Project Title

The effectiveness and cost effectiveness of acupressure for the control and management of chemotherapy-related acute and delayed nausea.

Research objectives

Primary objective:

1. To assess the clinical effectiveness of self-acupressure using wristbands in addition to standard care in the management of chemotherapy-induced (acute and delayed) *nausea* compared to patients receiving standard care with sham acupressure wristbands and standard care alone.

Secondary objectives:

2. To assess the cost effectiveness and extent of use of usual care in patients using acupressure wristbands in addition to standard care for the management of chemotherapy-induced nausea compared to patients receiving standard care with sham acupressure wristbands and standard care alone.
3. To assess the level of quality of life in patients using acupressure wristbands in addition to standard care in the management of chemotherapy-induced nausea and vomiting compared to patients receiving standard care with sham acupressure wristbands and standard care alone.
4. To assess the clinical effectiveness of self-acupressure using wristbands in addition to standard care in the management of chemotherapy-induced (acute and delayed) *vomiting* compared to patients receiving standard care with sham acupressure wristbands and standard care alone.
5. To ascertain for which emetogenic level of chemotherapy regimens (ie. high, moderate or low emetogenic chemotherapy) self-acupressure using wristbands in addition to standard care is more or less effective in terms of nausea compared to patients receiving standard care with sham acupressure wristbands and standard care alone.
6. To ascertain whether any improvement in chemotherapy-induced nausea and vomiting from using acupressure wristbands is different in males and females.
7. To ascertain whether there is an age effect from the use of acupressure wristbands in relation to chemotherapy-induced nausea and vomiting.

Existing research

Significant developments in antiemetic therapy over the past two decades have improved the control of chemotherapy-related vomiting. By contrast, chemotherapy-related nausea, both acute and delayed, is still a significant problem in clinical practice, with 42–52% of patients experiencing nausea on any one day in routine practice (Glaus *et al*, 2004). Surprisingly, despite improvements in the management of vomiting, post-chemotherapy nausea seems to have increased (Roscoe *et al*, 2000). Furthermore, clinicians often underestimate the experience of nausea, especially with regards to delayed nausea (Grunberg *et al*, 2004; Liau *et al*, 2005).

Chemotherapy-induced nausea and vomiting (CINV) can have a profound effect on the cancer treatment experience (Bergkvist & Wengstrom, 2006) and is associated with negative effects on daily life and overall quality of life, including effects on food intake, weight loss, effects on social interactions, dehydration, difficulty with sleeping and anxiety (Bergkvist & Wengstrom, 2006; Foubert & Vaessen 2005). In a

qualitative study of patients' experiences, unmanaged nausea was constant in some patients and made them exhausted for long periods after chemotherapy, making recovery between cycles longer (Bergkvist & Wengstrom, 2006). The impact of nausea is greater than that of vomiting (Griffin *et al*, 1996) and nausea has proven to be more difficult to control. The direct and indirect costs of the experience of nausea and vomiting, especially of delayed symptoms, are considerable (Ihbe-Heffinger *et al*, 2004). Antiemetic trials have traditionally focused primarily on vomiting and emetic episodes, upon which the effectiveness of many antiemetic drugs is judged. Little attention has been directed to the concept of chemotherapy-induced nausea despite the fact that it is increasingly recognised that nausea and vomiting are related but separate entities (ASHP 1999; Miller & Kearney 2004). The need for these two symptoms to be treated as two separate entities is strongly advocated (Miller & Kearney 2004).

The reasons behind this incomplete management of CINV are multifaceted. They include health professionals' limited understanding of the complex concept of CINV and its different phases; limited assessment in clinical practice of CINV and its risk factors; using more emetogenic chemotherapy protocols than in the past; not understanding clearly all the pathways involved in the development of CINV; and more focus given to the vomiting experience than nausea in clinical trials (Molassiotis, 2005).

As antiemetic medications do not fully control nausea during chemotherapy, non-pharmacological interventions in addition to antiemetics have been tested over the years, especially in the 1980s, including relaxation techniques, coping preparation, imagery, and distraction techniques, with positive results in most studies (for a review see Burish & Tope, 1992). Acupuncture and its non-invasive form of acupressure have been tested several times after the classic early work of Dundee (1987; 1989). In a literature search using the key words 'acupressure', 'nausea', 'vomiting', 'emesis', 'chemotherapy', 'cancer' and combinations, we have identified 10 studies specific to oncology, reviewed elsewhere (Molassiotis *et al*, 2007a), with 7/10 studies showing positive results and a further two approaching statistical significance. These studies have used a variety of acupressure methods, such as the 'ReliefBand' (a small battery-operated TENS device designed to stimulate the P6 acu-point) (Pearl *et al*, 1999; Roscoe *et al*, 2002; Treish *et al*, 2003); a SeaBand (a small elastic band with a round plastic button applying constant mild pressure on the P6 acu-point) (Dundee & Yang, 1990; Dundee *et al*, 1991; Wright 2005); direct pressure on the acu-point P6 (Shin *et al*, 2004) or P6 and ST36 points together (Dibble *et al*, 2000). Most studies had small sample sizes of 18–50 patients. The largest study to date ($n = 739$) testing acupressure and acustimulation showed improvements in nausea and vomiting in men while there was a similar trend in women to reduce acute symptoms only, although the latter did not reach statistical significance (Roscoe *et al*, 2003). No improvement in nausea/vomiting was shown in a small study by Roscoe *et al* (2005) in women with breast cancer using acustimulation (ReliefBand) wristbands. The latter two studies are suggestive of a possible gender effect. However, most past studies are hampered by small sample sizes, the wide variety of (non-standardised) antiemetics used, differences in the risk factors for nausea and vomiting in these samples, the range of emetogenicity of chemotherapy regimens used and sampling issues. A recent Cochrane systematic review of the literature highlights that acupressure reduces acute nausea but not delayed nausea, and has no benefit for vomiting (Ezzo *et al*, 2006). However, the review was primarily focused on acupuncture rather than acupressure, all different methods of acupressure were examined together and the results regarding specifically vomiting are questionable (as many of the studies included in the review had samples with little, if any, vomiting across experimental and control groups).

Our own work

Over the past 8 years the lead applicant has developed a programme of research in the management of chemotherapy-induced nausea and vomiting that feeds into the current application. This has involved the assessment of the effectiveness of non-pharmacological interventions for the management of CINV including progressive muscle relaxation training and imagery techniques (Molassiotis *et al*, 2002a); pilot testing of acupressure (Molassiotis *et al*, 2007a); identification of risk factors for CINV development such as age, gender and anxiety (Molassiotis *et al*, 2002b); the management of anticipatory nausea and

vomiting (Aapro *et al*, 2005), the development of international clinical guidelines for managing CINV (Roila *et al*, 2006) and radiation-induced nausea and vomiting (Maranzano *et al*, 2006); exploration and further clarification of the concept of chemotherapy-induced nausea as a separate entity from vomiting (Molassiotis *et al*, 2008a), the assessment of CINV levels in current clinical practice in the UK (Molassiotis *et al*, 2008b) and the development of a CINV relevant clinical scale for the assessment of acute and delayed symptoms (Molassiotis et at, 2007b). The latter is the only chemotherapy-specific scale available to date. In our qualitative study of the experience of chemotherapy-related *nausea* in seventeen patients with cancer in the UK and USA, nausea was described as distressing and complex symptom (Molassiotis *et al*, in press-a). Preliminary evidence indicates that nausea is part of a cluster of symptoms. Self-management techniques, such as dietary strategies and distraction techniques, were rooted in participants' understanding of nausea and their beliefs about what caused nausea. While self-management was common in almost all patients, acupressure was not one of the approaches used. In our latest study, an observational prospective evaluation using patient self-reports, 102 patients with cancer receiving their first chemotherapy treatment participated. They were followed up for 4 cycles of chemotherapy, providing a total of 272 assessments of nausea and vomiting. The results indicated that acute vomiting was experienced by 15.7% of the patients in cycle 1 and delayed vomiting by 14.7%, while acute nausea was present in 37.3% of the patients and delayed nausea in 47.1%, which increased over the four cycles. Moderately emetogenic chemotherapy had the highest incidence of CINV and acute symptoms were more controlled than delayed symptoms. The data suggested that, while vomiting is relatively well controlled, nausea is a significant problem in practice; it also highlighted the high cost of inappropriate use of antiemetics, which was £17,524 for every 100 patients treated over 4 cycles (Molassiotis *et al*, 2008b).

Research methods

The design of the study will be a randomised controlled trial with 3 arms. Each arm will consist of usual care plus one of (1) self administered acupressure wristbands, (2) sham acupressure wristbands, and (3) no additional treatment. The duration of the patients' involvement will be for four cycles of chemotherapy, as after 4 cycles patients not responding to the given chemotherapy may discontinue it, may be offered a different chemotherapy regimen, a different treatment plan or may be offered supportive care only.

Subjects will be allocated to the trial groups through computer-generated randomisation to be carried out remotely by the trials unit of the Christie Hospital NHS Foundation Trust. The randomisation method to be used will consist of minimisation with a random element (stochastic minimisation), balancing for gender (males/female; Molassiotis *et al*, 2002b; du Bois *et al*, 1991), age (16–24; > 24–50; > 50; Molassiotis *et al*, 2002b; Morrow *et al*, 1991) and three levels of emetogenic chemotherapy (low, moderate and high according to international ASCO and MASCC classifications; Kris *et al*, 2006; Roila *et al*, 2006).

Biases will be minimised through: a) carefully developed inclusion and exclusion criteria that take into consideration the range of factors and sources of nausea and vomiting in cancer patients other than chemotherapy (ie. intestinal obstruction); b) the use of covariates for variables that are closely linked with nausea and cannot be excluded as they are present in a large proportion of the population (ie. anxiety) (Molassiotis *et al*, 2002b; Andrykowski *et al*, 1992), to be incorporated during the data analysis as a covariate in ANCOVA models; and c) the use of stratification for other key risk factors for nausea development during chemotherapy (ie. age, gender) at the randomisation stage. Stratification, prior to randomisation, is important to ensure that known prognostic factors are equally distributed before measuring the treatment-related variables.

Pilot study using this design

We have carried out a two-arm pilot study of 36 breast cancer patients using acupressure wristbands (Sea Band™) (Molassiotis *et al*, 2007a). The current application is based on methods tested in this pilot

study. While it is acknowledged that this study was limited, key findings suggested that acupressure improved the nausea *experience* as well as nausea and vomiting *occurrence* and *distress* across the first five days of chemotherapy. Nevertheless, improvements were higher in relation to nausea than vomiting. Mean percentage of improvement was 44.5% in the experimental subjects over the control subjects. The study showed that an acupressure trial is feasible, with high levels of compliance (only 1 patient stopped using wristbands due to arm swelling), although one-third of the patients did not return completed assessments. The lack of follow up techniques (ie. reminder letters), which was due to time constraints, is partly responsible for this figure, and it is acknowledged as a limitation of the pilot study. However, missing data in the returned assessments was almost non-existent, and patient logs for acupressure usage were fully completed.

The use of sham acupressure and acupressure have also been used in another pilot trial we have carried out recently for the management of cancer-related fatigue (Molassiotis *et al*, in press-b), and it was shown that patients in the sham group who were informed they were receiving one of two combinations of (acu)-points were blinded until the end of the trial and that this group had little improvement compared to the real acupressure group, suggesting that this technique was a credible placebo and thus capable of minimising the likely effect of placebo on the study's findings.

Planned interventions, both experimental and control

The design of the study involves a phase III pragmatic randomised trial.

Sample: The target population will be a heterogeneous group of cancer patients meeting inclusion criteria and about to receive chemotherapy of high, moderate and low emetogenic potential. Heterogeneity is important in order to address issues of response to different types of emetogenic chemotherapy, and by gender and age, as past literature highlights these are important in assessing the effectiveness of treatments for chemotherapy-related nausea and vomiting. Minimally emetogenic chemotherapy will not be included, as clinical guidelines recommend no antiemetic treatment and the nausea/vomiting level is $< 10\%$.

In the acupressure group, in addition to standard antiemetics, patients will be provided with a pair of SeaBand wristbands (Sea-Band Ltd, Leicestershire, UK). These bands are elastic wristbands with a 1 cm protruding round plastic button (stud). These are available in two sizes, a standard one and a larger one. Patients wear the wristband with the stud pressing the P6 acu-point, which is located on the anterior surface of the forearm, approximately three-finger width up from the crease of the wrist between the tendons of the Palmaris longus and flexor carpi radialis. Patients will be provided with a pair of acupressure wristbands and they will be instructed to wear them on both arms and take them off only when showering/bathing. An instruction sheet with a picture of point P6 and how to locate the point will also be provided to patients. Patients will be instructed to wear the wristbands from the morning before chemotherapy administration and for the subsequent 6 days (total = 7 days). No other complementary therapies use will be recommended during the course of acupressure (although any such use will be documented).

In the sham acupressure group, in addition to standard antiemetics, patients will be provided with a pair of the identical appearing wristbands, with the only difference being that the sham wristband will have a flat button (made from felt) in place of the protruding stud, thus exerting no pressure on the P6 point. There is an ongoing scientific debate on what constitutes an appropriate sham treatment, and it is acknowledged that there is no sham method in acupuncture and acupressure studies that can be widely accepted as the optimal method. It is now increasingly believed that sham acupuncture/acupressure designs cannot detect the whole placebo effect and may generate false negative results (Paterson & Dieppe, 2005; Kaptchuk *et al*, 1996; Mason *et al*, 2002; White *et al*, 2001), depending on the method

used. We have debated the appropriateness of other sham methods, but either they were not blinded enough for the purposes of the trial (ie. had to be slightly dissimilar to real acupressure wristbands) or could be perceived as treatments themselves (ie. acupressure at other points in the forearm or elsewhere where we have no information as to an effect on the experience of nausea). Patients in the clinics could also talk to each other and realize they have different interventions or check the P6 point on the internet. Hence, we resolve to use an acupressure technique which appears to be exactly the same as the active treatment with the only exception being the type of stud used. This was also agreed by practitioners too, who have been consulted about their views on the most appropriate sham method. Furthermore, while it is acknowledged that many patients may have heard of the use of such wristbands, the results of our pilot study suggest that their understanding of how acupressure works is limited (Molassiotis *et al*, 2007a). In addition, the results of our qualitative study on self-management of CINV suggest that acupressure is not commonly used by patients (Molassiotis *et al*, 2008a). An assessment of patient blinding at the end of the trial will also be incorporated in this trial.

The control group will receive standard antiemetics alone. Standard antiemetics for all three groups will be based on ASCO and MASCC international antiemetic guidelines with the exception of NK1 receptor antagonists (ie. aprepitant) recommended in highly emetic chemotherapy, which is not available currently in the NHS. Hence, for highly emetic chemotherapy, patients should receive a 5-HT3 receptor antagonist (ie. Zofran 8 mg) and dexamethasone 8 mg intravenously before chemotherapy and the same orally for 3 days post chemotherapy; for moderately emetogenic chemotherapy a 5-HT3 receptor antagonist (Zofran 8 mg) and dexamethasone 8 mg intravenously before chemotherapy and a 5-HT3 receptor antagonist or dexamethasone (preferred) for 2 days post-chemotherapy; and for low emetogenic chemotherapy dexamethasone 8 mg before chemotherapy and no other treatment post chemotherapy (Kris *et al*, 2006; Roila *et al*, 2006). All patients will receive rescue antiemetics if nausea and/or vomiting is persistent and fail to respond to the antiemetic treatment (ie. severe nausea or >5 vomiting episodes), based on the experience of each clinician (as agreed guidelines for rescue antiemetics have not been developed to date).

During the course of the trial, three focus group interviews will be organised with 6–8 patients in each of these groups who have received active acupressure. An attempt will be made to also include patients who have dropped out from the trial. This will be an exploratory nested qualitative study within the trial to explore the patients' experience of receiving acupressure, how they found the use of acupressure, whether the wristbands impacted/restricted the patients daily living, if they would recommend the use of wristbands to others, and whether there were any perceived effects or benefits beyond the CINV. It will also attempt to tease out from subjects reasons for non-compliance (if any) and difficulties the patients experienced wearing these bands. Data will be recorded and transcribed verbatim, at which point it will be analysed using standard content analysis methods.

Planned inclusion/exclusion criteria

Inclusion criteria:

- Patients scheduled to receive their first chemotherapy cycle.
- Patients scheduled to receive highly, moderately and low emetogenic chemotherapy (as per ASCO and MASCC classifications).
- Patients scheduled to receive a chemotherapy regime as a single or multiple administration repeated every 2-week, 3-week or 4-week cycles.
- Patients who are acupressure wristband-naïve (in terms of never having tried for themselves such a wristband, although they may have seen or heard about such wristbands).
- Patients of either gender and older than 16 years old.
- Patients with any cancer diagnosis receiving chemotherapy without concurrent use of radiotherapy.
- Patients receiving chemotherapy as outpatients or inpatients.
- Patients willing to participate in the study and be randomised into one of the three study groups.

Exclusion criteria:

- Patients scheduled to receive radiotherapy concurrently with chemotherapy and during the assessment period of four cycles for each patient.
- Patients unable to self care (ie. unable to use wristbands appropriately; mental incapacity preventing continuous and optimal use of wristbands) as judged by the investigators.
- Patients with liver disease (as nausea is common presenting symptom).
- Patients with metabolic risk factors for nausea (ie. electrolyte imbalances causing nausea/vomiting).
- Patients with mechanical risk factors for nausea (ie. intestinal obstruction).
- Patients experiencing nausea and/or vomiting due to use of opioids.
- Patients with lymphoedematous arms.
- Patients with chronic alcohol use (as it is associated with minimal levels of nausea and/or vomiting).

Proposed sample size

In our pilot study (Molassiotis *et al*, 2007a), the mean score for nausea experience averaged over 5 days was 2.79 (weighted average SD 3.15) in the control group and 1.45 (weighted average SD 2.76) in the intervention group. At least 135 participants per arm would be required to detect this pair wise difference between arms using a *t*-test with a conservative Bonferroni-adjusted significance level of $0.05/3 = 0.017$ at a power of 90%. The pilot study suggested an attrition rate of 33%, so initially, at least 202 participants would be required per arm. As the standard deviations (SDs) are much larger than the means in the pilot data, they are suggestive of highly skewed distributions; hence the equivalent nonparametric test (the Mann–Whitney test) will be used. As the asymptotic relative efficiency of the Mann–Whitney test is at worst 0.864, the sample size for a Mann–Whitney test is, in the worst case, equal to the sample size for the *t*-test divided by 0.864. This would increase the required sample size to 156 per arm before attrition, 233 after attrition, totaling 699 across the three arms.

Recruitment will take place in the largest single-site cancer centre in the UK, and cancer units or centres of district general hospitals and university hospitals, including the Christie Hospital NHS Trust and its peripheral clinics where chemotherapy is administered (Oldham Hospital & Tameside Hospital), Hope Hospital in Salford and Trafford General Hospital, the Liverpool Royal Infirmary and three cancer units associated with the University of Plymouth (South Devon Healthcare NHS Foundation Trust, Plymouth Hospitals NHS Trust, Royal Cornwall Hospitals NHS Trust). Available statistics from the Christie Hospital NHS Trust alone show that around 9,000 patients receive chemotherapy every year, with approximately two-thirds of these patients receiving chemotherapy in 3-weeks cycles. Recruitment rates are based on a similar antiemetic study we have conducted over four cycles of chemotherapy (Molassiotis *et al*, under review), where it has taken us 6 months to recruit 102 patients and retain 65% over the four cycles of chemotherapy. Based on similar recruitment levels at each of the 9 sites listed above, we estimate that recruitment will be completed in 16 months, with a further 3 months required to complete the follow up of the final patients.

Statistical analysis

Appropriate descriptive statistics will be estimated for all baseline socio-demographic and clinical variables by arm, and for outcome variables (scores on nausea and vomiting subscales) by arm. The association between baseline socio-demographic or clinical variables and outcome variables will be assessed using appropriate between-group tests or correlations depending on skewness. Primary outcome variables will be compared between the arms using *t*-tests, one-way analysis of variance, Mann–Whitney tests and Kruskal–Wallis tests, bearing in mind any skewness in the data. Mixed models (repeated measures analysis of variance with between-group factors and anxiety as covariate) will be used to compare outcome variables measured at repeated time points between the arms. An intention-to-treat analysis model will

be followed. As the primary outcome variable will be assessed over several days repeatedly, an aggregate score of all assessments in each cycle will be calculated before any modeling analysis.

The effect of missing values will be assessed by comparing the numbers and percentages of participants with missing values in the three arms of the study; differences in baseline variables between participants with observed and missing outcomes in each arm; and for participants with observed outcomes, differences in baseline variables between the three arms. Logistic regression models will be used to assess potential factors affecting drop-out.

For the interview part of the trial, data will be tape-recorded and transcribed verbatim, at which point it will be analysed using content analysis methods. This will include identifying key themes and developing categories using the interview questions as the framework of analysis.

Proposed outcome measures

Primary outcome:

#Rhodes Index of Nausea & Vomiting (Rhodes & McDaniel, 1999). This is a 12-item validated scale measuring nausea and vomiting experience, incidence and severity. This 12-item scale, taking 2–3 min to complete, will be done daily from the day before chemotherapy (to capture any anticipatory nausea) up to seven days post chemotherapy (= 8 assessments/cycle).

Secondary outcomes:

#MASCC Antiemesis Tool (MAT) designed by the Multinational Association of Supportive Care in Cancer (MASCC) (Molassiotis *et al*, 2007b). This 8-item scale assesses in a simple way both acute and delayed nausea and vomiting incidence and extent and was designed specifically for chemotherapy-related nausea and vomiting. This short clinical scale has shown satisfactory internal reliability ($\alpha = 0.77$), contrasted-groups and concurrent validity, and high recall of events up to 3 weeks post chemotherapy. The MAT is designed to be used once-per-cycle with retrospective patient recall of events, minimising the patient burden. Factor analysis has clearly identified three factors, namely vomiting, acute nausea and delayed nausea (Molassiotis *et al*, 2007b). The scale will be completed at day 10 of each cycle (= 4 assessments).

#FACT-G. This is a well-validated quality-of-life scale focusing on functional assessment (Fairclough & Cella, 1996). This functional scale will not only provide quality-of life-indications, but also changes in other symptoms/side effects that may have resulted from any improved management of nausea (ie. appetite). High internal consistency and construct validity have been reported in past studies using the FACT scales in various cancer populations. Completion time is about 5 min. This scale will be completed at baseline and then at day 10 of each cycle (= 5 assessments).

#Hospital Anxiety & Depression Scale (Zigmond & Snaith, 1983). This is a 14-item scale assessing anxiety with 7 items and depression with a further 7 items. Each item is answered on a 4-point scale (0–3). Scores on each sub-scale thus range between 0 (no symptoms) and 21 (numerous and severe symptoms). In this study, data will be obtained at baseline, the score of which will be used as a covariate in the final statistical analysis of the data, as anxiety and depression are key risk factors for the development of nausea/vomiting (Molassiotis et al, 2002b; Andrykowski et al, 1992). This scale has been used extensively with cancer patients as a screening tool and has been reported to have excellent psychometric properties. Completion time is approximately 2–5 min.

#Patient Expectations of Nausea/Vomiting. As this is a key risk factor identified in the literature (Molassiotis et al, 2002b; Andrykowski et al, 1992), as 2-item scale will be developed assessing the patient expectation for nausea and vomiting, measured on a 10-point ordinal scale. This will be incorporated in the final analysis of outcomes. Patients will also be asked how much they believe this method will help them alleviate nausea and how much faith they have in complementary therapies using 10-point scales. At the

end of each cycle, all patients will be asked to rate their overall tolerance of the chemotherapy on a 4-point scale, from 'very well' to 'very poorly' and record the reason for their choice.

#Measure of blindness of study. Patients in the intervention and sham arms of the study will be asked at the end of the study in which group they think they were allocated.

#Sociodemographic and treatment characteristics will be obtained from the patients' records and the patients themselves. These will include gender, age, educational level, marital status, experience with nausea in the past such as during pregnancy, motion sickness or nausea when eating certain foods, use of/experience with other complementary therapies to manage nausea in the past, cancer diagnosis, stage of disease, and chemotherapy protocol used and dosage. Such a questionnaire is already developed by the team and used in the past in other nausea/vomiting studies. Medication use (standard and rescue antiemetics) during study participation will also be obtained from the pharmacy records.

Drop out cases will be asked to complete the Rhodes nausea experience 4-item subscale and failing this to answer a single item from the FACT scale about their nausea level. Scales will be given to patients to complete at home and return them back to researchers using a pre-paid envelope. Patients will be asked to complete their daily assessments of nausea at the same time in the evening to have a consistent time frame for measuring change. Patients who do not send back the completed scales within 2–3 days from the time they are suppose to return them will receive a reminder letter.

Measurement of costs

Costs will be identified, measured and valued using a micro-costing approach (by which each component of resource use is identified, estimated and a unit cost derived from market prices and national estimates (Curtis and Netten, 2006). The cost analysis will be performed from the perspective of the health service provider *and* from a societal perspective. Included in the health care provider costs will be those accrued by the acute trusts and PCTs. Costs to the patients and their families, including social care, will be considered as the additional costs for society. Indirect costs in terms of workdays lost will also be included.

Data will be collected prospectively and retrospectively using multiple sources including patient records and patient self reported questionnaires. The questionnaires will report health service utilisation subsequent to and as a result of chemotherapy induced nausea/vomiting (e.g. GP visits), patient out of pocket expenses such as over the counter medicines or transport together with use of services in the social sector such as home help and support from family and friends. Valuation of resource items including hospital resources (e.g. bed days and staff time) and community resources (e.g. GP visits, home help) use will be carried out using national estimates (Curtis and Netten, 2006); market prices will be assigned to medication; non-market items, specifically patient time and informal help provided by family and friends, will be valued using market wage rates; out of pocket expenses (e.g. bus fares) will use financial expenditures.

In more detail, *direct medical* costs will be defined as those of prophylactic or rescue antiemetic medications, drug administration devices, staff time associated with preparing and administering medication and tending to patients with CINV, hospitalizations due to CINV, hospital outpatient or GP visits due to CINV and costs for over-the-counter medications or other complementary therapies. *Direct non-medical* costs will be those for transportation and need for assistance, such as additional childcare. *Indirect* costs will be based exclusively on the number of workdays lost due to CINV. Costs that will not be included in this evaluation will be costs for chemotherapy agents, preplanned visits or hospitalizations for the purpose of chemotherapy administration, diagnostic and laboratory tests, and other patient management costs not directly related to CINV.

Analysis of Economic Data: The total cost of each arm of the trial will be calculated by combining the resource use and unit cost data. No discounting is necessary given the time period of data collection (less

than 1 year); sensitivity analysis will be carried out to account for uncertainty where estimates in cost data are used. Differences in costs between the three arms will be tested for using independent sample *t*-tests. Cost data in each of the arms will be analysed alongside the quality-of-life measures with the data combined and analysed using cost effectiveness ratios (i.e. the difference in costs between alternatives relative to the difference in effectiveness between the same alternatives). Cost per quality adjusted life year (QALY) will be presented.

Table of assessments:

	Baseline assessment	Chemo days –1,0,1,2,3,4,5,6×4 cycles	Chemo day 10×4 cycles	End of study participation
Rhodes Index of NV		✗		
MAT			✗	
FACT-G	✗		✗	
HADS	✗		✗	
Patient Expectations Qr	✗			
Sociodemographic variables	✗			
Blindness assessment				✗
Disease/treatment variables	✗			✗
Health economics assessment	✗	✗	✗	✗

Service user involvement

Service users will be involved at 3 levels. The first has been at the development phase of this proposal, with the contribution of the Chair of the NCRI Consumer Liaison group, who is a named co-applicant in the study, and reviews by expert patients. The second level will be monitoring the trial project and guiding it within its scientific framework through chairing and participating in the trial's Steering committee and the DMEC. Finally, users will advise us in planning appropriate patient-focused dissemination of the trial results at the end of the study. For reviews, contacts, active involvement and access, the research partners' strategy and mechanisms through the NCRI Cancer Experiences Collaborative will be utilised.

References

1. Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. *Supportive Care in Cancer* 2005, **13**:117–121.
2. Andrykowski, M. A.and M. E. Gregg (1992). The Role of Psychological variables in Post-Chemotherapy Nausea: Anxiety and Expectation. *Psychosomatic Medicine*. **54**:48–58.
3. ASHP. Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *American Journal of Health Systems & Pharmacy* 1999, **56**:729–764.
4. Bergkvist K, Wengstrom Y. Symptom experiences during chemotherapy treatment – with focus on nausea and vomiting. *European Journal of Oncology Nursing*. 2006, **10**:21–29.

5. Burish, T. G., D. M. Tope (1992). Psychological Techniques for Controlling the Adverse Side Effects of Cancer Chemotherapy: Findings from a Decade of Research. *Journal of Pain and Symptom Management*. **7**:287–301.

6. Curtis, L. & Netten, A. 2006. *Unit Costs of Health and Social Care 2006*. PSSRU: Canterbury.

7. Dibble SL, Chapman J, Mack KA, Shih AS. Acupressure for nausea: results of a pilot study. *Oncology Nursing Forum* 2000; **27**(1):41–47.

8. du Bois, A. *et al.* (1992). Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: a study with ondansetron. *European Journal of Cancer*. **28**(2–3):450–457.

9. Dundee JW, Yang J, McMillan C. Non-invasive stimulation of the P6 (Neiguan) antiemetic acupuncture point in cancer chemotherapy. *Journal of the Royal Society of Medicine* 1991; **84**(4):210–212.

10. Dundee JW, Yang J. Prolongation of the antiemetic action of P6 acupuncture by acupressure in patients having cancer chemotherapy. *Journal of the Royal Society of Medicine* 1990; **83**(6):360–362.

11. Dundee JW, Ghaly RG, Fitzpatrick KT, Abram WP, Lynch GA. Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *Journal of the Royal Society of Medicine* 1989; **82**(5):268–271.

12. Dundee JW, Ghaly RG, Fitzpatrick KT, Lynch GA, Abram WP. Acupuncture to prevent cisplatin-associated vomiting. *Lancet*. 1987; **1**(8541):1083.

13. Ezzo JM, Richardson MA, Vickers A, *et al.* Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database of Systematic Reviews*, 2006.

14. Fairclough, DL & Cella DF. (1996) Functional Assessment of Cancer Therapy (FACT-G): Non-response to individual questions. *Quality of Life Research*, **5**:321–329.

15. Foubert J, Vaessen G. Nausea: the neglected symptom? *European Journal of Oncology Nursing* 2005, **9**:21–32.

16. Glaus A, Knipping C, Morant R, Böhme C, Lebert B, Glawogger B, Fernandez Ortega P, Hüsler A, Deuson R. Chemotherapy-induced nausea and vomiting in routine practice: a European perspective. *Supportive Care in Cancer* 2004, **12**:708–715.

17. Griffin AM, Butow PN, Coates AS, *et al.* On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. *Annals of Oncology* 1996, **7**:189–195.

18. Grunberg SM. Chemotherapy-induced nausea and vomiting: prevention, detection, and treatment – how are we doing? *Journal of Supportive Oncology* 2004, **2**(Suppl 1):1–10.

19. Ihbe-Heffinger A, Ehlken B, Bernard R, *et al.* The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. *Annals of Oncology*. 2004, **15**:526–536.

20. Kaptchuk TJ. Uptake of alternative medicine. *Lancet* 1996; **347**(9006):972.

21. Mason S, Tovey P, Long AF. Evaluating complementary medicine: methodological challenges of randomised controlled trials. *British Medical Journal* 2002; **325**(7368):832–834.

22. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, *et al.* American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *Journal of Clinical Oncology* 2006, **24**:2932–2947.

23. Liau CT, Chu NM, Liu HE, Deuson R, Chen JS. Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians' and nurses' estimation vs. patients' reported outcomes. *Supportive Care in Cancer* 2005, **13**:277–286.

24. Maranzano E, Feyer PCh, Molassiotis A, *et al.* Evidence-based recommendations for the use of antiemetics in radiotherapy. *Radiotherapy & Oncology*. 2005; **76**(3):227–233.

25. Miller M, Kearney N. Chemotherapy-related nausea and vomiting-past reflections, present practice and future management. *European Journal of Cancer Care* 2004, **13**:71–81.

26. Molassiotis A. Managing nausea and vomiting after cancer treatments: patients still suffer unnecessarily. *European Journal of Oncology Nursing* 2005, **9**:4–5.

27. Molassiotis A, Stricker CT, Eaby B, Velders L, Coventry PA. Understanding the concept of chemotherapy-related nausea: the patient experience. *European Journal of Cancer Care* 2008a, **17**:444–453.

28. Molassiotis A, Sylt P, Diggins H. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomized controlled trial. *Complementary Therapies in Medicine* 2007c, **15**:3–12.

29. Molassiotis A, Clements C, Rittenberg C, *et al.* A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. *Supportive Care in Cancer* 2008b, **16**:201–208.

30. Molassiotis A, Helin AM, Dabbour R, Hummerston S. The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients. *Complementary Therapies in Medicine* 2007a, **15**:3–12.

31. Molassiotis A, Coventry PA, Stricker CT, Clements C, Eaby B, Velders L, Rittenberg C, Gralla RJ. Validation and psychometric properties of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC Antiemesis Tool (MAT). *Journal of Pain & Symptom Management* 2007b, **34**:148–159.

32. Molassiotis A, Yung HP, Yam BMC, Chan FYS, Mok TSK. The effectiveness of progressive muscle relaxation training in managing chemotherapy-induced nausea and vomiting in Chinese breast cancer patients: a randomized controlled trial. *Supportive Care in Cancer* 2002a, **10**:237–246.

33. Molassiotis, A. *et al.* Pretreatment factors predicting the development of postchemotherapy nausea and vomiting in Chinese breast cancer patients. *Supportive Care in Cancer* 2002b, **10**:139–145.

34. Morrow, G. R. *et al.* Predicting development of anticipatory nausea in cancer patients: prospective examination of eight clinical characteristics. *Journal of Pain & Symptom Management* 1991, **6**:215–223.

35. Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *British Medical Journal* 2005; **330**(7501):1202–1205.

36. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. *Cancer Nursing* **22**:307–311, 1999.

37. Rhodes, V. A. and R. W. McDaniel. The Index of Nausea, Vomiting, and Retching: a new format of the Index of Nausea and Vomiting. *Oncology Nursing Forum* 1999, **26**:889–894.

38. Roila F, Hesketh PJ, Herrstedt J; & Antiemetic Subcommitte of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Annals of Oncology* 2006; **17**(1):20–28. [PI part of the working group for these guidelines].

39. Roscoe JA, Morrow GR, Hickok JT, *et al.* Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in the community. *Journal of Pain & Symptom Management* 2000, **20**:113–121.

40. Roscoe, J. A., *et al.* Acustimulation Wristbands For The Relief Of Chemotherapy-Induced Nausea. *Alternative Therapies in Health & Medicine* 2002, **8**:56–63.

41. Roscoe JA, Morrow GR, Hickok JT, *et al.* The efficacy of acupressure and acustimulation wrist bands for the relief of chemotherapy-induced nausea and vomiting. A University of Rochester Cancer Center Community Clinical Oncology Program multicenter study. *Journal of Pain & Symptom Management* 2003; **26**(2):731–242.

42. Roscoe JA, Matteson SE, Morrow GR, *et al.* Acustimulation wrist bands are not effective for the control of chemotherapy-induced nausea in women with breast cancer. *Journal of Pain & Symptom Management* 2005; **29**(4):376–384.

43. Shin YH, Kim TI, Shin MS, Juon HS. Effect of acupressure on nausea and vomiting during chemotherapy cycle for Korean postoperative stomach cancer patients. *Cancer Nursing* 2004, **27**:267–274.

44. Treish I, Shord S, Valgus J. Randomised double-blind study of the Reliefband as an adjunct to standard antiemetics in patients receiving moderately-high to highly emetogenic chemotherapy. *Supportive Care in Cancer* 2003, **11**:516–521.

45. White AR, Filshie J, Cummings TM. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complementary Therapies in Medicine* 2001, **9**(4):237–45.

46. Wright LD. The use of motion sickness bands to control nausea and vomiting in a group of hospice patients. *American Journal of Hospice and Palliative Care* 2005, **22**:49–53.

47. Zigmond AS, Snaith RP.The hospital anxiety and depression scale. *Acta Psychiatra Scandinavica* 1983 Jun;**67**(6):361–70.