but did not fulfill the criteria of eligible subjects should participate at least 75% of intervention term. Of the intervention (Qigong and exercise control) groups, 36 patients discontinued the intervention and the key reasons given were transportation barrier (n=9), demands from family related commitment (n=9), patient non-preference or rejection of the choice of activity on trial (n=6), job commitment (n=6), medical illness (n=6). The rate of failing to adhere to intervention (defined as participation in fewer than 75% of scheduled sessions) was 17.8% (35/197 women).

Common barriers during the recruitment process

For the 131 participants who started the intervention, the adherence rate for Qigong group and exercise control group were 63% and 65% respectively. Among them, Chinese (n=80) and Malay (n=32) demonstrated attrition rate of 24% (n=19) and 25% (n=8) respectively, while Indian (n=19) participants had the highest dropout rate of 47% (n=9). However, these differences were not significant (p<0.05, Fisher's Exact test). Table 3 showed the common barriers during the recruitment process. These barriers were further grouped as the patient-level,

Table 3. Recruitment Barriers Encountered in this Trial

Patient Barriers	Facilitator Barriers	Institutional Barriers
Transportation**	Time constraint	Lack of parking lots
Patient non-preference	Lack of manpower	Funding
Family commitment**	Lack of research training	Lack of proper place
Job commitment**	Lack of autonomy for some level of staffing	Poor Employer Support
Medical illness**		

**Drop-outs (Also retention barriers)

Table 4. Retention Barriers (Reasons for Drop-out Across Ethnic and Age Groups)

Retention Barriers	Transportation (%)	Family Commitment (%)	Job Commitment (%)	Medical Illness (%)	Patients motivation (%)
Ethnic (n):					
Chinese (19)	5 (26)	3 (16)	4 (21)	2 (11)	5 (26)
Malay (8)	2 (25)	4 (50)	0	1 (13)	1 (13)
Indian (9)	2 (22)	2 (22)	2 (22)	3 (33)	0
Age(n):					
30-39 (1)	0	1 (33)	0	0	2 (67)
40-49 (12)	4 (33)	2 (17)	4 (33)	1 (8)	1 (8)
50-59 (17)	3 (18)	5 (29)	2 (12)	5 (29)	2 (12)
60-65 (4)	2 (50)	1 (25)	0	0	1 (25)

*Drop-outs= participants who started but are unable to attend at least 6 out of 8 sessions (i.e. the predetermined criteria of KL Qigong trial of at least 75% attendance)

facilitator-level and institutional-level barriers. At the patient barrier, issues with getting transportation, lack of preference for participation, family-childcare-job commitments and after effects of treatment and cancer were offered as reasons for refusal to participate. Apart from the many patient-related barriers, there were also clinician-related barriers offered by the co-investigators of the trial which included time-constraint issue, lack of support staff and lack of proper training to notify essential details regarding clinical-trials to patients. The institutional barriers were mainly due to lack of funding to support such behavioral trials, and barriers offered by survivors included the difficulty securing parking space and inability to obtain leave from unsupportive employers.

Retention barriers according to ethnic and age groups

Table 4 presents the retention barriers according to ethnic and age groups. Ethnic wise, the reasons given by Indian patients for their inability to complete the trial included having - no transportations, competing family commitments, and issues from after effects of medical treatment or/and illness. Factors contributed to Chinese patients to withdraw from the trial include transportation issue, job commitment and patient non-preference (unable to sustain interest to continue). For Malay patients, family related commitment was reported as their key barrier.

With age group, participants who aged 50-59 reported highest drop-out rate (n=17). Three major reasons offered by the non-participant were family commitment, medical illness and transportation. Equal number of five participants had reported for both conflicting family commitments and poor medical health reasons while three of them reported no transportation. The individual logistic barriers faced by different age group are presented in Table 4.

Discussion

A successful trial requires adequate and appropriate subject recruitment and high adherence to the interventions being studied. Complex interventions involving complex engagement from participants or several behavioral interventions, e.g. alteration of sedentary lifestyles, pose particular challenges for recruitment and retention within clinical trials. These investigations required sufficient power size to offset expected dropouts since its required high commitments from participants. Undertaking such trials amongst cancer patients, coupled with conducting within a multicultural setting creates additional problems that need proactive planning for foreseen and unforeseen challenges. Based on a review done by Brown (2000), different barriers among different ethnic groups in America have been identified. Among all, lack of awareness, transportation issues, family or job commitment and concerns related to requirement and cost of the trial were the major factors inhibiting women cancer survivors for participating and sustaining a clinical trial (Brown, 2000). Lack of awareness of cancer trial has also been highlighted as a key barrier across many studies (Williams, 2004), perpetuating distrust of medical trials. Furthermore, complex program beset with practical difficulties is not unfamiliar as in all, if not most interventions (Hasson, 2012). A recent physical activity survey in a multiethnic setting also reported more effort needed for increasing awareness amongst the patients, due to the various different cultural beliefs about exercise engagement (Loh, 2011).

Low participation rates and high dropout rates within clinical trials are well established problems that have been frequently observed in trials of exercise interventions in cancer patients. In an eight weeks exercise-diet intervention trial in Washington, less than 50% (39.6%) of the total breast cancer survivors (n=99) responded to the call for participation. Of the 40 interested participants, 17 (43%) survivors were eligible but only 10 (41%) were enrolled (McTiernan et al., 1998). In another trial conducted at Canada by Courneya (Courneya et al., 2003), a recruitment rate of 14% was reported with only 28.2% (n=91) responded to initial invitation and 53 postmenopausal breast cancer survivors randomized into the 15-week long exercise trial groups (intervention or control). In USA, Irwin et al. (2008) reported a recruitment rate of only 9.5% postmenopausal breast cancer survivors (n=75, out of 788 potential survivors). Of the 75 participants, 50 of them were successfully recruited via cancer registry and 25 of them were from self-referred method (Irwin et al., 2008).

Issues of low adherence especially involving multiethnic population in New York have been reported (Moadel et al., 2007). In their RCT (164 recruited patients) evaluating efficacy of yoga in multiethnic African America, Hispanic, Non-Hispanic White and other breast cancer survivors, only 128 (78%) patients completed the 12-week weekly intervention. Similar low adherence rate was reported by Oh et al. (2010) for their 10-week Qigong trial held at Sydney which documented a drop-out rate of 33%. Reasons for the drop-out were

not identified but with multiethnic population, there may be added issues of varying language, culture, social norms and group acceptance. To our best knowledge, our trial is the first study that explores the feasibility of physical activity trial among breast cancer survivors in a multiethnic Malaysian context. Thus, the information gathered here would be useful to provide insight into the possible barriers in recruitment and adherence of an intervention based clinical trial.

In this study, key factors of low-adherence rate were lack of transportation and the needs to fulfill family demands or commitment. Participants that fall under this category were unable to drive or choose not to drive within the busy traffic, with lack of parking facilities in Kuala Lumpur and required helps from immediate family members. Public transportation was reported as either expensive (taxi) and/or unreliable (public buses). These barriers, commonly reported together with work obligations, lack of time, long travelling times and lack of child-care support are not unfamiliar in the literature (Foley and Moertel, 1991; Klabunde, 1999; Crosson, 2001; Barrett, 2002; William, 2004). However, in Malaysia, issues related to multiple roles (being a mother, wife and employee) remained a main juggling role for many women breast cancer survivors, and thus interferes in their engagement in self management program and participation in physical activity (Loh, 2007; Loh et al., 2011). Clinical trial venue should perhaps be set at community based where it is more accessible for the patients. Strategy like pairing of patients from similar location could be preplanned for car pooling purposes, and financial aid for transportation should be considered during funding application. Indeed, specific approaches tailored to specific minority.

Research evidence suggests that age of patients is a common predictor of attrition, although direction of the effect of age is less consistent. Some studies report older patients whilst others reported younger patients to be at a greater risk of leaving (Honas, 2003). Our study showed that patients in their 50's were the most prevalent age group (47.2%) not being able to sustain the eight weeks program. This group had made an effort initially but many withdrew later citing numerous logistic barriers. As Asian countries have a stronger family bonding and expected social roles, it is not uncommon for these women to commit energy and time for the family and to put preference to family events (Courneya, et al., 2003; Loh et al., 2007; Fang, 2011) over their individual needs. This finding calls for proactive planning to be in place when recruiting Asian patients in their 50's especially for trial with long term commitment (more than two months). There may be a need to engage the support of family members so that these survivors can 'be released' temporarily to focus on their own health and wellbeing, without feeling guilty.

Future qualitative study with these women may help to uncover some viable solutions by soliciting the women's perspectives on likely options. Cultural and language-barriers have often been implicated as reason for low recruitment and poor retention of cancer participants (Ford et al., 2008; Gul and Ali, 2010; Symonds et al., 2012). In

our Qigong trial, language was not the major barrier but cultural issues may well be a key contributor to the attrition rate as we observed a pattern in the different ethnic groups. A recent study by Hui and colleagues (2012) showed that high cancer patients attrition were associated with various patient characteristics and a high baseline symptom burden such as dyspnea (OR, 1.06; $p=0.01$), fatigue (OR, 1.08; $p=0.01$), Hispanic race (OR, 1.87; $p=0.002$), higher level of education ($p=0.02$), longer study duration ($p=0.01$), and outpatient studies ($p=0.05$). It is worth investigating the underlying factors that kept participants away from engaging in healthful survivorship activities such as a randomized physical activity trial.

A major limitation in our trial was the strategies that we used to patient recruitment. A variety of recruitment strategies such as mailing, referral from physician and advertising via posters, media and breast cancer support group might yield a better result. Also, our trial was lacked of external motivation such as rewards and recognition for participants who completed the trial. Besides, our trial may have possible selection bias because participants of the trial were mostly from urban area and these patients might have positive attitude in physical activity. Thus, the result must be interpreted with caution as the majority of the participants were from urban areas and may not be representative of non-urban survivors. In addition, the low participation rate may also mean that generalization is compromised because those who did participate might be more healthy or motivated. Overall, these lessons related to recruitment-retention barriers for complex intervention clinical trials may be applicable across Asia Pacific since there is a general lack of public awareness of cancer and/or, on the association of activity and cancer recurrence.

In conclusion, to ensure clinical trials are able to achieve high participation and low attrition rates among eligible participants, future study should focus on these expressed barriers and solutions are proactively sought to overcome to minimize barriers. Dedicated manpower and clinical centre can facilitate the recruitment process. Knowledge-based information should be conveyed to the patient to increase their interest to participate in physical activity based clinical trials. Greater attention should be given to the barriers faced to ensure higher successful rate in recruitment and completion of a trial. Promoting the significance of clinical-trials across Asia countries is a dire challenge and a policy priority is required to put into place to achieve higher level evidence-based practice at this continuum to suit with the global health agenda.

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