A pragmatic, randomised controlled trial of the effects of live relaxation on mood, coping, and quality of life (LIVEREL).

1. Introduction

In 1998, a systematic review of the use of complementary and alternative medicine (CAM) in cancer patients reported an average use across 13 countries of 31%, although the range was wide (7-64%) (Ernst and Cassileth, 1998). Estimates of the use of complementary and alternative medicines (CAM) by cancer patients in the UK have ranged from 32% in patients undergoing radiotherapy (Maher et al., 1994) to 16% in unselected oncology patients (Downer et al., 1994). Clearly, there is a significant demand for these interventions in the UK and there is an urgent need to evaluate effectiveness (Walker and Anderson, 1999; Ernst and White, 2000).

In a nationally representative telephone random survey of 1,204 British adults, 20% had used a complementary treatment in the previous 12 months, and this extrapolates to an annual national expenditure of £1.6 billion (Ernst and White, 2000). Despite this popularity, a survey of all medical research charities in 2002 found that, as a proportion of total budget, only 0.31% had been spent on CAM research (Wider and Ernst, 2003).

Relaxation is amongst the most popular complementary therapies used by patients with cancer (Downer et al., 1994; Maher et al., 1994). In addition to studies of the effects of relaxation therapy on treatment-induced nausea, vomiting and related side-effects (Burish et al., 1988) two randomised, controlled trials (RCTs) of the psychological effects of relaxation have been reported in patients with breast cancer. Bridge et al (1988) evaluated the effects of relaxation with, or without, 'peaceful' imagery in 154 women receiving radiotherapy as out-patients. Compared with the control group, total mood disturbance was significantly less in the two intervention groups. The combination of relaxation and peaceful imagery was significantly better than relaxation on its own. The second randomised study was very small (Gruber et al., 1993). Thirteen patients with Stage 1 breast cancer were randomised to a delayed treatment control or to group relaxation training, relaxing imagery and electromyographic biofeedback. Although immunological and biochemical changes were observed, a between-group analysis did not find any significant changes in quality of life or other psychological measures. Studies with mixed groups of cancer patients have reported beneficial effects on mood (Baider et al., 1994; Bindemann et al., 1991; Burish et al., 1988; Holland et al., 1991).

We have been using relaxation-based interventions in cancer since 1980 (Walker, 2004; Walker, Walker, Walker and Sharp, in press). Funded by the Cancer Research Campaign, we carried out a prospective, randomised study of relaxation training combined with guided imagery in 96 women with locally advanced breast cancer (Walker et al., 1999). Women were randomised to a high level of support with, or without, relaxation and guided imagery (live training sessions plus audio recordings for home practice). Acceptability was excellent: 96 out of a consecutive series of 97 women agreed to participate in the study (Walker et al., 1999). Compared with women in the control group, patients who received the psychological intervention had significantly better quality of life, mood, and coping during the 37 week protocol. However, 49% of the patients practised relaxation less than daily, and the intervention was of less benefit to them.

We are currently in the final stages of a 4-year randomised controlled trial to evaluate the psychoneuroimmunological effects of relaxation and guided imagery, alone and in combination, in patients with colorectal cancer. This study will provide valuable information about the acceptability of audio-recorded relaxation and imagery in men and women with colorectal cancer.
The relative acceptability and effectiveness of live versus recorded relaxation training instructions has received surprisingly scant attention. Morrow (1984) randomised 10 patients to live plus recorded versus recorded instructions. They had all previously developed anticipatory nausea to chemotherapy. Four of the five patients in the recorded instructions only group, and none of the patients in the other group, developed conditioned nausea listening to the tape. The study, however, did not assess the effect of the two methods on the relaxation response itself. An early study of 60 patients receiving minor tranquilisers and sedatives showed that the two methods did not differentially reduce medication intake or physiological indices (Tamez, Moore and Brown, 1978). However, this was a relatively small study in a non cancer population, with non-cancer-related outcomes. Moreover, in clinical practice, a more important question is whether or not adding live training sessions to recorded training sessions makes a worthwhile difference. The relative efficacy and acceptability of recorded versus recorded plus live training is not known in a cancer population. This is an important issue. Live relaxation may enhance acceptability and improve effectiveness. However, there is a significant cost in terms of staff (and patient) time.

In summary, relaxation (with and without imagery) has been shown to be beneficial in terms of quality of life in various cancer patient populations. However, the optimum method of training is not known. The purpose of this study, therefore, is to compare the effects of recorded instructions (RECREL) versus recorded instructions plus live training (LIVEREL) in patients attending the Oncology Health Centres in Kingston upon Hull.

2. The need for a trial

2.1 What are the principal research questions to be addressed?

a) In patients attending the Oncology Health Centres for the first time, what is the relative effectiveness of LIVEREL and RECREL (i.e. ‘treatment as usual’ including audio recorded relaxation as part of support within the Oncology Health Centres) on mood, coping and quality of life?

b) What is the relative cost-effectiveness of LIVEREL and RECREL?

c) What are the immediate effects of live versus recorded relaxation instructions on blood pressure and pulse rate?

If patients randomised to LIVEREL have significantly higher relaxation scores on the Mood Rating Scale than those randomised to RECREL, we would conclude that the beneficial effects of LIVEREL was due to the extra social contact and/or the effects of live feedback on performance.

2.2 What are the null hypotheses?

a) LIVEREL and RECREL will have equivalent effects on mood, coping, quality of life and physiological parameters.

b) LIVEREL and RECREL will be equally cost effective.

2.3 Why is a trial needed now?

As indicated above, there is considerable demand for CAM in people with cancer, and health service commissioners are under pressure to fund CAM for cancer patients within the NHS. However, in the context of evidence-based medicine, this is very difficult to justify in the absence of appropriate explanatory and/or pragmatic RCTs.

From a practical clinician’s point of view, it would be very helpful to know the relative effectiveness of LIVEREL and RECREL. It would also be useful to have information about which intervention is likely to be most beneficial for a particular patient.
2.4 Systematic reviews

There are no specific systematic reviews of the effects of live versus recorded training. We have also searched the International Cancer Research Portfolio website and did not find any relevant ongoing studies.

2.5 How will the results be used?

The results will be of potential value as follows:

(a) If LIVEREL is more effective or cost effective than RECREL, nursing and paramedical staff elsewhere should be taught how to carry out live relaxation, and positive results in this study would have wide applicability within the NHS and beyond.
(b) If LIVEREL is more effective or cost effective than RECREL, work would be needed to evaluate the optimal training method for staff.

3 The proposed trial

3.1 Summary

One hundred and fifty-six patients will be randomised to receive either LIVEREL (3 sessions) or RECREL as part of their overall management within the Oncology Health Centres (treatment as usual). Patients will be first-time attendees at the Oncology Health Centres with confirmed colorectal cancer, gynaecological cancer, lung cancer or prostate cancer, and life expectancy of at least 18 weeks. Patients with clinically significant depression will be included and will receive appropriate antidepressant therapy concomitantly. Patients will be excluded if they have a history of functional psychosis.

Randomisation will be carried out remotely and will be stratified for type of cancer and current oncological treatment (chemotherapy, radiotherapy, hormone therapy or nothing1).

The primary endpoint will be 8 weeks after randomisation; secondary endpoints will be 4 weeks, and 12 weeks after randomisation. The primary outcome will be relaxation scores on the Mood Rating Scale. Secondary measures will be total score of the Brief Profile of Mood States, the Functional Assessment of Cancer Therapy Scale (general version), positive and negative mood (Mood Rating Scale, Hospital Anxiety Scale) and EuroQuol scores. Clinically significant distress will be assessed at baseline and at 12 weeks using the Structured Clinical Interview using DSM-IV criteria.

The study has been powered to detect a difference of 20 points on the relaxation scale of the MRS. Analysis will be by ‘intention to treat’. The outcomes will be analysed using analysis of covariance, adjusted for T stage, age and baseline scores. Planned subgroup analysis will be carried out for patients who are clinically anxious and also for patient who are clinically depressed. The effects of expectancy on outcomes will also be assessed. The effects of the two interventions on concomitant health service use will also be compared.

An embedded study of the immediate effects of live versus recorded relaxation on mood, pulse, and blood pressure will be carried out at week 4.

3.2 Design

This is a single-centre, prospective, pragmatic, randomised, controlled clinical trial (Phase 3).

3.3 What are the planned interventions?

1 For patients receiving multiple concurrent treatments, the hierarchy for randomisation will be chemotherapy, radiotherapy and hormone therapy.
All interventions will be carried out in the Oncology Health Centres at Castle Hill and Princess Royal Hospitals, Kingston upon Hull (House of Commons, 2004; Walker et al., 2003 a and b).

Patients will be randomised to one of two interventions:

**Intervention 1**

Patients randomised to RECREL will be taught progressive muscular relaxation and cue-controlled relaxation (Hutchings et al., 1980), with imagery of the patient’s choice\(^2\), by means of audio recordings based on scripts used in our previous studies of patients with breast cancer, colorectal cancer, and lymphoma, and with healthy volunteers (Johnson et al., 1996; Ratcliffe et al., 1995, Walker et al., 1999a). Each therapist will record these scripts in his/her own voice. Patients will be asked to practice once daily at home for 8 weeks (daily diary records to be kept as in PERI). To control for patient contact, they will receive three audio recorded training sessions (progressive muscular relaxation, with or without guided imagery) at weeks, 1, 2 and 4 in the Oncology Health Centres.

**Intervention 2**

Patients randomised to LIVEREL will receive the same audio recordings and will be given identical instructions to practice daily at home for 8 weeks. In addition, they will be given three sessions of live training (40 minutes) at weekly intervals from our clinical nurse specialists (behavioural oncology).

An external consultant skilled in these methods will assess the competency of each of the nurses and their ability to adhere to the protocol. In addition, to ensure protocol adherence, a random sample of live sessions will be observed by a clinical psychologist during the study period.

All patients will be invited to attend, or telephone, one of the Oncology Health Centres whenever they wish, and they will receive treatment as usual in the Centres when they attend (House of Commons, 2004; Walker et al., 2003 a and b). This includes access to the Clinical and Research Nurse Specialists (Behavioural Oncology) and, if indicated clinically, the clinical psychologists. All patients with clinically significant problems will receive treatment according to current local practice and any psychosocial or psychopharmacological interventions will be documented. They will also have access to other support services.

Records of telephone and other contact with the Centres will be kept (using the contact cards used in previous studies).

3.4 What are the proposed practical arrangements for allocating participants to trial groups?

Patients eligible for inclusion will be invited to participate at their first attendance at the Oncology Health Centre.

Randomisation will be carried out remotely by the Clinical Trials Section of the Institute of Rehabilitation, and will be stratified for type of cancer. A permuted blocks design will be used and sequences will be determined using Instat2.

3.5 What are the proposed practical methods for protecting against other sources of bias?

a) Interview and questionnaire assessments of each patient will be carried out by a Clinical and Research Nurse Specialist (Behavioural Oncology) who is not involved any aspect of that

\(^2\) In addition to “special place” imagery, imagery could include for example, special place, fighting spirit, surveillance and/or healing imagery (Walker et al, in press).
b) All baseline assessments will be carried out before randomisation.

c) Questionnaires will be scored by a Clinical and Research Nurse Specialist (Behavioural Oncology) who is not involved in any aspect of a patient’s clinical management.

d) The Complementary Medicines Questionnaire will be used to monitor concomitant use of CAM, and the Social Support Questionnaire will be used to evaluate perceived adequacy of support (both questionnaires used successfully in PERI and in our reflexology study).

3.6 What are the planned inclusion/exclusion criteria?

Inclusion criteria:
1. at least 18 years of age
2. histologically confirmed colorectal cancer, gynaecological cancer (ovarian, endometrial, cervical) lung, or prostate cancer.
3. accessing the Oncology Health Service for the first time

Exclusion criteria:
1. WHO performance status 2, 3 and 4;
2. clinically significant cognitive impairment or dementia
3. inability to complete Quality of Life questionnaires
4. inability or unwillingness to give informed consent
5. history of functional psychosis.

3.7 What is the proposed duration of treatment?

For patients in both arms, treatment will last for eight weeks.

3.8 What is the proposed duration of follow up?

Final follow up is 12 weeks after randomisation.

3.9 What are the proposed outcome measures?

(a) Primary outcome (Week 8)

- Relaxation scale score on the Mood Rating Scale (MRS), (Anderson et al., 2000; Johnson et al., 1996; Walker et al., 1997; Walker et al., 1999; Wesnes et al., 1997b)

(b) Secondary outcomes (Weeks 4, and 12)

- Functional Assessment of Cancer Therapy: General version (FACT-G) (Cella et al., 1993)
- Hospital Anxiety and Depression Scores (HADS) (Hermann, 1997; Walker et al., 1999; Zigmond & Snaith, 1983)
- Mood Rating Scale (MRS) (remaining scales) (Anderson et al., 2000; Johnson et al., 1996; Walker et al., 1997; Walker et al., 1999; Wesnes et al., 1997)
- Brief Profile of Mood States (Cella et al, 1987)
- EuroQol (EQ-5D) (Brooks, 1996; EuroQoL Group, 1990)
- Health Service Use (HSU)
- Social Support Questionnaire (SSQ)
- Patient Satisfaction Questionnaire (PSQ) (Walker et al., 1999)

The Complementary Methods Questionnaire (CMQ) (developed for our current studies (Walker et al, 2006) will be used to monitor concomitant use of complementary medicines.

Patients will also be assessed at baseline and at eight weeks for clinically significant psychiatric morbidity using the Diagnostic and Statistical Manual (Revision IV) (DSM-IV-TR) of the American Psychiatric
At baseline, before randomisation, patients will be given a brief description of the two interventions and they will be asked to complete a Patient Preference Questionnaire (PPQ) which will involve rating on a five point scale the extent to which they would like to be randomised to each intervention, and a forced-choice overall preference.

Assessments will be completed in the order shown in Figure One.

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<th>Baseline (Pre-randomisation)</th>
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To determine the short term effects of live and recorded instructions, at week 4 patients randomised to LIVEREL will be given a session of live training, whilst patients randomised to RECREL will listen on their own to the recording at the Centre. The MRS and Brief POMS will be administered immediately before, and immediately after, the live or recorded relaxation session in the Oncology Health Centres, blood pressure and pulse will also be assessed using an automated method (used in PERI) before and after the intervention.

3.10 How will the outcome measures be assessed at follow up?

Patients will complete the questionnaires in the order indicated in the table above. The assessments will be carried out by a nurse not involved in the patient’s management and they will be completed in a private room.

3.11 What is the proposed sample size?

A sample size of 70 in each group will have 80% power to detect a difference in means of 20.0 on the MRS Relaxation Scale (the difference between a Group 1 mean of 74.0 and a Group 2 mean of 54.0) assuming that the common standard deviation is 42.03. This is equivalent to an effect size of 0.48.

In our reflexology trial, only 4% of women did not provide endpoint data. Allowing conservatively for over 10% attrition in the proposed trial, we will recruit 156 patients (2 groups of 78). Our power calculations have used nQuery ((Elashoff, 2000) and a two-tailed significance level of 5%.

3.12 What is the planned recruitment rate?

Recruitment will commence on 1st September and will continue until 1st October 2010, or as soon as 156
patients have been randomised. Approximately 1,500 new patients are seen annually in the Oncology Health Service. In an audit of patients attending during a consecutive 5-day periods in June 2006, 21% had colorectal cancer, 16% had lung cancer, 8% had prostate cancer and 4% had gynaecological cancer.

3.13 Are there likely to be problems with compliance?

In our previous study of women with locally advanced breast cancer, 96 out of 97 consecutive women agreed to participate, and none dropped out of the study (Walker et al., 1999). We are proposing to include a different group of patients who may be less compliant. However, we expect that most patients will be willing to practice audio recorded relaxation because, clinically, we have found relaxation to be very acceptable in this population. However, if some patients practice less than others (as recorded in the daily diaries), we shall regard this as a finding rather than a problem in this pragmatic trial, and explore any such finding through a ‘dose response’ analysis.

3.14 What is the likely rate of loss to follow up?

Based on our previous experience, follow up data should be available for approximately 90% of the patients recruited.

3.15 How many centres will be involved?

This is a single centre study.

3.17 Are there any planned subgroup analyses?

1. We shall test the effect of patient preference assessed using the PPQ; for each intervention, patients randomised to their preferred treatment will be compared with those who were not.
2. If there is sufficient variability, we shall examine the effects of compliance on outcomes.

3.18 Frequency of analyses

No interim analyses are planned.

3.19 Health service issues

We shall estimate the additional local NHS costs of delivering relaxation, and use sensitivity analysis to take account of how these costs could vary across localities. We shall ask patients to use the Health Care Use Questionnaire developed for PERI to record all their contacts within health and social care throughout the study period.

4 Trial Management

4.1 What are the arrangements for the day to day management of the programme?

The Oncology Health Centres Senior Management Team meets weekly, and will review progress every week. In addition, the Oncology Health Centre Team meets monthly and study progress will be a standing item on the agenda.

4.2 What will be the responsibilities of the applicants?

- Professor Walker and Dr Sharp will be joint Principal Investigators.
- Dr D M Sharp, and M B Walker will oversee the interventions.
- Professor Walker and Dr Sharp will provide statistical advice and supervise the analysis.

Professor L G Walker is Lead clinician for the Humber and Yorkshire Coast Cancer Network for
4.4 What will be the responsibilities of the named collaborators?

The named collaborators have agreed to assist with recruitment.

4.5 Has the trial been developed or approved by an NCRI Clinical Studies Group

No

4.6 Who are the trial statisticians?

Professor L G Walker and Dr D M Sharp.

4.7 What measures have you or will you take to ensure that patients entered on the studies are informed about the results?

All publications are made freely available in the Oncology Health Centres and patients will be informed to this effect at the time of recruitment.

4.8 Data Monitoring and Trial Steering Committee

Professor Roger Watson, Professor of Nursing Studies, University of Sheffield (Chair)
Professor Michael Wang, Professor of Clinical Psychology, University of Leicester
Dr D M Sharp, Senior Lecturer in Behavioural Oncology, University of Hull (Joint PI)
Professor Leslie G Walker (Joint PI)

4.10 Consumer involvement

In 2000, an Oncology Health Service Partnership Group was established to provide advice regarding Centre policy, developments and research. Current membership includes seven patients and relatives, the Divisional Manager (Cancer and Diagnostic Services), the Yorkshire Coast and Humber Network Lead Clinician, the Head of the Academic Surgical Unit, a Macmillan Nurse and three representatives from the Oncology Health Centres. They have discussed the details of this application and have given their enthusiastic support for the application.

4.11 Other management aspects

None

5 Ethics

An application for Ethical Approval has been submitted.

6. Timelines

September 2007 Preparation of Case Report Forms, staff recruitment and training.
October 2007- October 2010 Recruitment of patients, delivery of interventions and follow-up assessments.
Nov 2010- Feb 2011 Data analysis and preparation of report.

7. Resources Requested
The Oncology Health Centres are already staffed and will provide the NHS infrastructure for the study. Patients will receive medical, surgical and radiological treatment according to existing local protocols, and will incur no extra costs.

8. References


Ernst E and White A (2000). The BBC survey of complementary medicine in the UK. Complementary Therapies in Medicine, 8, 32-36.


31 March 08