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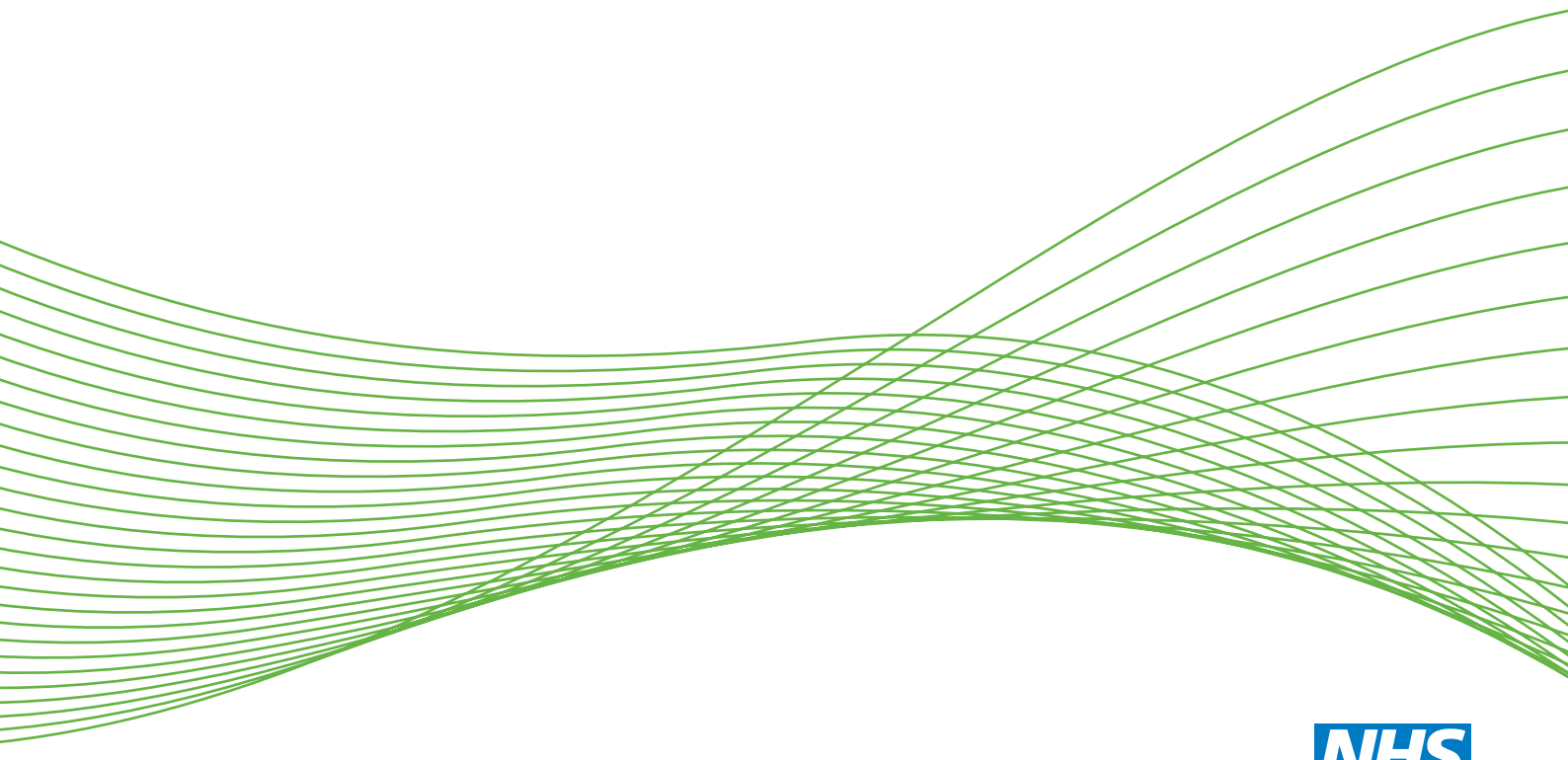

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Abstract

The effectiveness and cost-effectiveness of acupressure for the control and management of chemotherapy-related acute and delayed nausea: Assessment of Nausea in Chemotherapy Research (ANCHoR), a randomised controlled trial

A Molassiotis,[1,2]* W Russell,[1] J Hughes,[3] M Breckons,[4] M Lloyd-Williams,[3] J Richardson,[4] C Hulme,[5] S Brearley,[6] M Campbell,[1] A Garrow[7] and WD Ryder[8]

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Background: Chemotherapy-induced nausea and vomiting remain difficult symptoms to manage in clinical practice. As standard antiemetic drugs do not fully eliminate these symptoms, it is important to explore the adjuvant role of non-pharmacological and complementary therapies in antiemetic management approaches. Acupressure is one such treatment showing highly suggestive evidence so far of a positive effect, meriting further investigation.

Objectives: The primary objective was to assess the effectiveness and cost-effectiveness of self-acupressure using wristbands compared with sham acupressure wristbands and standard care alone in the management of chemotherapy-induced nausea. Secondary objectives included assessment of the effectiveness and cost-effectiveness of the wristbands in relation to vomiting and quality of life and exploration of any age, gender and emetogenic risk effects.

Design: Randomised three-arm sham-controlled trial (Assessment of Nausea in Chemotherapy Research or ANCHoR) with an economic evaluation. Arms include the wristband arm, the sham wristband arm and the standard care only arm. Randomisation consisted of minimisation with a random element balancing for gender, age (16–24, >24–50, >50 years) and three levels of emetogenic chemotherapy (low, moderate and high). Qualitative interviews were incorporated to shed more light on the quantitative findings.

Setting: Outpatient chemotherapy clinics in three regions in the UK involving 14 different cancer units/centres.

Participants: Chemotherapy-naive cancer patients receiving chemotherapy of low, moderate and high emetogenic risk.

Intervention: The intervention was acupressure wristbands pressing the P6 point (anterior surface of the forearm).

Main outcome measures: The Rhodes Index for Nausea/Vomiting, the Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool and the Functional Assessment of Cancer Therapy – General (FACT-G). At baseline participants completed measures of anxiety/depression, nausea/vomiting expectation and expectations from using the wristbands.

Results: In total, 500 patients were randomised in the study arms (166 standard care, 166 sham acupressure and 168 acupressure) and data were available for 361 participants for the primary outcome. The primary outcome analysis (nausea in cycle 1) revealed no statistically significant differences between the three arms, although the median nausea experience in patients using wristbands (both real and sham ones) was somewhat lower than that in the antiemetics only group (median nausea experience scores for the four cycles: standard care arm 1.43, 1.71, 1.14, 1.14; sham acupressure arm 0.57, 0.71, 0.71, 0.43; acupressure arm 1.00, 0.93, 0.43, 0). A gender effect was evident ($p = 0.002$), with women responding more favourably to the use of sham acupressure wristbands than men (odds ratio 0.35 for men and 2.02 for women in the sham acupressure group; 1.27 for men and 1.17 for women in the acupressure group). This suggests a placebo effect. No significant differences were detected in relation to vomiting outcomes, anxiety and quality of life. Some transient adverse effects were reported, including tightness in the area of the wristbands, feeling uncomfortable when wearing them and minor swelling in the wristband area ($n = 6$).There were no statistically significant cost differences associated with the use of real acupressure bands (£70.66 for the acupressure group, £111.13 for the standard care group and £161.92 for the sham acupressure group). In total, 26 subjects took part in qualitative interviews. The qualitative data suggested that participants perceived the wristbands (both real and sham) as effective and helpful in managing their nausea during chemotherapy.

Conclusions: There were no statistically significant differences between the three arms in terms of nausea, vomiting and quality of life, although apparent resource use was less in both the real acupressure arm and the sham acupressure arm compared with standard care only; therefore; no clear conclusions can be drawn about the use of acupressure wristbands in the management of chemotherapy-related nausea and vomiting. However, the study provided encouraging evidence in relation to an improved nausea experience and some indications of possible cost savings to warrant further consideration of acupressure both in practice and in further clinical trials.

Trial registration: ISRCTN87604299.

Source of funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 17, No. 26. See the HTA programme website for further project information.

Contents

List of abbreviations

ANCHoR	Assessment of Nausea in Chemotherapy Research
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
BNF	*British National Formulary*
CI	confidence interval
CL	cumulative logit
DMEC	Data Monitoring and Ethics Committee
eMIT	electronic Market Information Tool
EQ-5D	European Quality of Life-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy – General
GEE	generalised estimating equation
5-HT_3	5-hydroxytryptamine type 3
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
LOCF	last observation carried forward
MASCC	Multinational Association of Supportive Care in Cancer
MAT	Multinational Association of Supportive Care in Cancer Antiemesis Tool
MHRA	Medicines and Healthcare products Regulatory Agency
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Clinical Excellence
NMB	net monetary benefit
OR	odds ratio
QALY	quality-adjusted life-year
SD	standard deviation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Scientific summary

Background

Although chemotherapy-related vomiting is relatively well controlled with current antiemetics, nausea remains a significant problem for patients and a difficult symptom for clinicians to manage. The role of complementary therapies, and particularly acupressure at the P6 (Neiguan) point, as adjunctive treatments to pharmacological antiemetics has been investigated in a number of studies in the past. Both positive and negative results have been reported in the literature, providing highly suggestive but not conclusive evidence. Many past studies, however, are hampered by methodological problems, including small sample sizes, minimal control of risk factors for chemotherapy-related nausea and vomiting and no control of the antiemetic drugs used. Hence, there is a need to clarify whether or not acupressure is effective and cost-effective in the management of chemotherapy-related nausea and vomiting using a robust methodological design with a well-powered sample size.

Objectives

Primary objective

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

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 compared with that in patients undergoing standard care with sham acupressure wristbands and standard care alone for the management of chemotherapy-induced nausea.
3. To assess the quality of life of patients using acupressure wristbands in addition to standard care compared with that of patients receiving standard care with sham acupressure wristbands and standard care alone in the management of chemotherapy-induced nausea and vomiting.
4. To assess the clinical effectiveness of self-acupressure using wristbands in addition to standard care compared with that of standard care with sham acupressure wristbands and standard care alone in the management of chemotherapy-induced (acute and delayed) vomiting.
5. To ascertain for which emetogenic level of chemotherapy regimen (i.e. high, moderate or low) self-acupressure using wristbands in addition to standard care is more or less effective in terms of nausea compared with standard care with sham acupressure wristbands and standard care alone.
6. To ascertain whether or not any improvement in chemotherapy-induced nausea and vomiting from using acupressure wristbands is different between men and women.
7. To ascertain whether or not there is an age effect from the use of acupressure wristbands in relation to chemotherapy-induced nausea and vomiting.

Methods

A randomised three-group sham-controlled trial (Assessment of Nausea in Chemotherapy Research or ANCHoR) was designed to test the effects of acupressure in the management of chemotherapy-related nausea and vomiting. Patients with heterogeneous cancer diagnoses receiving chemotherapy of low, moderate and high emetogenic potential were randomised to receive acupressure wristbands in addition to standardised antiemetics, sham acupressure wristbands in addition to standardised antiemetics or

antiemetics alone. The randomisation method used consisted of minimisation with a random element (stochastic minimisation), balancing for gender, age (16–24, > 24–50, > 50 years) and three levels of emetogenic chemotherapy [low, moderate and high according to international American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC) classifications]. Patients were instructed to wear the wristbands throughout the day for the first 7 days during each cycle of chemotherapy. The primary outcome assessment using the Rhodes Index of Nausea, Vomiting and Retching was carried out daily for 7 days per chemotherapy cycle over four cycles. Other assessments, completed at day 6 of each of the four cycles, included the MASCC Antiemesis Tool, the European Quality of Life-5 Dimensions (EQ-5D) utility scale and the Functional Assessment of Cancer Therapy – General (FACT-G) quality-of-life scale. At baseline participants completed measures of anxiety and depression, nausea/vomiting expectation and expectations from using the acupressure wristbands. An economic evaluation was also carried out based on drug and health service utilisation from the perspective of the health and social care provider and presenting incremental cost-effectiveness ratios with quality-adjusted life-years as the outcome. Finally, a nested qualitative interview study was incorporated to shed more light on the quantitative findings.

Results

In total, 500 patients were randomised in the study arms (166 standard care, 166 sham acupressure and 168 acupressure) and data were available for 361 participants for the primary outcome. The primary outcome analysis (nausea in cycle 1) revealed no statistically significant differences between the three groups, although nausea level in the patients using wristbands (both real and sham) was somewhat lower than that in the antiemetics only group (median nausea experience scores for the four cycles: standard care arm 1.43, 1.71, 1.14, 1.14; sham acupressure arm 0.57, 0.71, 0.71, 0.43; acupressure arm 1.00, 0.93, 0.43, 0). Adjusting for gender, age and emetic risk of the chemotherapy, the odds ratio (OR) of a lower nausea experience was 1.18 for the acupressure group and 1.42 for the sham acupressure group. A gender interaction effect was evident in the data ($p = 0.002$), with women responding more favourably to the use of sham acupressure wristbands than men (OR 0.35 for men and 2.02 for women in the sham group; 1.27 for men and 1.17 for women in the real acupressure group). This suggests a placebo effect. No significant differences were detected in relation to vomiting outcomes, anxiety and quality of life. The cost-effectiveness evaluation revealed no significant differences (*t*-tests) between the costs of each arm. Total costs (all drug and NHS costs) were £70.66 for the acupressure group, £111.13 for the standard care group and £161.92 for the sham acupressure group. However, caution is needed in interpreting these results because of very small changes in utility and the influence of a few high-cost outliers. A total of 26 subjects from all three groups took part in in-depth qualitative interviews. Four themes emerged from the data: 'Deciding to participate', 'Perceptions and experiences of complementary therapies', 'Experience of taking part in the trial' and 'Experience of using the wristbands'. The qualitative data overall suggested that the participants perceived the wristbands (both real and sham) as effective and helpful in managing their nausea experience during chemotherapy. Minor and transient side effects from the use of the wristbands were observed.

Conclusions

No clear conclusions can be made about the use of acupressure wristbands in the management of chemotherapy-related nausea and vomiting as the results did not reach statistical significance. However, the differences observed may be of clinical importance for patients and may potentially lead to lower health-care utilisation. The use of wristbands was safe and perceived to be effective by patients. Before rejecting this intervention we need to consider the therapeutic effect of placebos in situations such as the management of nausea, when low-cost and safe interventions may enhance the effect of antiemetic drugs even in the absence of clearly statistically significant effects. The study provided encouraging evidence in relation to an improved nausea experience as well as a suggestion of potential health resource-use

benefits; further consideration of the use of acupressure wristbands both in practice and in further clinical trials is therefore warranted.

Trial registration

This study is registered as ISRCTN87604299.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Literature review

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.[1] Surprisingly, despite improvements in the management of vomiting, postchemotherapy nausea seems to have increased.[2] Furthermore, clinicians often underestimate the experience of nausea, especially with regards to delayed nausea.[3,4]

Chemotherapy-induced nausea and vomiting can have a profound effect on the cancer treatment experience[5] and is associated with negative effects on daily life and overall quality of life, including in relation to food intake, weight loss, social interactions, dehydration, difficulty with sleeping and anxiety.[5,6] 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.[5] The impact of nausea is greater than that of vomiting,[7] 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.[8] Antiemetic trials have traditionally focused primarily on vomiting and emetic episodes, on 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.[9,10] The need for these two symptoms to be treated as two separate entities is strongly advocated.[10]

The reasons behind this incomplete management of chemotherapy-induced nausea and vomiting are multifaceted. They include health professionals' limited understanding of the complex concept of chemotherapy-induced nausea and vomiting and its different phases; limited assessment in clinical practice of chemotherapy-induced nausea and vomiting and its risk factors; using more emetogenic chemotherapy protocols than in the past; not understanding clearly all the pathways involved in the development of chemotherapy-induced nausea and vomiting; and more focus given to the vomiting experience than nausea in clinical trials.[11]

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.[12] Acupuncture and its non-invasive form of acupressure have been tested several times after the classic early work of Dundee *et al.*[13,14] In a literature search of MEDLINE, PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) using the key words 'acupressure', 'nausea', 'vomiting', 'emesis', 'chemotherapy', 'cancer' and combinations, between 1990 and May 2005, we have identified 10 studies specific to oncology, reported elsewhere,[15] with 7 out of 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 transcutaneous electrical nerve stimulation (TENS) device designed to stimulate the P6 acupoint];[16–18] an acupressure wristband (a small elastic band with a round plastic button applying constant mild pressure on the P6 acupoint);[19–21] and direct pressure on the P6 acupoint[22] or P6 and ST36 acupoints together.[23] 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 and a similar trend in women to reduce acute symptoms only, although the latter did not reach statistical significance.[24] No improvement in nausea/vomiting was shown in a small study by Roscoe *et al.*[25] in women with breast cancer using acustimulation (ReliefBand) wristbands. These 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[26] of the literature highlights that acupressure reduces acute nausea but not delayed nausea, and has no benefit for vomiting. 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 chemotherapy-induced nausea and vomiting including progressive muscle relaxation training and imagery techniques;[27] pilot testing of acupressure;[15] identification of risk factors for chemotherapy-induced nausea and vomiting development such as age, gender and anxiety;[28,29] the management of anticipatory nausea and vomiting;[30,31] the development of international clinical guidelines for managing chemotherapy-induced nausea and vomiting[32,33] and radiation-induced nausea and vomiting;[34,35] exploration and further clarification of the concept of chemotherapy-induced nausea as a separate entity from vomiting;[36] assessment of chemotherapy-induced nausea and vomiting levels in current clinical practice in the UK;[37,38] and development of a chemotherapy-induced nausea and vomiting-relevant clinical scale for the assessment of acute and delayed symptoms.[39] This last is the only chemotherapy-specific scale available to date. In our qualitative study of the experience of chemotherapy-related nausea in 17 patients with cancer in the UK and USA,[36] nausea was described as a distressing and complex symptom. 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. Although self-management was common in almost all patients, acupressure was not one of the approaches used. In an observational prospective evaluation using patient self-reports, 102 patients with cancer receiving their first chemotherapy treatment participated.[37] Participants were followed up for four 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%, whereas 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 chemotherapy-induced nausea and vomiting, and acute symptoms were more controlled than delayed symptoms. The data suggested that, although 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 four cycles.[37]

Chapter 2 Research objectives

Primary objective

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

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 compared with that in patients receiving standard care with sham acupressure wristbands and standard care alone for the management of chemotherapy-induced nausea.
3. To assess the quality of life in patients using acupressure wristbands in addition to standard care compared with that in patients receiving standard care with sham acupressure wristbands and standard care alone in the management of chemotherapy-induced nausea and vomiting.
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5. To ascertain for which emetogenic level of chemotherapy regimen (i.e. high, moderate or low) self-acupressure using wristbands in addition to standard care is more or less effective in terms of nausea compared with patients receiving standard care with sham acupressure wristbands and standard care alone.
6. To ascertain whether or not any improvement in chemotherapy-induced nausea and vomiting from using acupressure wristbands is different between men and women.
7. To ascertain whether or not there is an age effect from the use of acupressure wristbands in relation to chemotherapy-induced nausea and vomiting.

Chapter 3 Research methods

Design of the study

The study was a randomised controlled trial with three arms (Assessment of Nausea in Chemotherapy Research or ANCHoR). The three arms consisted of usual care plus (1) self-administered acupressure wristbands, (2) sham acupressure wristbands and (3) no additional treatment. The duration of the patients' involvement was for four cycles of chemotherapy, as after four cycles patients not responding to the given chemotherapy may discontinue it, may be offered a different chemotherapy regimen or a different treatment plan, or may be offered supportive care only.

Subjects were allocated to the trial groups through computer-generated randomisation carried out remotely by the trials unit of the Christie NHS Foundation Trust, Manchester. The randomisation method used consisted of minimisation with a random element (stochastic minimisation), balancing for gender,[29,40] age (16–24, > 24–50, > 50 years)[29,41] and three levels of emetogenic chemotherapy [low, moderate and high according to international American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC) classifications].[32,42]

Biases were minimised through (1) exclusion criteria that leave out some of the factors and sources of nausea and vomiting in cancer patients other than chemotherapy (i.e. intestinal obstruction); (2) 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 (i.e. anxiety),[29,43] to be incorporated during the data analysis as a covariate in analysis of covariance (ANCOVA) models; and (3) the use of stratification for other key risk factors for nausea development during chemotherapy (i.e. 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 had carried out a two-arm pilot study of 36 breast cancer patients comparing acupressure wristbands (plus antiemetics) with standard antiemetics only.[15] The present trial has been based on methods tested in this pilot study. Although 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 5 days of chemotherapy. Improvements were higher in relation to nausea than in relation to vomiting. Mean overall percentage of improvement (pre to post assessment) in the experimental subjects was 44.5%. The study showed that an acupressure trial is feasible, with high levels of compliance (only one patient stopped using the wristband, because of arm swelling), although one-third of the patients did not return completed assessments. The lack of follow-up techniques (i.e. reminder letters), which was due to time constraints, is partly responsible for this and is acknowledged as a limitation of the pilot study. However, missing data in the returned assessments were almost non-existent, and patient logs for acupressure usage were fully completed.

Sham acupressure and acupressure have also been used in another pilot trial that we have carried out recently for the management of cancer-related fatigue;[44] patients in the sham group who were informed that they were receiving one of two combinations of (acu)points were blinded until the end of the trial and this group had little improvement compared with 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.

Experimental and control interventions

The study was a Phase III pragmatic randomised trial.

The target population was a heterogeneous group of cancer patients meeting the inclusion criteria and about to receive chemotherapy of high, moderate and low emetogenic potential. Heterogeneity is important to address issues of response to different types of emetogenic chemotherapy, as well as by gender and age, as past literature highlights that these are important in assessing the effectiveness of treatments for chemotherapy-related nausea and vomiting. Minimally emetogenic chemotherapy was not 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 were provided with a pair of widely available acupressure wristbands. These bands are elastic wristbands with a 1-cm protruding round plastic button (stud). They are available in two sizes, standard and large. Patients wore the wristband with the stud pressing the P6 acupoint, which is located on the anterior surface of the forearm, approximately a three-finger width up from the crease of the wrist between the tendons of the palmaris longus and flexor carpi radialis. An instruction sheet with a picture of acupoint P6 and how to locate the point was also provided to patients. Patients were provided with a pair of acupressure wristbands and instructed to wear them on both arms and take them off only when showering/bathing. Patients were instructed to wear the wristbands from the morning before chemotherapy administration and for the subsequent 6 days (total 7 days). No other complementary therapy use was recommended during the course of acupressure (although any such use was documented).

In the sham acupressure group, in addition to standard antiemetics, patients were provided with a pair of identical-appearing wristbands, with the only difference being that the sham wristband had the button on the exterior of the wristband and patients were instructed to wear the wristband with the button away from what is the P6 point. There has been an ongoing scientific debate on what constitutes an appropriate sham treatment, and it has been acknowledged that there is no sham method in acupuncture and acupressure studies that can be widely accepted as the optimal method. It is increasingly believed that sham acupuncture/acupressure designs cannot detect the whole placebo effect and may generate false-negative results,[45–48] depending on the method used. We had debated the appropriateness of other sham methods but either they were not blinded enough for the purposes of the trial (i.e. they were slightly dissimilar to real acupressure wristbands) or they could be perceived as treatments themselves (i.e. acupressure at other points in the forearm or elsewhere where we had no information as to an effect on the experience of nausea). Patients in the clinics could also talk to each other and realise that they have different interventions or check the P6 point on the internet. Hence, we resolved to use an acupressure technique that appeared to be exactly the same as the active treatment with the only exception being the place of the stud on the wristband (interior or exterior to the band) used. This was also agreed by practitioners who had been consulted about their views on the most appropriate sham method. Furthermore, although it was acknowledged that many patients may have heard of the use of such wristbands, the results of our pilot study suggested that their knowledge of acupressure wristbands would be limited.[15] In addition, the results of our qualitative study on self-management of chemotherapy-induced nausea and vomiting suggested that acupressure was not commonly used by patients.[36] An assessment of blinding at the end of the trial was not conducted as patients had not been informed of the use of both sham and real acupressure bands during the trial, but had instead been informed that two different types of wristbands were being evaluated, with the approval of the ethics committee. Clinicians did not know the patients' group allocation.

The control group received standard antiemetics alone. Standard antiemetics for all three groups were based on ASCO and MASCC international antiemetic guidelines with the exception of neurokinin 1 (NK1) receptor antagonists [e.g. aprepitant (Emend®, Merck)] recommended in highly emetic chemotherapy, which were not available in the NHS. Hence, for highly emetic chemotherapy, patients received a

5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist [i.e. ondansetron 8 mg (Zofran®, GlaxoSmithKline)] and dexamethasone 8 mg intravenously before chemotherapy and the same orally for 3 days post chemotherapy; for moderately emetogenic chemotherapy a 5-HT_3 receptor antagonist (ondansetron 8 mg) and dexamethasone 8 mg intravenously before chemotherapy and a 5-HT_3 receptor antagonist or dexamethasone for 2 days post chemotherapy; and for low emetogenic chemotherapy dexamethasone 8 mg before chemotherapy and no other treatment post chemotherapy].[32,42] All patients received rescue antiemetics if nausea and/or vomiting was persistent and they failed to respond to the antiemetic treatment (i.e. severe nausea or more than five vomiting episodes), based on the experience of each clinician (as agreed guidelines for rescue antiemetics had not been developed to date).

Inclusion/exclusion criteria

Inclusion criteria

- Patients scheduled to receive their first chemotherapy cycle.
- Patients scheduled to receive chemotherapy with high, moderate and low emetogenic potential (as per ASCO and MASCC classifications).
- Patients scheduled to receive a chemotherapy regimen given as a single or a multiple administration repeated in 2-, 3- or 4-week cycles.
- Patients who were acupressure wristband naive (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 >16 years.
- Patients with any cancer diagnosis receiving chemotherapy without concurrent use of radiotherapy.
- Patients receiving chemotherapy as outpatients or inpatients.
- Patients who were 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.
- Patients unable to self-care (i.e. 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 a common presenting symptom).
- Patients with metabolic risk factors for nausea (i.e. electrolyte imbalances causing nausea/vomiting).
- Patients with mechanical risk factors for nausea (i.e. intestinal obstruction).
- Patients experiencing nausea and/or vomiting resulting from the use of opioids.
- Patients with lymphoedematous arms.
- Patients with chronic alcohol use (chronic alcohol use is associated with minimal levels of nausea and/or vomiting).

Proposed sample size

In our pilot study[15] the mean score for nausea experience averaged over 5 days was 2.79 [weighted average standard deviation (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% and so, initially, at least 202 participants would be required per arm. As the SDs are much larger than the means in the pilot data, they are suggestive of highly skewed distributions; hence, the equivalent non-parametric 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 equal, in the worst case, 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 and 233 after attrition, equalling 699 across the three arms.

Recalculation of sample size requirements during the trial

Because of a slower recruitment rate than envisaged initially, it was felt necessary to reconsider the sample size requirements. The Clinical Trials Unit analysed the first 141 cases that provided complete data over all four cycles. The SD for this cohort of patients was 2.75, slightly lower than the SD of 3 that we included in the initial power calculations. We had also calculated the power of the study to 90%, whereas the standard power in most studies is 80%. We adjusted the power down to 80%, which is the standard power accepted. With these adjustments the sample required was 480 participants. This change was agreed with both the Data Monitoring and Ethics Committee (DMEC) and the Health Technology Assessment (HTA) programme.

There were 361 cases with data on the primary outcome (117, 118 and 126 in the standard care only, sham acupressure and real acupressure arms respectively). Pair-wise trial arm comparisons were planned and as the data were skewed a non-parametric test (Mann–Whitney) was used, and this has an asymptotic relative efficiency of at worst 0.864 compared with the *t*-test. Thus, our effective sample sizes are around 117×0.864, which is about 100. With such a sample size there is approximately 80% power to detect a standardised difference in means of 0.46 in a two-tailed test at the 0.017 level of significance.

Recruitment took 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 NHS Foundation Trust and its peripheral clinics where chemotherapy is administered (Royal Oldham Hospital, Tameside General Hospital, Leighton Hospital, Stepping Hill Hospital at Stockport, Macclesfield District General Hospital, North Manchester General Hospital), the Royal Liverpool Hospital, Clatterbridge Centre for Oncology, St Helens Hospital, Southport General 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 NHS Foundation Trust alone had shown that around 9000 patients receive chemotherapy every year, with approximately two-thirds of these patients receiving chemotherapy in 3-week cycles. Recruitment rates were based on a similar antiemetic study that we had conducted over four cycles of chemotherapy,[37] which had taken 6 months to recruit 102 patients, with 65% retained over the four cycles of chemotherapy. Based on similar recruitment levels at each of the 14 sites listed above, we had estimated that recruitment would be completed in 16 months, with a further 3 months required to complete the follow-up of the final patients. Three dedicated researchers and 30 cancer network research nurses recruited patients and collected the data. Data collection was audited regularly and discussed with the Trial Steering Committee and the DMEC.

Statistical analysis

Descriptive statistics have been estimated for all baseline sociodemographic and clinical variables by arm and for outcome variables (scores on nausea and vomiting subscales) by arm. The association between baseline sociodemographic or clinical variables and outcome variables has been assessed using between-group tests or correlations depending on skewness. Primary outcome variables have been compared between the arms using *t*-tests, one-way analysis of variance (ANOVA), Mann–Whitney tests and Kruskal–Wallis tests, bearing in mind any skewness in the data. Ordinal regression models were employed to permit covariate-adjusted analyses of a grouped version of the primary outcome. An extension of the proportional odds regression model was used for longitudinal analyses over cycles and this was fitted with a generalised estimating equation (GEE) approach. An intention-to-treat analysis model has been followed. As the primary outcome variable was assessed over several days repeatedly, an aggregate score of all assessments in each cycle was calculated before any modelling analysis.

The effect of missing values was 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. There were no clear associations between known predictors

of nausea and cases missing the nausea primary outcome. This fact along with the highly non-normal distribution of the primary response (for which imputation methods are not so well developed) informed our decision not to apply multiple imputation analyses.

Randomisation method

The trial arm allocation method was minimisation with a random element over the margins of three factors: gender, age (16–24, > 24–50, > 50 years) and emetogenic risk (low, moderate, high). The first 20 cases were allocated completely at random and thereafter the allocation probability vector was (0.6, 0.3, 0.1) to the arms that would result in the least to the most imbalance respectively. Researchers telephoned the randomisation office staff with the patient details and the staff used an in-house program to obtain the allocated trial arm.

Outcome measures

Primary outcome

Rhodes Index of Nausea, Vomiting and Retching

The Rhodes Index of Nausea, Vomiting and Retching[49] is an eight-item validated scale measuring nausea and vomiting experience, incidence and severity. In this study the nausea experience subscale has been used (as shown in *Appendix 1*) for power calculations of the sample size, using the mean score across all assessment days in each cycle as the end point. From the nausea experience score, incidence and severity can also be isolated. Scores can range from 0 to 12, with higher scores indicating higher levels of the symptom experience. This scale, taking 1–2 minutes to complete, was scored daily from the day before chemotherapy (to capture any anticipatory nausea) up to 7 days post chemotherapy, that is, eight assessments per cycle.

Secondary outcomes

Multinational Association of Supportive Care in Cancer Antiemesis Tool

The MASCC Antiemesis Tool (MAT)[39] is an eight-item scale that 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.[39] The scale (see *Appendix 2*) was completed at day 10 of each cycle (i.e. four assessments).

Functional Assessment of Cancer Therapy – General quality-of-life scale

The Functional Assessment of Cancer Therapy – General (FACT-G)[50] is a well-validated quality-of-life scale focusing on functional assessment. This functional scale has provided not only quality-of-life indications, but also changes in other symptoms/side effects that may have resulted from any improved management of nausea (e.g. 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 minutes. This scale (see *Appendix 3*) was completed at baseline and then at day 10 of each cycle (i.e. five assessments).

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale[51] is a 14-item scale assessing anxiety with seven items and depression with a further seven items. Each item is answered on a 4-point scale (0–3). Scores on each subscale thus range between 0 (no symptoms) and 21 (numerous and severe symptoms). There are separate scores for anxiety and depression. In this study the anxiety subscale was obtained at baseline (see *Appendix 4*), with the score used as a covariate in the final statistical analysis of the data, as anxiety is a

key risk factor for the development of nausea/vomiting.[29,43] 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 minutes.

Patient expectations of nausea/vomiting

As this is a key risk factor identified in the literature,[29,43] a two-item scale was developed assessing patient expectations for nausea and vomiting, measured on a 10-point ordinal scale. We have used the same measurement approach elsewhere in the past[52] although no validation of these two items has formally taken place. This was incorporated in the final analysis of outcomes. Patients were also asked how much they believed that the acupressure wristbands had helped them alleviate nausea and how much faith they had in complementary therapies, also using 10-point scales (see *Appendix 5*).

Sociodemographic and disease/treatment variables

Sociodemographic and treatment characteristics were obtained from the patients' records and the patients themselves (see *Appendix 6*). These included 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 in the past, cancer diagnosis, stage of disease and chemotherapy protocol used and dosage. Such a questionnaire had already been developed by the team and used in the past in other nausea/vomiting studies.[15,29] Medication use (standard and rescue antiemetics) during study participation was obtained from pharmacy records. Furthermore, although not formally required, researchers asked patients about any side effects (or patients could volunteer side effect information) and these were recorded in a descriptive manner.

Assessment scales were provided to patients for self-completion at home; completed forms were returned to researchers using a prepaid self-addressed envelope. Patients were 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 were reminded to return their completed scales when attending for chemotherapy and were also contacted at an early stage during the trial when the researcher would remind them of the instructions for completing and returning the scales. *Table 1* shows the timing of the completion of the study assessment forms.

TABLE 1 Timing of completion of study assessment forms

Assessment scale	Baseline assessment	Chemotherapy days –1, 0, 1, 2, 3, 4, 5, 6×four cycles	Chemotherapy day 10×four cycles	End of study participation
Rhodes Index of Nausea, Vomiting and Retching		✗		
MAT			✗	
FACT-G	✗		✗	
Hospital Anxiety and Depression Scale	✗		✗	
Patient expectations questionnaire	✗			
Sociodemographic variables	✗			
Disease/treatment variables	✗			✗
Health economics assessment	✗	✗	✗	✗

Wristband compliance and audit

Patients who had been randomised to the acupressure and sham acupressure groups were also asked to provide information about the length of time that they had worn their wristbands on the day of chemotherapy and the 6 subsequent days. A wristband compliance questionnaire (see *Appendix 7*) was given to the patients per cycle to complete and return in the prepaid envelope together with the other completed scales.

In addition to compliance with wearing wristbands, it was important to determine whether or not patients were wearing the wristbands correctly according to the instructions they had been given. A wristband audit was conducted at two Manchester sites (Christie NHS Foundation Trust and Macclesfield District Hospital) and two Liverpool sites (Clatterbridge Centre for Oncology and the Royal Liverpool Hospital). Research nurses who were involved with patient recruitment to the trial assessed how correctly patients were wearing their wristbands when they attended for chemotherapy treatment. In total, observations were carried out for 35 pairs of wristbands. An audit proforma is shown in *Appendix 8*.

The trial did not come under Medicines and Healthcare products Regulatory Agency (MHRA) regulations as it was not a clinical trial of an investigational medicinal product as defined by EU Directive 2001/20/EC; a procedure for the reporting of serious adverse events was therefore not required. However, patients were regularly asked about their experiences with regard to wearing wristbands (e.g. when attending for chemotherapy and during routine telephone communication during the trial) and about any problems associated with the wristbands (e.g. if a larger size was required, if the wristband caused any kind of discomfort, if the wristband became damaged). These were logged by the researchers, with appropriate advice offered to patients.

Measurement of costs

Costs were identified, measured and valued using a microcosting approach (in which each component of resource use was identified, estimated and a unit cost derived from market prices and national estimates[53]). The cost analysis was performed from the perspective of the health service provider and from a societal perspective. Included in the health-care provider costs were those accrued by the acute trusts and the primary care trusts. Costs to the patients and their families, including social care, were considered as the additional costs for society. Indirect costs in terms of workdays lost were also included.

Data were collected prospectively and retrospectively using multiple sources including patient records and patient self-reported questionnaires (see *Appendices 9* and *10*). The questionnaires reported 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 and the 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) was carried out using national estimates;[53] market prices were assigned to medication; non-market items, specifically patient time and informal help provided by family and friends, were valued using market wage rates; and out-of-pocket expenses (e.g. bus fares) were also calculated.

In more detail, direct medical costs were defined as the costs of prophylactic or rescue antiemetic medications, drug administration devices, staff time associated with preparing and administering medication and tending to patients with chemotherapy-induced nausea and vomiting, hospitalisations due to chemotherapy-induced nausea and vomiting, hospital outpatient or GP visits due to chemotherapy-induced nausea and vomiting and over-the-counter medications or other complementary therapies. Direct non-medical costs were those for transportation and need for assistance, such as additional childcare. Indirect costs were based exclusively on the number of workdays lost due to chemotherapy-induced nausea and vomiting. Costs that were not included in this evaluation were costs for chemotherapy agents,

preplanned visits or hospitalisations for the purpose of chemotherapy administration, and diagnostic and laboratory tests, and other patient management costs not directly related to chemotherapy-induced nausea and vomiting.

Analysis of economic data

The total cost of each arm of the trial was calculated by combining the resource use and unit cost data. No discounting was necessary given the time period of data collection (< 1 year). Sensitivity analysis was carried out to account for uncertainty when estimates of cost data were used. Differences in costs between the three arms were tested for using independent sample *t*-tests. Cost data in each of the arms were 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) data are presented.

Nested qualitative study

There was an exploratory nested qualitative study within the trial that explored patients' reasons for consenting to take part in the trial and their experiences of participating in a randomised controlled trial for acupressure wristbands.

A number of qualitative studies have explored patients' experiences of receiving treatment with acupuncture, and their findings have suggested that the treatment is associated with eliciting benefits beyond the alleviation of the patients' presenting condition.[54–56] These expanded effects of care include improvements in physical/mental health and emotional well-being and changes in personal identity and lifestyle, and can result in patients 'feeling normal again' and 'regaining their lives'. Despite the burgeoning qualitative research exploring the experiences of patients receiving acupuncture, to date no study has been conducted to explore the experiences of users of acupressure or acupressure wristbands. To address this gap in the evidence base, a nested qualitative study was conducted with patients taking part in the main trial.

Objectives

1. To outline patients' experiences of using acupressure wristbands.
2. To outline the reasons why patients consent to take part in a clinical trial of acupressure wristbands.
3. To outline patients' experiences of taking part in a randomised controlled trial of acupressure wristbands.

Sample

A purposive sample of patients who had taken part in the clinical trial of the effectiveness and cost-effectiveness of acupressure wristbands for chemotherapy-induced nausea and vomiting participated in one-to-one semistructured interviews. Patients were recruited from each of the three geographical sites, represented all three study arms, had either high or low scores for the item about their expectation of effect from the wristbands and either had or did not have experience using complementary therapies in general.

Methodology

Interviews were conducted by three members of the research team and were directed by a topic guide. Topic guides were updated throughout the study to incorporate emerging themes. Interviews were audiotaped and transcribed verbatim. Interviews lasted for between 30 and 70 minutes. Transcripts were analysed thematically using framework analysis, a manual, matrix method, which facilitates thematic and cross-case interpretation.[57,58] Analysis proceeded in five stages:

1. familiarisation – transcripts were read and reread by members of the research team until they became familiar with and immersed in the data

2. identification of the thematic framework – key issues, concepts and themes arising from the data were identified and grouped thematically to construct a conceptual framework
3. indexing – two of the research team independently applied the thematic framework to the same transcript to explore any differences in application; the thematic framework was then applied systematically to all of the data
4. charting – thematic matrices were constructed for all identified categories/subcategories to further summarise and synthesise the indexed data
5. detection, categorisation and classification – the original research questions were reconsidered and the charts examined in order to define concepts, map the range and nature of phenomena, find any associations and provide explanations.

Research governance

The sponsor of the study was the University of Manchester. The MHRA has confirmed that this trial does not fall under the Medicines for Human Use (Clinical Trials) Regulations 2004, as described earlier.

Trial Steering Committee

A Trial Steering Committee was formed, which was chaired by a patient representative. Other members included a medically trained expert in chemotherapy nausea who was independent of the study, an acupressure practitioner, a representative of the trials unit (statistician), the lead applicant and two of the co-applicants, one of whom was the study's user/co-applicant. This committee was responsible for trial safety and assurance of scientific validity and was convened four times: once after completion of the preparatory part of the trial, twice more during the recruitment phase and once after data cleaning and before data analysis.

Data Monitoring and Ethics Committee

An independent DMEC was set up by the Christie NHS Foundation Trust Clinical Trials Unit in accordance with standard procedures to review accruing trial data on a regular basis and also to ensure that a sufficient number of patients were enrolled, reporting back to and guiding the Trial Steering Committee and also reporting to the HTA programme through the Trial Steering Committee. The members of this committee were not linked to the study in any way.

Trial management

The Christie NHS Foundation Trust Clinical Trials Unit was responsible for data management. It is based within the research and development division of the Christie NHS Foundation Trust. The unit manages international, national and local studies and its portfolio during the conduct of our trial included three international studies, 14 randomised studies and 12 other studies. These included a number of studies with funding from Cancer Research UK through the Clinical Trials Advisory and Awards Committee (CTAAC) route. The unit has a strategic alliance with the Medical Research Council Clinical Trials Unit in London, and the development and operation of the Christie unit is supported by the MRC unit.

The Clinical Trials Unit has robust governance and management systems that have been subjected to a MHRA Good Clinical Practice inspection, with the inspectors describing the systems for the management of clinical trials as 'robust'. This study was conducted in accordance with the unit's standard operating procedures; these cover all aspects of the management of clinical trials and the unit can assure funders that the studies supported are managed within a quality framework that has been reviewed by the MHRA. The unit has been responsible for the monitoring of the trial to ensure that it is conducted in accordance with the protocol, research governance framework and applicable regulations. A full list of standard operating procedures is available on request and on the unit's website. The unit had the capacity and capability to support a trial of this nature (indeed it has in its portfolio another national study on complementary therapies using acupuncture) and was able to identify a project lead to oversee the work of the data manager. The data manager was responsible for ensuring that the data generated

by the study were reviewed appropriately by the DMEC, and the trials supported by the unit are typically reviewed through these mechanisms. Randomisation and statistical analysis have been supported by the unit's statisticians.

Service user involvement

Service users were involved at three levels. The first has been at the development phase of this proposal, with the contribution of the chairperson of the National Cancer Research Institute (NCRI) Consumer Liaison Group, who was a named co-applicant in the study, and reviews by expert patients. The second level was monitoring the trial project and guiding it within its scientific framework through chairing and participating in the Trial Steering Committee and the DMEC. Finally, users have advised 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 have been utilised.

Chapter 4 Main findings

Patient recruitment

Three main study centres were involved in patient recruitment, namely Manchester, Liverpool and Plymouth. Recruitment began with a month-long pilot phase in Manchester at the Christie NHS Foundation Trust to test recruitment processes. The first case was randomised on 23 March 2009. A phased recruitment launch followed in the two remaining centres with patient recruitment starting in Liverpool in May 2009 and in Plymouth in June 2009. The last case was randomised on 15 October 2010. In total, 14 hospital sites were involved in recruitment (*Table 2*) and 500 cases were randomised (166 standard care, 166 sham acupressure and 168 acupressure).

Monthly recruitment for the trial is given in *Figure 1*.

A CONSORT flow diagram (*Figure 2*) shows the numbers of participants recruited and randomly assigned to the three trial arms and who received the intended interventions and were analysed for the primary outcome.

Descriptive statistics by trial arm

The majority of the participants were female, married and aged > 50 years. The key diagnoses of the sample included breast and colorectal cancer and the majority had received moderately emetogenic chemotherapy (including anthracycline-based chemotherapy). Other sociodemographic and clinical data are provided in *Table 3*.

TABLE 2 Trial recruitment per study site

Main centre and total number of patients recruited	Breakdown of recruitment per study site
Manchester (244 patients randomised over 76 weeks)	119 from Christie NHS Foundation Trust (including initial pilot phase) 50 from Royal Oldham Hospital 1 from Tameside General Hospital 5 from Leighton Hospital 39 from Stepping Hill Hospital 26 from Macclesfield District General Hospital 4 from North Manchester General Hospital
Liverpool (161 patients randomised over 71 weeks)	33 from Clatterbridge Centre for Oncology 79 from Royal Liverpool Hospital 41 from St Helens Hospital 8 from Southport General Infirmary
Plymouth (95 patients randomised over 64 weeks)	2 from Torbay District General Hospital 88 from Derriford Hospital 5 from Royal Cornwall Hospital

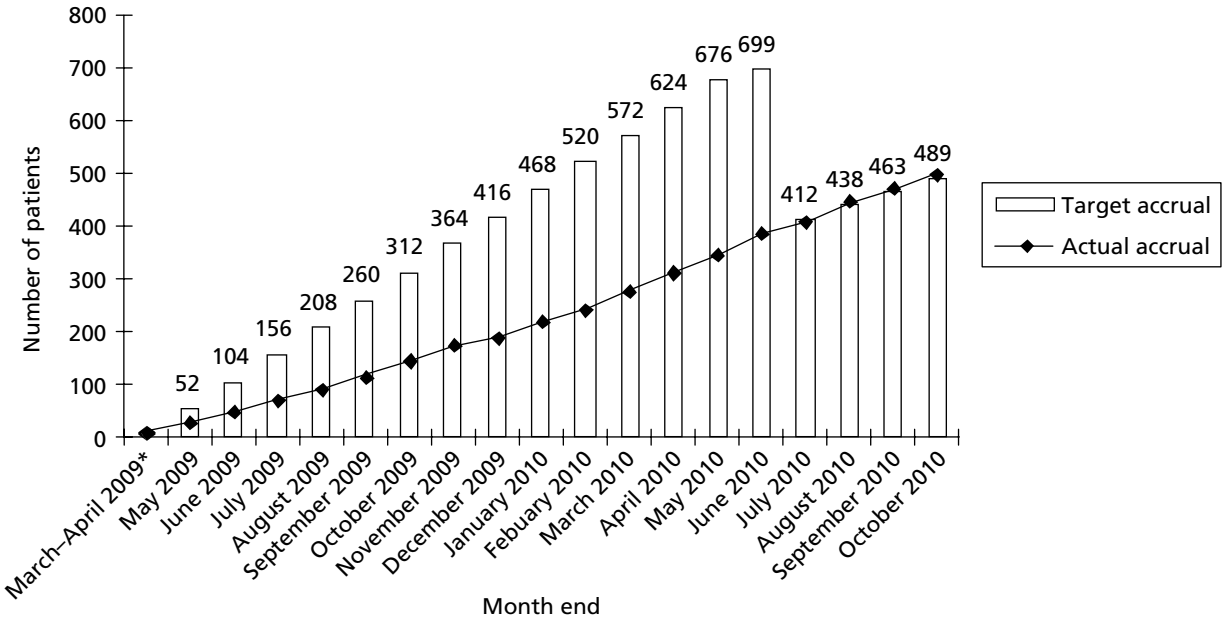

FIGURE 1 Trial recruitment by month. Monthly target accrual was recalculated after sample size adjustment in May 2010, with the agreement of the HTA team. Power was initially calculated to 90% but as recruitment was slower than expected the sample size was recalculated to 80% power.

Assessment of missing data for the primary outcome

A total of 500 cases were randomised, but there are data for only 361 of these cases for the primary outcome, i.e. the primary outcome is missing in around 28% of cases. *Table 4* illustrates, for the remaining 497 cases, the proportion of cases in which the primary outcome is missing by various factors thought to influence nausea propensity (three cases were allocated to 'No acupressure' but there are no records in the trial database for these three cases, i.e. no completed screening forms and no returned data form). There are no marked associations between any of these factors and the probability of the primary outcome being missing.

Inevitably there is a further dropout of cases with each cycle, as illustrated in *Table 5*.

Table 6 shows the mean nausea experience of the patients using the Rhodes Index of Nausea, Vomiting and Retching scale. Scores range from 0 to 12, with higher scores indicating higher levels of nausea. Both the sham and acupressure arms experienced less nausea than the standard care arm, although the difference did not reach statistical significance. It is important to note that these mean values represent very low levels of nausea. Only at cycle 4 did the results become significant ($p < 0.05$), with the acupressure group reporting no nausea experience.

Tables 7 and *8* show the frequencies of the nausea and vomiting experience, respectively, categorised over five ranges of experience.

Tables 9 and *10* present descriptive data of acute and delayed nausea, respectively, based on the MAT scale, showing similar results to those obtained with the Rhodes Index of Nausea, Vomiting and Retching scale. *Tables 11* and *12* report the data for acute and delayed vomiting, respectively, based on the MAT scale.

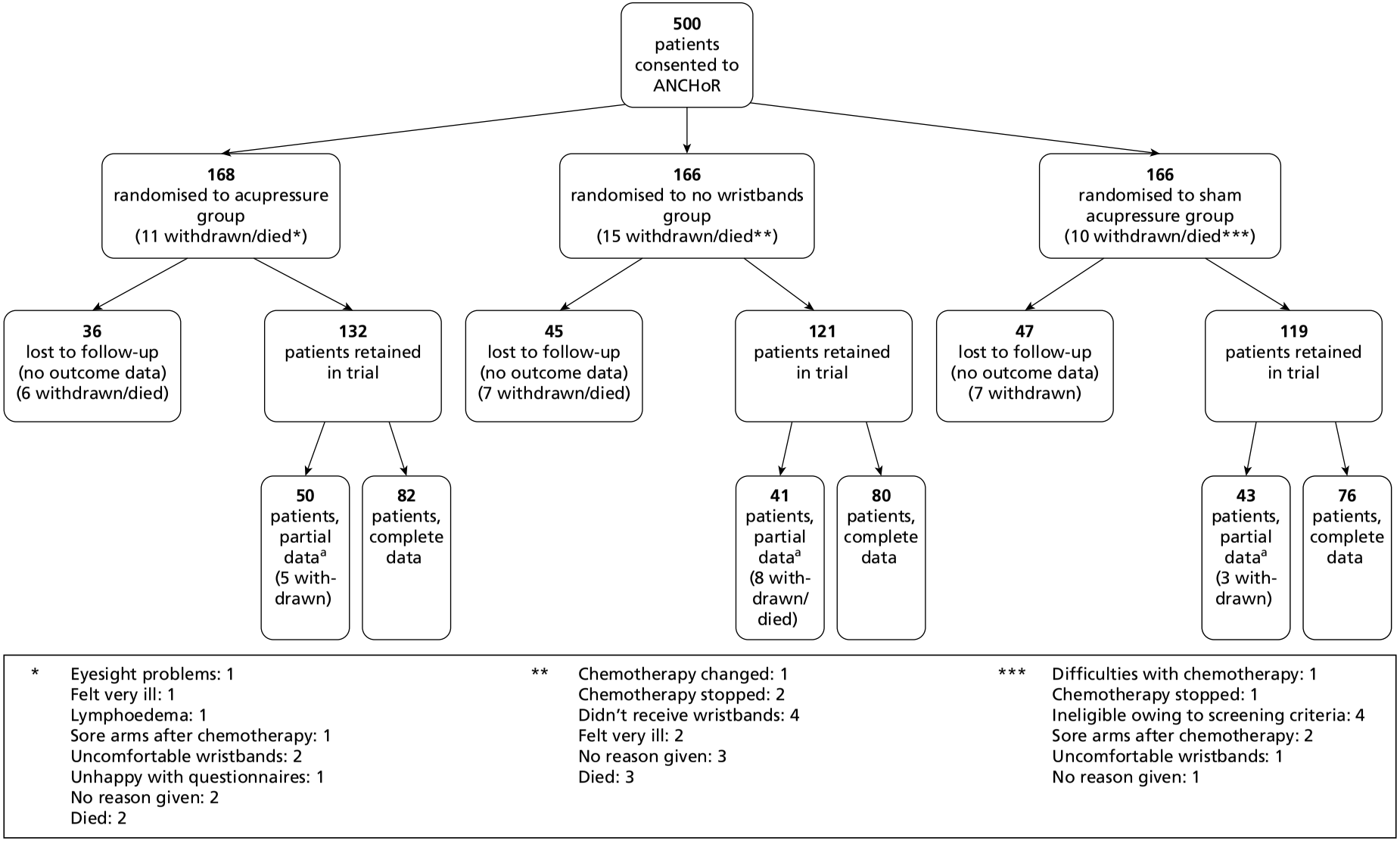

FIGURE 2 Patient recruitment into the ANCHoR trial: Manchester, Liverpool and Plymouth sites, March 2009 to October 2010. a, Partial data indicate data collected from less than the complete dataset (baseline plus four cycles of chemotherapy), that is, when at least one assessment was missing. Data represented in this figure include the pilot phase, March–April 2009.

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TABLE 3 Sociodemographic and clinical data of the sample

	None (*n*)	Sham bands (*n*)	Acupressure bands (*n*)
Gender			
Male	38	37	39
Female	128	129	129
Age group (years)			
≤50	51	55	54
51+	115	111	114
Marital status			
Single	18	15	24
Married	85	83	88
Divorced or separated	20	27	21
Widowed	13	16	11
Missing	30	25	24
Educational attainment			
Primary school	0	3	2
Secondary school	68	74	69
College/diploma	37	26	43
University/degree	20	14	17
Postgraduate	6	12	8
Missing	35	37	29
Ethnic origin			
Caucasian	111	110	121
Black	0	1	2
Asian/Chinese	2	2	2
Mixed	1	3	0
Missing	52	50	43
Religious affiliation			
Christian	114	106	122
Muslim	1	2	3
Hindu	0	1	0
None	17	18	12
Prefers not to say	1	4	2
Other	5	8	7
Missing	28	27	22
Occupational group			
Professional	40	44	36

TABLE 3 Sociodemographic and clinical data of the sample (*continued*)

	None (*n*)	Sham bands (*n*)	Acupressure bands (*n*)
Managerial and technical	17	16	23
Skilled non-manual	14	11	16
Skilled manual	14	12	11
Unskilled	14	16	15
Not applicable	28	33	43
Missing	39	34	24
***Occupational status*[59]**			
Employed full-time	50	36	33
Employed part-time	22	17	26
Retired	46	50	51
Unemployed	2	4	3
Casual worker	0	0	1
Not working due to ill health	10	20	17
Housewife	5	11	10
Other	2	3	4
Missing	29	25	23
Smoking history			
Never	63	62	66
Previously	56	51	62
Current	20	25	18
Missing	27	28	22
Cancer diagnosis			
Breast	89	90	82
Bowel (colon and rectum)	25	27	19
Gynaecological	20	15	21
Lung	7	10	21
Lymphoma	6	2	7
Oesophagus	4	5	2
Stomach	2	3	1
Pancreas	1	1	4
Melanoma	2	2	1
Bladder	1	1	2
Gall bladder	0	1	1
Head and neck	1	1	0

continued

TABLE 3 Sociodemographic and clinical data of the sample (*continued*)

	None (*n*)	Sham bands (*n*)	Acupressure bands (*n*)
Endocrine/thymus	0	1	1
Prostate	1	0	1
Child: Ewing's sarcoma	1	1	0
Child: non-Hodgkin's lymphoma	0	1	0
Missing	6	5	5
Emetogenic risk			
Low	13	11	12
Moderate	107	111	111
High	46	44	45

TABLE 4 The proportion of cases missing primary outcome data by various factors

Factor	Level	Missing primary outcome, *n*/*N* (%)	*p*-value[a]
Trial arm	None	46/163 (28)[b]	0.69
	Sham bands	48/166 (29)	
	Acupressure bands	42/168 (25)	
Age (years)	≤50	42/160 (26)	0.78
	51+	94/337 (28)	
Gender	Male	35/114 (31)	0.43
	Female	101/383 (26)	
Emetogenic risk	Low	12/36 (33)	0.69
	Moderate	87/327 (27)	
	High	37/134 (28)	
2-weekly CT	No	122/451 (27)	0.75
	Yes	14/46 (30)	
Baseline anxiety (83 missing)	Normal (0–7)	50/250 (20)	0.16
	Borderline (8–10)	22/76 (29)	
	Case (11–21)	24/88 (27)	
Nausea expectation (84 missing)	0–3	24/100 (24)	0.80
	4–6	52/224 (23)	
	7–10	18/89 (20)	

a Chi-squared tests of equal proportions.

b Three cases were allocated to 'No acupressure' but there are no records in the trial database for these three cases, i.e. no completed screening forms and no returned data forms.

TABLE 5 Dropout data by trial arm over the four cycles of chemotherapy

Dropout status	None	Sham bands	Acupressure bands	Total
Immediate (no outcome data)	45	47	36	128
Complete (all outcome data)	80	76	82	238
Cycle 1 then dropped out	12	14	14	40
Cycles 1 and 2 then dropped out	11	17	12	40
Cycles 1–3 then dropped out	14	11	12	37
Intermittent data	4	1	12	17
Total	166	166	168	500

TABLE 6 Mean Rhodes Index of Nausea, Vomiting and Retching nausea experience (days 0–6)

Cycle	None[a]	Sham bands[a]	Acupressure bands[a]
1	1.43 (0, 0, 3.71, 8.57) ($n = 117$)	0.57 (0, 0, 2.64, 9.17) ($n = 118$)	1.0 (0, 0, 2.97, 7.50) ($n = 126$)
2	1.71 (0, 0, 3.43, 10.14) ($n = 109$)	0.71 (0, 0, 2.14, 10.29) ($n = 105$)	0.93 (0, 0, 3.43, 9.57) ($n = 114$)
3	1.14 (0, 0, 3.86, 11.86) ($n = 96$)	0.71 (0, 0, 2.29, 9.71) ($n = 88$)	0.43 (0, 0, 3.00, 10.14) ($n = 103$)
4	1.14 (0, 0, 4.00, 9.14) ($n = 81$)	0.43 (0, 0, 2.43, 8.57) ($n = 77$)	0.00 (0, 0, 1.82, 9.86) ($n = 90$)

a Data are median (min., lower quartile, upper quartile, max.)

TABLE 7 Numbers of participants in each nausea experience score range (based on Rhodes Index of Nausea, Vomiting and Retching nausea experience subscale, days 0–6)

	Score					
	0	(0–2]	(2,4]	(4,6]	> 6	NA
Cycle 1						
None	34	35	21	14	13	49
Sham bands	36	47	19	8	8	48
Acupressure bands	41	38	28	11	8	42
Cycle 2						
None	32	29	27	9	12	57
Sham bands	36	41	13	10	5	61
Acupressure bands	43	29	19	10	13	54
Cycle 3						
None	33	22	19	14	8	70
Sham bands	33	31	10	9	5	78
Acupressure bands	43	29	11	8	12	65
Cycle 4						
None	27	23	13	10	8	85
Sham bands	36	16	15	7	3	89
Acupressure bands	53	17	8	6	6	78

NA, no data available.

TABLE 8 Numbers of participants in each vomiting experience score range (based on Rhodes Index of Nausea, Vomiting and Retching vomiting experience subscale, days 0–6)

	Score					
	0	(0–1]	(1,2]	(2,3]	> 3	NA
Cycle 1						
None	76	24	11	4	3	48
Sham bands	80	27	7	3	1	48
Acupressure bands	85	24	9	7	1	42
Cycle 2						
None	74	20	9	2	3	58
Sham bands	74	21	6	4	0	61
Acupressure bands	90	16	2	4	2	54
Cycle 3						
None	75	13	3	0	5	70
Sham bands	68	15	4	0	1	78
Acupressure bands	81	15	3	1	3	65
Cycle 4						
None	60	11	3	5	2	85
Sham bands	61	12	1	2	1	89
Acupressure bands	76	9	3	1	1	78

NA, no data available.

Primary outcome analysis

The primary outcome is the mean nausea experience (days 0–6) for cycle 1 measured using the Rhodes Index of Nausea, Vomiting and Retching scale. As can be seen from *Figure 3* the data are highly skewed. The possible range of scores is from 0 to 12, but, in fact, 111/361 (31%) are exactly zero and around half of all values are < 1. No transformation would be successful in normalising such a distribution.

The distribution by trial arm is shown in *Figure 4*. Because of the highly skewed distribution, the non-parametric Kruskal–Wallis test has been used for the primary comparison of the trial arms. This overall test is non-significant ($p = 0.14$).

Provision for pair-wise comparisons (Mann–Whitney *U*-tests) with a Bonferroni adjustment was made in the trial design: none compared with acupressure ($p = 0.23$), none compared with sham acupressure ($p = 0.05$), sham acupressure compared with acupressure ($p = 0.40$). It should be noted that the reference value for statistical significance is 0.017 and so none of these pair-wise comparisons is statistically significant.

Regression analyses for the nausea primary outcome data

As noted previously, the data are highly skewed and no transformation will be successful in normalising the distribution. The approach adopted here is to group the values into five ordered categories and to utilise regression methods for ordinal data. The categories were chosen after inspection of *Figure 3*. The

TABLE 9 Multinational Association of Supportive Care in Cancer Antiemesis Tool – acute nausea: numbers of participants reporting a score from 0 to 10

	Score					
	0	1–3	4–6	7–9	10	NA
Cycle 1						
None	63	20	14	11	9	49
Sham bands	65	33	9	8	5	46
Acupressure bands	72	29	14	8	7	38
Cycle 2						
None	56	28	14	6	6	56
Sham bands	71	21	4	8	2	60
Acupressure bands	68	25	7	8	8	52
Cycle 3						
None	52	24	10	7	3	70
Sham bands	53	21	9	4	2	77
Acupressure bands	65	15	10	8	4	66
Cycle 4						
None	44	17	10	7	3	85
Sham bands	49	16	8	5	1	87
Acupressure bands	61	12	8	4	3	80

NA, no data available.

first category, 'Zero', was chosen as it represented no nausea at all and a large fraction of cases fell into this category (31%). The choice of the other categories was somewhat arbitrary. Five categories is fairly typical for ordinal regression models in the literature and it is desirable that no category has a very small frequency. Category 5 has a broad range but includes only 8% of cases; subdividing it further would be counterproductive. Having chosen the lowest and highest categories the remaining three were simply selected to have equal width. *Table 13* shows the categories and the frequencies by trial arm ($n = 361$).

The main tool used was the proportional odds regression model:[60]

$$\text{Logit}[\Pr(Yi \leq k/xi)] = \alpha_k + \beta^T xi \quad (1)$$

where $k = 1, 2, 3, 4$ denotes category; $i = 1, 2, \ldots, n$ denotes case; Yi is the response category for the ith case; xi is a vector of covariate values for the ith case (including the trial arm); αk is an intercept term for the kth category; $\beta$is a vector of parameters to be estimated; and $\text{Logit}(p) = \log[p/(1-p)]$.

Unadjusted fit

The snippet of output in *Table 14* is for an unadjusted fit using all of the available data ($n = 361$).

These data show that:

- the likelihood ratio test of the proportional odds assumption is non-significant ($p = 0.51$) meaning that there is no good evidence against this assumption
- the likelihood ratio test for the trial arm effects is non-significant ($p = 0.34$)

TABLE 10 Multinational Association of Supportive Care in Cancer Antiemesis Tool – delayed nausea: numbers of participants reporting a score from 0 to 10

	Score					
	0	1–3	4–6	7–9	10	NA
Cycle 1						
None	49	24	21	13	11	48
Sham bands	61	25	14	7	9	50
Acupressure bands	58	30	25	8	7	40
Cycle 2						
None	43	23	22	11	6	61
Sham bands	54	24	17	7	2	62
Acupressure bands	57	28	17	9	5	52
Cycle 3						
None	43	22	15	8	5	73
Sham bands	42	26	14	4	3	77
Acupressure bands	56	19	13	10	4	66
Cycle 4						
None	35	20	10	8	6	87
Sham bands	44	16	13	4	1	88
Acupressure bands	57	14	6	7	2	82

NA, no data available.

- the estimated odds ratio (OR) of a lower (i.e. better) score for acupressure than for the control is $e^{0.2418} = 1.27$ [95% confidence interval (CI) 0.80 to 2.03]
- the estimated OR of a lower (i.e. better) score for sham acupressure than for the control is $e^{0.3354} = 1.40$ (95% CI 0.87 to 2.24).

Hence, patients in the acupressure arm are 27% more likely to have less nausea/vomiting than patients in the control arm and patients in the sham arm are 40% more likely to have less nausea/vomiting than patients in the control arm.

Adjusted fit (age, gender and emetogenic risk)

The snippet of output presented in *Table 15* is for an adjusted fit using all of the available data ($n = 361$).

Table 16 shows the results of the regression analysis assessing variables that affect the primary outcome of nausea. It indicates that, irrespective of arm allocation, subjects who were > 50 years old and male had a better nausea outcome. Also, the emetogenicity of the drug was a significant factor in the nausea outcome.

These data show that:

- the likelihood ratio test of the proportional odds assumption is non-significant ($p = 0.66$) meaning that there is no good evidence against this assumption
- the likelihood ratio test for the trial arm effects after adjustment for age group, gender and emetogenic risk group is non-significant ($p = 0.34$)

TABLE 11 Multinational Association of Supportive Care in Cancer Antiemesis Tool – acute vomiting: numbers of participants reporting a score from 0 to 10

	Score					
	0	1–3	4–6	7–9	10	NA
Cycle 1						
None	99	10	4	2	2	49
Sham bands	106	12	1	1	1	45
Acupressure bands	110	11	5	1	3	38
Cycle 2						
None	97	8	1	4	0	56
Sham bands	94	7	4	1	0	60
Acupressure bands	101	9	2	0	3	53
Cycle 3						
None	91	3	1	1	1	69
Sham bands	81	5	1	1	0	60
Acupressure bands	91	8	3	0	0	66
Cycle 4						
None	75	4	1	1	0	85
Sham bands	72	6	0	1	0	87
Acupressure bands	86	3	0	1	0	78

NA, no data available.

- the estimated OR of a lower (i.e. better) score for acupressure than for the control (for identical age group, gender and emetogenic risk group) is $e^{0.1689} = 1.18$ (95% CI 0.74 to 1.90)
- the estimated OR of a lower (i.e. better) score for sham acupressure than for the control (for identical age group, gender and emetogenic risk group) is $e^{0.3520} = 1.42$ (95% CI 0.88 to 2.30).

Hence, considering the three risk factors presented in *Table 16* and the adjusted data presented earlier, patients in the acupressure arm are 18% more likely to have less nausea/vomiting than patients in the control arm and patients in the sham arm are 42% more likely to have less nausea/vomiting than patients in the control arm.

It is of interest to consider the impact of adding a trial arm by term interaction effect to the fitted model for each of age group, gender and emetogenic risk group in turn. A regression analysis presents the findings of this analysis (*Table 17*).

This indicates that there is evidence to suggest that treatment effects may vary with gender. This merits further investigation (see *Simple illustration of primary outcome by trial arm and gender*).

Adjusted fit (age, gender, emetogenic risk, cycle frequency, anxiety and nausea expectation)

There were further values missing for the baseline Hospital Anxiety and Depression Scale anxiety score and the pretreatment nausea expectation score. Hence, the snippet of output presented in *Table 18* is for an adjusted fit using all of the available data ($n = 315$).

TABLE 12 Multinational Association of Supportive Care in Cancer Antiemesis Tool – delayed vomiting: numbers of participants reporting a score from 0 to 4

	Score					
	0	1	2	3	4	NA
Cycle 1						
None	99	9	6	2	3	47
Sham bands	103	7	3	2	2	49
Acupressure bands	108	8	7	2	3	40
Cycle 2						
None	94	7	3	0	2	60
Sham bands	98	3	2	1	1	61
Acupressure bands	104	7	3	0	2	52
Cycle 3						
None	86	2	2	1	2	73
Sham bands	80	5	2	1	1	77
Acupressure bands	90	6	2	2	1	67
Cycle 4						
None	71	2	2	2	3	86
Sham bands	71	3	2	2	0	88
Acupressure bands	80	4	1	1	0	82

NA, no data available.

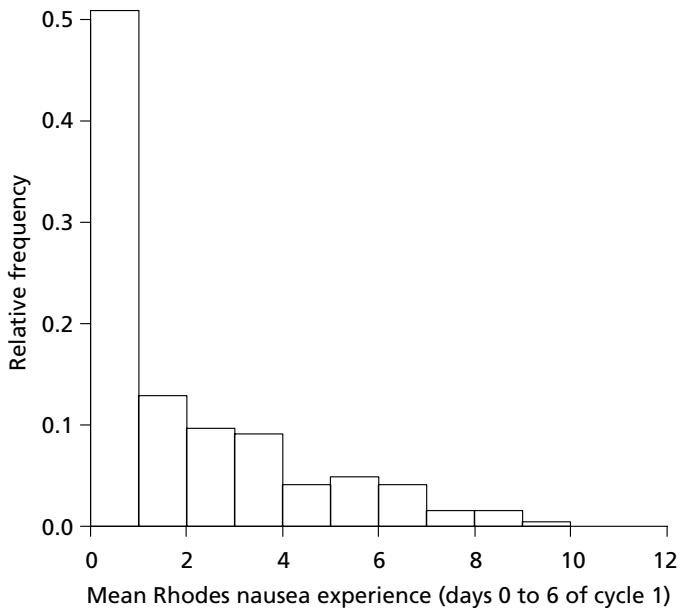

FIGURE 3 Primary outcome distribution ($n = 361$). The intervals are [0,1], (1,2], (2,3], … [11,12]. The first and last intervals are closed at both ends and intervals in between are open at their lower bound and closed at their upper bound.

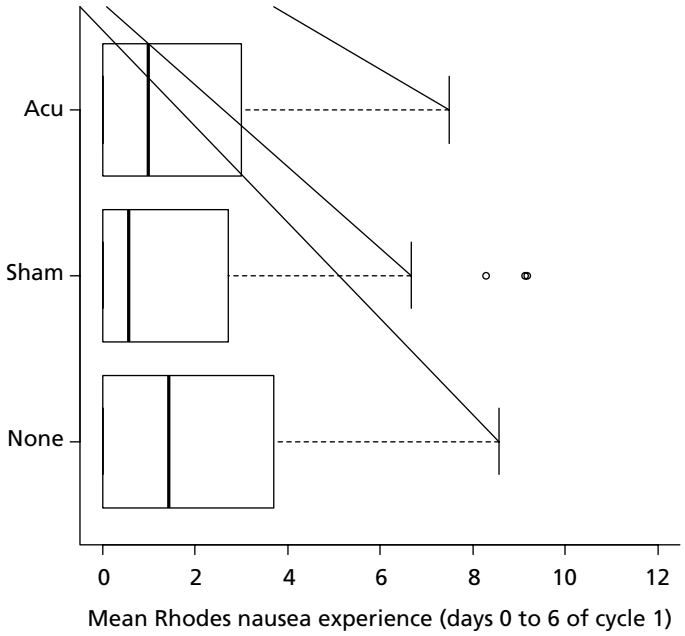

FIGURE 4 Box and whisker plot of the primary outcome by trial arm.

TABLE 13 Ordered categories of nausea experience by trial arm: numbers of participants in each range of nausea scores

Category	Nausea score	None	Sham bands	Acupressure bands
1	0	34	36	41
2	(0, 2)	35	47	38
3	(2, 4)	21	19	28
4	(4, 6)	14	8	11
5	(6, 12)	13	8	8

TABLE 14 Unadjusted fit model for nausea experience

Coefficients	Definition	Value	Standard error	*t*-value
ArmSham	(Sham = 1, otherwise = 0)	0.3354	0.2356	1.424
ArmAcupressure	(Acu = 1, otherwise = 0)	0.2418	0.2334	1.036
Intercepts		**Value**	**Standard error**	***t*-value**
1|2		–1.0138	0.1836	–5.5203
2|3		0.3777	0.1775	2.1281
3|4		1.3821	0.1943	7.1138
4|5		2.2506	0.2343	9.6047

Residual deviance: 1055.186.
Akaike information criterion: 1067.186.

TABLE 15 Adjusted fit model for age, gender and emetogenic level in relation to nausea experience

Coefficients	Value	Standard error	*t*-value
ArmSham	0.3520	0.2400	1.4670
ArmAcu	0.1689	0.2368	0.7131
Age51Plus	0.7445	0.2141	3.4766
GenderMale	0.7554	0.2692	2.8060
EmetogenicRiskLow	1.3783	0.4918	2.8025
EmetogenicRiskModerate	0.3369	0.2164	1.5572
Intercepts	**Value**	**Standard error**	***t*-value**
1|2	–2.0399	0.2793	–7.3029
2|3	–0.4924	0.2579	–1.9094
3|4	0.5786	0.2627	2.2021
4|5	1.4753	0.2909	5.0720

Residual deviance: 1006.691.
Akaike information criterion: 1026.691.

TABLE 16 Regression analysis: variables influencing the primary outcome (four variables model)

Term	df	*p*-value
Arm	2	0.34
Age ≥ 51 years	1	0.0005
Male	1	0.005
Emetogenic risk group	2	0.013

df, degrees of freedom.

TABLE 17 Regression analysis: trial arm by term interaction effect (four variables model)

Interaction term	df	*p*-value
Arm × (Age ≥ 51)	2	0.70
Arm × Male	2	0.002
Arm × (Emetogenic risk group)	4	0.88

df, degrees of freedom.

TABLE 18 Adjusted fit model for age, gender, emetogenic level, timing of delivery of chemotherapy and anxiety and nausea expectation in relation to nausea experience

Coefficients	Value	Standard error	*t*-value
ArmSham	0.26417	0.25973	1.0171
ArmAcu	0.12936	0.25220	0.5129
Age51Plus	0.51111	0.22929	2.2291
GenderMale	0.67565	0.32595	2.0729
EmetogenicRiskLow	1.23203	0.56228	2.1911
EmetogenicRiskModerate	0.29651	0.23076	1.2849
TwoWeekly	–0.06794	0.41474	–0.1638
Anxiety	–0.03628	0.02613	–1.3887
NauseaExpectation	–0.15455	0.05046	–3.0627
Intercepts	**Value**	**Standard error**	***t*-value**
1|2	–0.8360	0.3876	–2.1567
2|3	0.7305	0.3872	1.8868
3|4	1.8205	0.4011	4.5389
4|5	2.8123	0.4293	6.5504

Residual deviance: 868.2679.
Akaike information criterion: 894.2679.

A regression analysis, presented in *Table 19*, shows that age > 50 years, male gender and lower expectation of nausea are significantly linked with lower levels of nausea. The role of the emetogenicity of the chemotherapy in this analysis was borderline non-significant.

These data show that:

- the likelihood ratio test of the proportional odds assumption is non-significant ($p = 0.31$), meaning that there is no good evidence against this assumption
- the likelihood ratio test for the trial arm effects after adjustment for age group, gender, emetogenic risk group, cycle frequency, anxiety and nausea expectation is non-significant ($p = 0.60$)
- the estimated OR of a lower (i.e. better) score for acupressure than for the control (for identical values of the other covariates in the model) is $e^{0.1294} = 1.14$ (95% CI 0.69 to 1.88)
- the estimated OR of a lower (i.e. better) score for sham acupressure than for the control (for identical values of the other covariates in the model) is $e^{0.2642} = 1.30$ (95% CI 0.77 to 2.19).

Hence, considering the risk factors presented in *Table 19* and the adjusted data presented earlier in this section, patients in the acupressure arm are 14% more likely to have less nausea/vomiting than patients in the control arm, and patients in the sham arm are 30% more likely to have less nausea/vomiting than patients in the control arm.

It is of interest to consider the impact of adding a trial arm by term interaction effect to the fitted model for each of age group, gender, emetogenic risk group, cycle frequency, anxiety and nausea expectation in turn. The results of this analysis are presented in *Table 20* and show that only gender (with anxiety being a borderline non-significant variable) is significantly linked with the primary outcome, once again indicating that there is some evidence to suggest that treatment effects may vary with gender. This merits further investigation (see *Simple illustration of primary outcome by trial arm and gender*).

TABLE 19 Regression analysis: variables influencing the primary outcome (six variables model)

Interaction term	df	*p*-value
Arm	2	0.60
Age ≥51 years	1	0.025
Male	1	0.038
Emetogenic risk group	2	0.067
2-weekly CT	1	0.87
Anxiety	1	0.16
Nausea expectation	1	0.002

df, degrees of freedom.

TABLE 20 Regression analysis: trial arm by term interaction effect (six variables model)

Interaction term	df	*p*-value
Arm×(Age ≥51)	2	0.78
Arm×Male	2	0.023
Arm×(Emetogenic risk group)	4	0.93
Arm×(2-weekly)	2	0.14
Arm×Anxiety	2	0.08
Arm×(Nausea expectation)	2	0.16

df, degrees of freedom.

Simple illustration of primary outcome by trial arm and gender

The regression analyses above suggest that there may be a trial arm by gender interaction. To illustrate this, we may return to the box and whisker plots by trial arm further broken down by gender as shown in *Figures 5* and *6*. Given that we have seen a statistically significant interaction in the ordinal regression analyses, there is some justification to repeat the Kruskal–Wallis tests separately within the two gender strata. This yields significant results for men ($p = 0.04$; $n = 79$) and for women ($p = 0.01$; $n = 282$). Descriptively, the difference appears to be with the sham arm having a beneficial effect for women but a detrimental effect for men. This is a post hoc analysis and should be interpreted with due caution especially as there are a limited number of men.

Longitudinal regression analyses of mean Rhodes Index of Nausea, Vomiting and Retching nausea experience scores

The mean Rhodes Index of Nausea, Vomiting and Retching nausea experience scores (days 0–6) have also been calculated for cycles 2, 3 and 4. Once again, the scores for each cycle have been grouped in the same manner as previously to a 5-point ordinal scale. These repeated ordinal data have been analysed using an extension of the proportional odds regression model described previously, this time fitted using a GEE approach.[61] A working autoregressive correlation structure has been assumed, but the regression parameters are robust to this assumption. All reported Wald tests have used the robust covariance estimates.

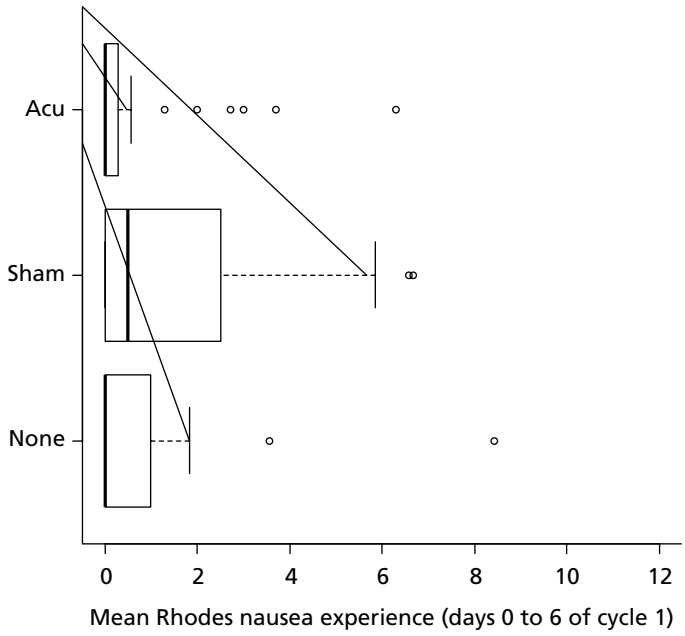

FIGURE 5 Box and whisker plot of the primary outcome by trial arm for men.

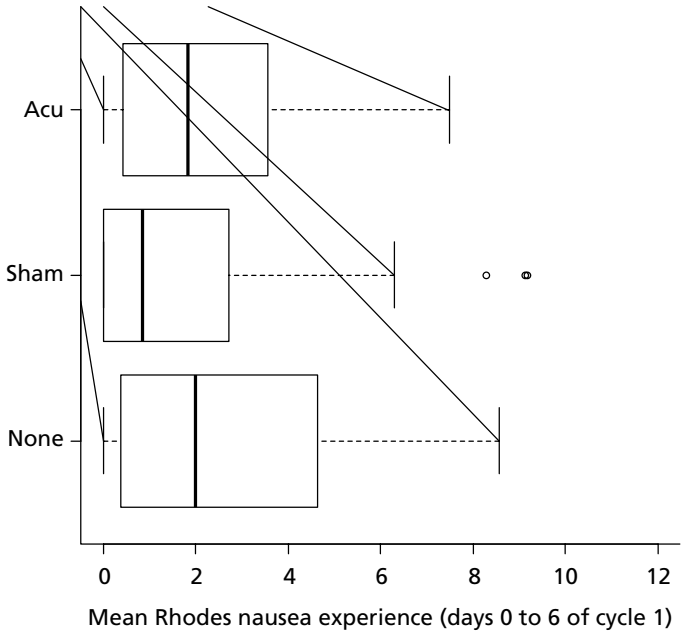

FIGURE 6 Box and whisker plot of the primary outcome by trial arm for women.

Unadjusted fit

First, a trial arm by cycle model was fitted and the interaction term was tested for significance (Wald test chi-squared on 6 df, $p = 0.25$). There being no formal evidence for different treatment effects with cycle, the simpler trial arm plus cycle model was fitted as presented in *Table 21*.

TABLE 21 Interaction effects in a model of trial arm by cycle

Coefficients	Estimate	Naive standard error	Naive *z*	Robust standard error	Robust *z*
Intercept 1|2	–0.9794	0.1399	–6.9980	0.1613	–6.069
Intercept 2|3	0.2440	0.1357	1.7972	0.1567	1.557
Intercept 3|4	1.1257	0.1439	7.8185	0.1628	6.910
Intercept 4|5	1.9900	0.1675	11.8760	0.1876	10.607
Sham	0.3823	0.1603	2.3851	0.1977	1.933
Acu	0.4255	0.1563	2.7225	0.2023	2.103
Cycle2	0.0406	0.1124	0.3609	0.0899	0.451
Cycle3	0.1680	0.1341	1.2530	0.0973	1.725
Cycle4	0.4708	0.1472	3.1984	0.1199	3.925

- The likelihood ratio test of the proportional odds assumption is non-significant ($p = 0.27$), meaning that there is no good evidence against this assumption.
- The estimated correlation parameter (95% CI) is 0.345 (0.001 to 0.997), that is, mild autocorrelation with a very wide CI.
- The Wald test for the trial arm effects on 2 df is of borderline significance ($p = 0.07$).
- The estimated OR of a lower (i.e. better) score for acupressure than for the control is $e^{0.4255} = 1.53$ (95% CI 1.12 to 2.09).
- The estimated OR of a lower (i.e. better) score for sham acupressure than for the control is $e^{0.3823} = 1.47$ (95% CI 1.06 to 2.02).
- The GEE approach is valid with an ignorable missing response mechanism (missing completely at random). All results should be interpreted with this in mind and sensitivity analyses with respect to missing data mechanisms will be performed.

Trial arm effects by gender from adjusted regression analyses

The regression analyses described previously for the cycle 1 nausea primary outcome revealed a trial arm by gender interaction. A parallel longitudinal analysis also displayed the same interaction (data not shown). A useful summary of the trial arm effects is given in *Tables 22* (cycle 1) and *23* (cycle-averaged data). The OR terms are the odds of a lower (i.e. better) nausea score for each of categories 1–4 in the 5-point ordinal scale described previously.

From these OR estimates and CIs we see that there was a statistically significant benefit for women in the sham arm (but not for men for whom the effect was in fact reversed). Both men and women appear to have enjoyed a benefit of similar magnitude in the acupressure arm but this is not formally statistically significant. The same caveats as mentioned previously apply, that is, this is a post hoc analysis, there are a relatively small number of men and assumptions have been made about missing data mechanisms.

Longitudinal analyses of secondary outcomes

Multinational Association of Supportive Care in Cancer Antiemesis Tool: acute and delayed nausea

Acute and delayed nausea were both scored from 0 to 10 and were highly skewed with large proportions on the 0 extreme. For regression analysis new ordered factors with five levels were created as in *Table 24*.

TABLE 22 Odds ratios and CIs for nausea experience in cycle 1

Effect	OR estimate[a]	95% CI
Sham acupressure compared with none (men)	0.35	0.12 to 1.03
Sham acupressure compared with none (women)	2.02	1.19 to 3.42
Acupressure compared with none (men)	1.27	0.40 to 4.08
Acupressure compared with none (women)	1.17	0.70 to 1.95

a From a proportional odds model adjusting for gender, age group and emetogenic risk group.

TABLE 23 Odds ratio and CIs for nausea experience: longitudinal outcomes (i.e. cycle-averaged effects)

Effect	OR estimate[a]	95% CI
Sham acupressure compared with none (men)	0.66	0.29 to 1.48
Sham acupressure compared with none (women)	1.71	1.10 to 2.65
Acupressure compared with none (men)	1.47	0.59 to 3.68
Acupressure compared with none (women)	1.44	0.93 to 2.23

a From a proportional odds model (GEE fit) adjusting for gender, age group, emetogenic risk group and cycle.

TABLE 24 New ordered factors with five levels for regression analysis

Group	Score
None	0
Mild	1–3
Moderate	4–6
High	7–9
Severe	10

The regression analyses followed a similar approach to that employed for nausea experience measured using the Rhodes Index of Nausea, Vomiting and Retching scale as described earlier. For both outcomes there was no evidence of an arm by cycle interaction but both outcomes exhibited evidence of an arm by gender interaction. *Tables 25* and *26* show the arm effect estimates for acute and delayed nausea respectively.

Multinational Association of Supportive Care in Cancer Antiemesis Tool: acute and delayed vomiting

The mean (days 0–6) MAT vomiting experience data were highly skewed. The data were grouped 0, (0,1), (1,2), (2,3) and > 3. When analysed with a longitudinal proportional odds model there was no evidence of any trial arm effects ($p = 0.47$, Wald test).

The MAT scale acute vomiting data were recorded as the number of times vomiting occurred in the 24 hours since chemotherapy. Descriptively there was no difference between the trial arms. The MAT scale delayed vomiting data were recorded as the number of days on which vomiting occurred (0–4). When analysed with a longitudinal proportional odds model there was no evidence of any trial arm effects ($p = 0.69$, Wald test).

TABLE 25 Longitudinal outcomes – cycle-averaged effects for the MAT scale: acute nausea

Effect	OR estimate[a]	95% CI
Sham acupressure compared with none (men)	0.32	0.12 to 0.82
Sham acupressure compared with none (women)	1.62	1.04 to 2.53
Acupressure compared with none (men)	0.63	0.21 to 1.96
Acupressure compared with none (women)	1.27	0.82 to 1.96

a From a proportional odds model (GEE fit) adjusting for gender, age group, emetogenic risk group and cycle.

TABLE 26 Longitudinal outcomes – cycle-averaged effects for the MAT scale: delayed nausea

Effect	OR estimate[a]	95% CI
Sham acupressure compared with none (men)	0.54	0.21 to 1.40
Sham acupressure compared with none (women)	1.74	1.12 to 2.68
Acupressure compared with none (men)	0.99	0.37 to 2.69
Acupressure compared with none (women)	1.49	0.97 to 2.28

a From a proportional odds model (GEE fit) adjusting for gender, age group, emetogenic risk group and cycle.

Longitudinal analyses for nausea and vomiting using post hoc dichotomies

In previous analyses these outcomes were mapped to a 5-point ordinal scale and proportional odds models were fitted. In each case a test of the proportional odds assumption was made and found to be non-significant. Essentially that implies that the odds of a lower score for a variable (notably trial arm) does not depend on the particular cut point. Most cases have low scores for nausea and vomiting and it is felt that a simple dichotomy may give an adequate simpler description (*Tables 27–32* provide data for the Rhodes Index of Nausea, Vomiting and Retching and the MAT scale). Longitudinal binomial models were fitted (cycle + arm using the GEE approach) with a general working correlation structure and a Wald test employed using the robust covariance estimates to assess the trial arm effects. The reason for the dichotomies stated above is that the models for ordinal data typically consider the cumulative logits (CL), that is, the log-odds of a lower score. With the five categories used for the nausea outcome we consider four such CLs evaluated at the category upper limits:

$$\mathrm{CL}(y) = \log[\mathrm{Prob}(Y \leq y)/\mathrm{Prob}(Y > y)],\ y = 0,\ 2,\ 4,\ 6 \qquad (2)$$

In a regression context we aim to see how covariates affect these CLs. In an unconstrained model there would be a term for each covariate for each of the four response categories. Nausea experience and vomiting experience are each scored from 0 to 12, whereas MAT is scored from 0 to 10. All of these distributions are markedly skewed, with those for vomiting being even more skewed than those for nausea. Five categories were selected for each but the definitions of these were permitted to vary from variable to variable. As the proportional odds assumption was not violated for each variable, the results should not be too sensitive to the particular dichotomy used.

TABLE 27 Frequency of nausea per trial arm: Rhodes Index of Nausea, Vomiting and Retching nausea experience (days 0–6) = 0–2 inclusive

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	69/117 (59)	61/109 (56)	55/96 (57)	50/81 (62)
Sham bands	83/118 (70)	77/105 (73)	64/88 (73)	52/74 (70)
Acupressure bands	79/126 (63)	72/114 (63)	72/103 (70)	70/90 (78)

The Wald test for the arm effects gave $p = 0.08$ with the ORs of the lower score being estimated at 1.62 for sham acupressure and 1.46 for acupressure compared with no bands.

TABLE 28 Frequency of vomiting per trial arm: Rhodes Index of Nausea, Vomiting and Retching vomiting experience (days 0–6) = 0–1 inclusive

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	100/118 (85)	94/108 (87)	88/96 (92)	71/81 (88)
Sham bands	107/119 (90)	95/105 (90)	83/88 (94)	73/77 (95)
Acupressure bands	109/126 (87)	106/114 (93)	96/103 (93)	85/90 (94)

The Wald test for the arm effects gave $p = 0.19$ with the ORs of the lower score being estimated at 1.74 for sham acupressure and 1.46 for acupressure compared with no bands.

TABLE 29 Multinational Association of Supportive Care in Cancer Antiemesis Tool: acute nausea frequency per trial arm = 0–3 inclusive

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	83/117 (71)	84/110 (76)	76/96 (79)	61/81 (75)
Sham bands	98/120 (82)	92/106 (87)	74/89 (83)	65/79 (82)
Acupressure bands	101/130 (78)	93/116 (80)	80/102 (78)	73/88 (83)

The Wald test for the arm effects gave $p = 0.18$ with the ORs of the lower score being estimated at 1.60 for sham acupressure and 1.29 for acupressure compared with no bands.

TABLE 30 Multinational Association of Supportive Care in Cancer Antiemesis Tool: delayed nausea frequency per trial arm = 0–3 inclusive

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	73/118 (62)	66/105 (63)	65/93 (70)	55/79 (70)
Sham bands	86/116 (74)	78/105 (74)	68/89 (76)	60/78 (77)
Acupressure bands	88/128 (69)	85/116 (73)	75/102 (74)	71/86 (83)

The Wald test for the arm effects gave $p = 0.13$ with the ORs of the lower score being estimated at 1.51 for sham acupressure and 1.43 for acupressure compared with no bands.

TABLE 31 Multinational Association of Supportive Care in Cancer Antiemesis Tool: acute vomiting frequency per trial arm = 0

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	99/117 (85)	97/110 (88)	91/97 (94)	75/81 (93)
Sham bands	106/121 (88)	94/106 (89)	81/88 (92)	72/79 (91)
Acupressure bands	110/130 (85)	101/115 (88)	91/102 (89)	86/90 (96)

The Wald test for the arm effects gave $p = 0.98$, with the ORs of the lower score being estimated at 1.05 for sham acupressure and 1.00 for acupressure compared with no bands.

TABLE 32 Multinational Association of Supportive Care in Cancer Antiemesis Tool: delayed vomiting frequency per trial arm = 0

	Cycle 1, *n*/*N* (%)	Cycle 2, *n*/*N* (%)	Cycle 3, *n*/*N* (%)	Cycle 4, *n*/*N* (%)
None	99/119 (83)	94/106 (89)	86/93 (92)	71/80 (89)
Sham bands	103/117 (88)	98/105 (93)	80/89 (90)	71/78 (91)
Acupressure bands	108/128 (84)	104/116 (90)	90/101 (89)	80/86 (93)

The Wald test for the arm effects gave $p = 0.69$, with the ORs of the lower score being estimated at 1.28 for sham acupressure and 1.05 for acupressure compared with no bands.

Results for the Hospital Anxiety and Depression Scale and the Functional Assessment of Cancer Therapy – General scale

These two scales were assessed at baseline and at cycles 1–4. Longitudinal linear models were fitted (GEE approach using unstructured covariance matrices) to the cycles 1–4 data using the relevant baseline variable as a covariate along with factors representing cycle and arm. There was no evidence of any trial arm effects on mean values, as can be seen from *Table 33*.

Scale reliability

A descriptive measure of scale reliability (Cronbach's alpha) has been calculated at baseline. FACT scales may be calculated with four or more completed items; however, for Cronbach's alpha analysis all items must be completed. As can be seen in *Table 34*, all scales used in the study had very good reliability values.

Wristband audit

In total, 35 'wrist pairs' were observed during the months August–November 2010 in the outpatient departments at four trial sites (Royal Oldham Hospital, Macclesfield District General Hospital, Liverpool Royal Hospital and Clatterbridge Centre for Oncology).

The vast majority of observations indicated that both wristbands (i.e. on both left and right wrists) were being worn correctly. In two instances a patient was observed to be wearing only one of a pair of wristbands on arrival at the outpatient department, with one patient having a swollen left arm and the other patient having removed one wristband in advance of chemotherapy administration with the intention of wearing the wristband after the chemotherapy had been given. Eight patients were not

TABLE 33 Analysis of Hospital Anxiety and Depression Scale and FACT-G scale data by trial arm

Variable	Scale	Cycle×arm *p*-value (model 1)[a]	Arm *p*-value (model 2)[b]	Sham bands[c]	Acupressure bands[c]
Anxiety	0–21	0.34	0.48	0.11 (0.38)	–0.35 (0.37)
Depression	0–21	0.15	0.40	0.02 (0.37)	0.45 (0.36)
PWB	0–28	0.07	0.71	0.48 (0.67)	0.02 (0.66)
SFWB	0–28	0.37	0.82	–0.13 (0.46)	–0.24 (0.39)
EWB	0–24	0.80	0.77	0.05 (0.39)	0.26 (0.38)
FWB	0–28	0.39	0.86	0.11 (0.68)	0.35 (0.65)
FACT-G	0–108	0.71	0.81	0.92 (1.67)	–0.06 (1.62)

EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SFWB, social well-being.

a Wald test from a *y*.baseline + cycle×arm model.

b Wald test from a *y*.baseline + cycle + arm model.

c The estimated difference in means from the 'None' group from model (2) with standard errors in parentheses. These effects are very small and non-significant.

TABLE 34 Cronbach's alpha reliability of the scales used in the trial for the current sample

Scale	Number of items	Time point	*n* complete	Cronbach's alpha
Rhodes Index of Nausea, Vomiting and Retching nausea experience	3	Cycle 1 day 1 (day following CT)	356	0.915
Rhodes Index of Nausea, Vomiting and Retching vomiting experience	3	Cycle 1 day 1 (day following CT)	358	0.883
Hospital Anxiety and Depression Scale: anxiety	7	Baseline	414	0.884
Hospital Anxiety and Depression Scale: depression	7	Baseline	420	0.824
FACT-G: PWB	7	Baseline	381	0.742
FACT-G: SFWB	7	Baseline	215	0.777
FACT-G: SFWB	6[a]	Baseline	377	0.844
FACT-G: EWB	6	Baseline	397	0.790
FACT-G: FWB	7	Baseline	354	0.863
FACT-G from four subscales	4	Baseline	363	0.743

CT, chemotherapy; EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SFWB, social well-being.

a Omitting sex-life question.

wearing their wristbands, with one patient having swollen hands and the remaining seven patients stating that they intended to wear their wristbands after chemotherapy had been administered. Three patients who were using spare wristbands offered to them by the research nurse correctly demonstrated their use.

Only four of the 68 wristbands observed (i.e. for left and right wrists) were positioned incorrectly. Three of these were worn incorrectly on the right wrist and one was worn incorrectly on the left wrist. *Figure 7* shows the distribution of wristband observations.

The condition of the wristbands was also noted by the research nurses for a total of 25 pairs. Six wristbands were in poor condition: two pairs of wristbands (one pair being worn for the fourth cycle of chemotherapy and one pair being worn for the second cycle of chemotherapy) were in generally poor condition and one pair of wristbands being worn for the third cycle of chemotherapy had loose acupressure buttons on both bands. All of these bands were replaced. In total, 22 pairs of wristbands were recorded as being in good condition.

Side effects from wearing the wristbands

A small number of patients in the trial reported problems with wearing their wristbands:

- One patient stated that the wristbands felt 'too tight' – this patient was offered larger wristbands and was advised not to continue wearing the bands if the large bands also felt tight.
- Six patients reported that their hands and/or arms had become swollen after receiving chemotherapy – two of these patients wanted to try wearing larger bands but all patients were advised not to wear the bands while the swelling persisted.
- One patient reported a painful arm after receiving chemotherapy, which made wearing the wristband uncomfortable – this patient was advised not to wear the wristband on the painful arm until the pain had subsided.
- One patient reported some swelling of their arms after wearing the wristbands – this patient was advised not to wear the wristbands but was also advised to attempt to wear the wristbands at a later stage once the swelling had subsided but to discontinue using the wristbands if swelling occurred on the second attempt to wear the bands.
- Two patients stated that they had experienced some 'irritation' from wearing the wristbands – both patients were advised to discontinue wearing them.
- Two patients stated that they had experienced some 'sensitivity' to the wristbands – both patients were advised to discontinue wearing them.
- One patient reported experiencing 'intolerance' to wearing the wristbands – the patient was advised to discontinue wearing them.
- One patient reported that the wristbands felt 'uncomfortable' – this patient was offered a pair of large-sized wristbands but these still felt 'uncomfortable' and so the patient was advised to stop wearing them.

In all of the cases above, patients were reminded to complete their wristband compliance questionnaires accordingly.

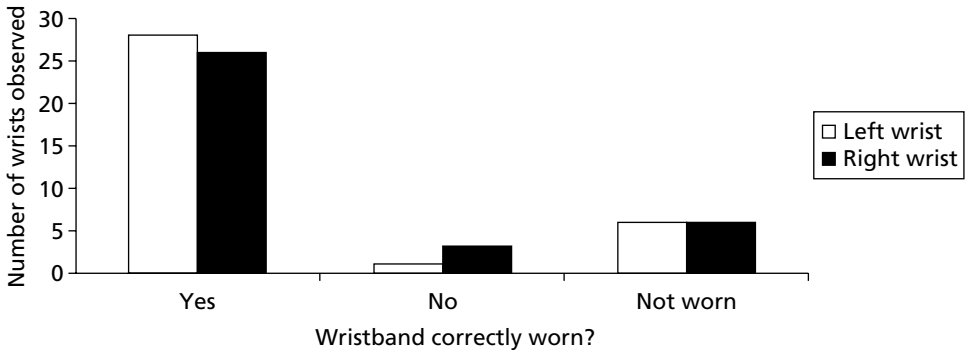

FIGURE 7 Wristband observations during the audit ($n = 70$).

Chapter 5 Health economics data

Context of the data

Aim and perspective

The aim was to assess the cost-effectiveness of self-acupressure using wristbands in addition to standard care compared with standard care with sham acupressure wristbands and standard care alone in the management of chemotherapy-induced (acute and delayed) nausea. The study adopted a NHS perspective in relation to cost evaluation to inform health policy relating to the use of acupressure bands in chemotherapy patients. A societal perspective for costs was adopted for sensitivity analysis. Reporting made reference to economic evaluation good practice.[62]

Time frame

Costs and benefits were calculated for the study period (four cycles of chemotherapy) only, which was 21 days. As the trial has a time frame of less than a year neither costs nor benefits were discounted.

Resource use and costs

Resource-use data collected in the trial and unit costs are presented in *Appendix 11*. These include number of visits to the GP, practice nurse, pharmacist, health visitor and specialist nurse, number of consultations during hospital stays and medication use.

Data were collected prospectively and retrospectively using multiple sources including patient records and patient self-reported questionnaires. The questionnaires report health service utilisation subsequent to and as a result of chemotherapy-induced nausea and vomiting. Direct medical costs incurred by the NHS and social services are defined as the costs of prophylactic or rescue antiemetic medications, drug administration devices, staff time associated with preparing and administering medication and tending to patients with chemotherapy-induced nausea and vomiting, hospitalisations due to chemotherapy-induced nausea and vomiting and hospital outpatient or GP visits due to chemotherapy-induced nausea and vomiting. The analysis did not include costs for chemotherapy agents, preplanned visits or hospitalisations for the purpose of chemotherapy administration and diagnostic and laboratory tests, and other patient management costs not directly related to chemotherapy-induced nausea and vomiting. The resource-use questionnaire completed by patients asked them to record only health service resource usage that was as a result of chemotherapy-related nausea or vomiting.

Appendix 12 lists each of the drugs that were prescribed within the study. The Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT)[63] was used to cost the drugs; however, when drugs were not listed on eMIT, costs were taken from the *British National Formulary* (BNF).[64] Expert opinion was elicited on the standard practice for antiemetics during chemotherapy and the standard dose for each of the drugs. As Zofran is the brand name of ondansetron we used this (higher) cost only when it was stated that Zofran was prescribed. All other ondansetron prescriptions were costed at the eMIT price for ondansetron.

The total cost of each arm of the trial is calculated by combining the resource use and unit cost data along with the cost of drugs and the price of the acupressure band. There were a number of assumptions that were made when analysing the cost data. The cost of the sham acupressure band was assumed to be the same as the cost of the acupressure band. If the patient did not fill in the resource-use form (left it blank), we assumed that the data were missing. Hospitalisations that led to one face-to-face contact were assumed to represent a short stay and those with more than one face-to-face contact were assumed to represent a long stay.

Assumptions relating to the reported medication use are indicated in the following section.

Assumptions made on antiemetic use

- All patients received a standard care:
  - moderate/high emetogenic risk: domperidone 20 mg four times a day for 7 days; ondansetron 8 mg intravenously on day of chemotherapy, 8 mg orally twice a day for 3 days; dexamethasone 8 mg intravenously on day of chemotherapy, 8 mg orally for 1 day, 4 mg for 1 day, 2 mg for 1 day.
  - low emetogenic risk: domperidone 20 mg four times a day for 7 days.
- Prolonged course = double the number of days on the antiemetic.
- If form stated 'as required' = 7 days on stated drug.
- Assumed that all medication was tablet form unless stated.
- When medication details were not provided (only 'antiemetics given' stated), assumed standard care.
- When doses were not recorded expert opinion was used on average normal dose of each drug.
- If not stated assume that next cycle is the same as the previous cycle.

Societal costs

Costs from the societal perspective were calculated by combining productivity loss and loss of earnings due to work absence and out-of-pocket expenses incurred as a result of chemotherapy-induced nausea and vomiting. For productivity loss we employed a human capital approach using the gross median weekly pay rate (£499) for full-time employees from the 2010 Annual Survey of Hours and Earnings[65] and divided this by five. This was then reduced to 80% to represent the fact that absence from work will not lead to a proportionate loss of productivity,[66] giving a daily productivity loss cost of £79.84. As there were a lot of missing data it was assumed that these reflected zero costs incurred.

Outcome measurement and valuation

Participant health-related quality of life was assessed using the European Quality of Life-5 Dimensions (EQ-5D),[67] which was included along with the patient resource-use questionnaires. Differences between the randomised groups at follow-up with respect to EQ-5D scores were investigated using non-parametric Mann–Whitney *U*-tests as the data were not normally distributed. Change scores over time were evaluated using independent *t*-tests.

Participant responses to the EQ-5D questionnaire were converted to health-state utility values using the UK tariff values[68] and an area under the curve approach. These values were then multiplied by duration (21 days) in each health state and divided by 365 to estimate QALYs. QALYs represent a quality-weighted survival value in which 1 QALY is the equivalent of 1 year of full health. Average QALYs between adjacent time points were calculated to generate smoothed estimates between time points. QALYs were calculated as:

$$\begin{aligned}\text{Total QALYs} = {} & ((\text{EQ5D\_T1} \times 21) + (\text{EQ5D\_T2m} \times 21)/2) + ((\text{EQ5D\_T2m} \times 21) \\ & + (\text{EQ5D\_T3m} \times 21)/2) + ((\text{EQ5D\_T3m} \times 21) + (\text{EQ5D\_T4m} \times 21)/2) \\ & + ((\text{EQ5D\_T4m} \times 21) + (\text{EQ5D\_T5m} \times 21)/2))/365 \end{aligned} \quad (3)$$

where T1, T2m, T3m, T4m and T5m are time points of assessment in the trial, that is, baseline and end of cycles 1, 2, 3 and 4 respectively.

Missing data

Respondents who fail to complete individual items of the EQ-5D are not allocated a utility index score.

The last observation carried forward (LOCF) method was employed to deal with missing time point data. In this trial there were four cycles of chemotherapy after the baseline observation. If a patient dropped out of the study after the third week, this value was then 'carried forward' and assumed to be the score for

the fourth cycle missing data point. Similarly, if a patient dropped out after baseline this value was carried forward to the first cycle of chemotherapy. Scores were carried forward to one consecutive time point only. Patients in whom more than one consecutive score was missing were omitted from the analyses. Scores were not carried backwards – that is, those without baseline scores did not have their first follow-up score carried backwards. The advantage of the LOCF approach is that it minimises the number of subjects who are eliminated from the analysis and it allows the analysis to examine the trends over time, rather than focusing simply on the end point. Assuming that scores are expected to improve over time, LOCF may be a conservative way of dealing with missing data. A full case analysis was conducted in the sensitivity analyses in which participants were excluded if they had missing scores from any time point.

We used the same method for missing resource-use data, carrying forward the last observation only once if there were missing data for the next time point. Patients were omitted from the analyses if they had more than one missing time point.

Economic evaluation

Descriptive statistics of costs and EQ-5D scores were calculated by subgroup. Parametric tests (Student's *t*-tests and ANOVA tests) and non-parametric tests (Wilcoxon signed-rank tests, Mann–Whitney tests and Kruskal–Wallis ANOVA tests) were conducted to evaluate differences in individual characteristics and health-related quality-of-life scores between groups. Mann–Whitney *U*-tests were used to evaluate the significance of differences in costs between groups as this test is less likely to be influenced by outliers. For the economic evaluation only costs of patients who had a QALY value were included.

The outcome of the cost-effectiveness analysis was an incremental cost per QALY.[61,69] We present incremental cost-effectiveness ratios (ICERs)[61,69] representing the ratios of the incremental cost and incremental benefits (QALYs) between acupressure and sham acupressure, between acupressure and standard care and between sham acupressure and standard care. The ICER represents the additional cost per one unit of outcome gained, in this case per QALY gained for each intervention compared with its next best alternative. As a guideline rule, the National Institute for Health and Clinical Excellence (NICE) accepts as cost-effective those interventions with an ICER of $<$ £20,000 per QALY. NICE states that, in general, if a treatment costs $>$ £30,000 per QALY it would not be considered cost-effective. We also present cost-effectiveness plane scatter plots illustrating the uncertainty surrounding the cost-effectiveness estimates.

The cost-effectiveness planes were derived using bootstrapping with replacement. This stochastic uncertainty analysis involved running 10,000 bootstrapped estimates of the incremental costs and QALYs. The bootstrap approach is a non-parametric method that treats the original sample as though it were the population and draws multiple random samples from the original sample. Cost-effectiveness acceptability curves were also generated to illustrate the probability that each treatment would be cost-effective given a range of acceptable threshold values.[70]

Sensitivity analyses were carried out to account for uncertainty in the cost and EQ-5D values. We performed the sensitivity analysis by adding and subtracting 20% of the costs and assessing the subsequent impact on the ICERs. The value of 20% is essentially arbitrary but it was considered likely to represent any uncertainty that might exist in parameter values. We performed a sensitivity analysis on the QALYs by conducting a full-case analysis on EQ-5D scores. In contrast to the LOCF, no missing data are imputed and patients with any missing data are omitted from the analyses. Sensitivity analyses were also carried out based on using an average group cost for those outliers with high costs and by adopting a societal perspective for costs, including productivity losses and lost earnings.

Net benefit values[71] were generated to enable more traditional analysis of therapy efficacy. Net benefit is a composite representation of cost-effectiveness and willingness to pay that is derived by rearranging the

ICER calculation and incorporating the willingness-to-pay threshold value (in this case the £20,000 per incremental QALY threshold of NICE). Net monetary benefit (NMB) is derived for each patient as:

$$\text{NMB} = (20{,}000 \times \text{QALYs}) - \text{costs} \quad (4)$$

The decision rule becomes to adopt an intervention if the NMB > 0. Because values are transformed from ratio to linear we can subsequently employ standard regression models on the data. Net benefit regression allows us to control for covariates and baseline between-group differences.[72] We applied the variables used for the primary end point regression analyses to NMB data with treatment arm included as an independent variable. Univariate ANOVA and linear regression models were generated.

Results

Data from 450 patients (157 acupressure, 146 standard care, 147 sham acupressure) were included in the base-case analysis.

Resource use and costs

There was very little reported resource use within the trial; thus, caution should be exercised in interpreting the results as a small number of high-resource-use consumers or a few instances of high-cost resource use may be unduly influencing the overall results. *Table 35* shows the number of times each of the health service resources was used by trial arm. The acupressure group used the fewest resources and the standard care group used the most.

In terms of the total NHS resource-use cost, the acupressure group used the least number of resources and also had the lowest cost. Mean total drug costs (including antiemetics and other drugs prescribed for chemotherapy-induced nausea and vomiting and antiemetic use outside of the routine pathway in each arm of the trial) for the groups were £37.07 (SD £101.72) for the acupressure group, £51.66 (SD £150.02) for the standard care group and £24.03 (SD £18.70) for the sham acupressure group. Mean total costs (drug costs plus all other NHS costs plus band costs) for the acupressure group were lower than those for the standard care group or the sham acupressure group (*Table 36*). 'All other NHS costs' include the resource use from *Table 35*. The NHS costs for the sham group appear higher than those for the other groups and this seems to be driven by a higher number of district nurse visits and a few patients in the

TABLE 35 Resource use by the trial participants

Services	Acupressure	Standard care	Sham acupressure
GP surgery visit	5	6	5
GP home visit	3	4	3
District nurse	4	11	17
Contact with oncology hotline for advice	6	11	9
Contact with hospital oncology nurse clinician for advice	9	9	6
Contact with hospital oncology clinic for advice	5	8	7
Hospital inpatient stay	10	14	9
Hospital A&E department	3	1	2
Hospital general outpatient clinic	1	0	2
Other services	3	1	1
Total instances of resource use	49	65	61

TABLE 36 Costs per arm of the trial

	Acupressure (£), mean (SD)	Standard care (£), mean (SD)	Sham acupressure (£), mean (SD)
n	72	62	60
Drug cost – cycle 1	5.47 (1.40)	5.60 (0.65)	5.17 (1.55)
Drug cost – cycle 2	11.71 (36.35)	15.36 (50.43)	5.15 (1.55)
Drug cost – cycle 3	9.92 (33.34)	15.39 (49.77)	6.86 (8.86)
Drug cost – cycle 4	9.96 (33.34)	15.31 (49.80)	6.86 (8.86)
Total drug cost	37.07 (101.72)	51.66 (150.02)	24.03 (18.70)
All other NHS costs – baseline	2.92 (17.56)	0.05 (0.0)	17.29 (124.90)
All other NHS costs – cycle 1	8.52 (34.91)	21.73 (76.90)	9.35 (38.74)
All other NHS costs – cycle 2	9.78 (44.44)	9.18 (44.48)	13.27 (86.59)
All other NHS costs – cycle 3	4.17 (25.80)	16.06 (73.89)	52.13 (303.28)
All other NHS costs – cycle 4	0.0 (0.0)	12.50 (80.47)	37.66 (283.54)
All other NHS costs total	25.39 (81.07)	59.52 (171.78)	129.69 (604.28)
Band cost	8.20 (0.00)	0.00 (0.00)	8.20 (0.00)
Total cost	70.66 (129.75)	111.18 (262.68)	161.92 (604.57)

sham arm of the trial having longer inpatient stays. There were no significant differences in costs between any of the treatment arms according to the *t*-tests; this was true for the whole sample as well as for the subsample who also had QALY data. Mean values were distorted by a small number of high-cost outlying patients leading to high levels of uncertainty around the mean cost estimates. Median total costs were £30.92, £22.72 and £30.92 for the acupressure, standard care and sham acupressure groups respectively. Mann–Whitney tests indicated that the standard care group had significantly lower total costs than the acupressure and sham acupressure groups (both $p < 0.001$); there was no significant difference in costs between the acupressure and sham acupressure groups ($p = 0.585$). No adjustments for multiple testing were considered necessary. *Figure 8* shows the cost distribution for the standard care group and illustrates the presence of a small number of high-cost outliers. A similar pattern was observed for the other two treatment arms.

Table 37 includes costs from the societal perspective. Lost earnings and productivity losses to employers through sickness absence appeared higher in the standard care group than in either of the band groups. Overall societal costs are similar for the band groups and significantly higher (over double) for the standard care group. However, as with the health-care costs, this result is partly driven by a small number of high-cost outlying individuals, making robust conclusions difficult.

Utility data

Tables 38 and *39* show the numbers of valid and missing EQ-5D questionnaires for each cycle between the three arms of the study when no scores are imputed and when values are imputed respectively. Mean EQ-5D scores are included for each cycle. Both the acupressure and sham acupressure groups showed a slight increase in EQ-5D from baseline to cycle 4 of chemotherapy, whereas the standard care group showed a slight decrease. In general, the results indicate small fluctuations in utility values throughout the trial period and four chemotherapy cycles, making it difficult to draw conclusions about the impact of chemotherapy-induced nausea and vomiting and its treatments on generic health-related quality of life. All of the observed changes were below the minimally important difference for the EQ-5D (which is estimated to range from 0.1 to 0.12[73]). *Table 40* provides the mean EQ-5D change scores between baseline and the follow-up points for the LOCF analysis; these were the values employed in the QALY

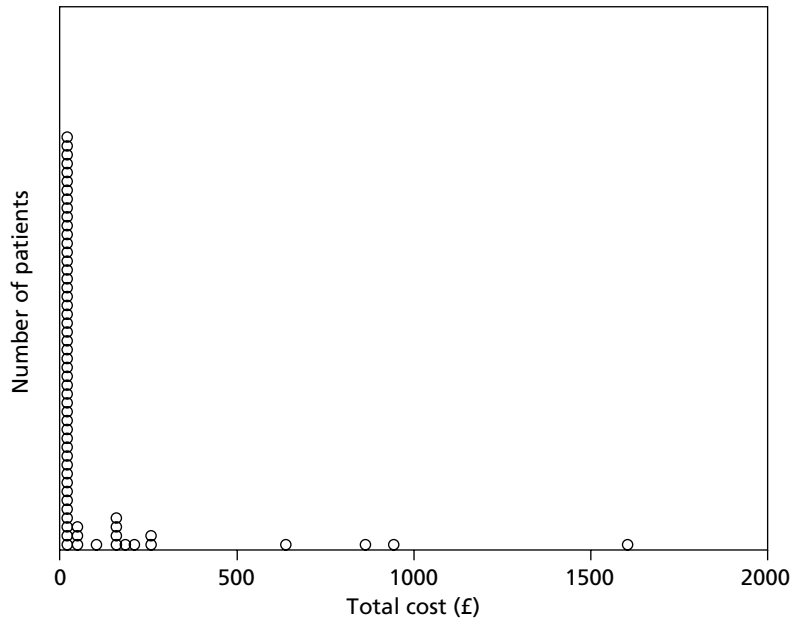

FIGURE 8 Total cost distribution for the standard care group.

TABLE 37 Societal costs

	Acupressure (£), mean (SD)	Standard care (£), mean (SD)	Sham acupressure (£), mean (SD)
n	72	62	60
Total days out of work	1.18 (6.77)	2.82 (9.89)	0.75 (3.45)
Total lost earnings	54.17 (391.44)	241.42 (1068.43)	31.50 (244.00)
Total expenditure	0.18 (1.15)	0.10 (0.53)	0.00 (0.00)
Social cost – baseline	0.00 (0.00)	19.82 (104.46)	0.00 (0.00)
Social cost – cycle 1	48.95 (255.68)	226.73 (922.55)	19.89 (101.05)
Social cost – cycle 2	52.70 (329.40)	97.17 (347.41)	25.21 (112.07)
Social cost – cycle 3	46.95 (374.77)	69.77 (295.67)	27.80 (159.23)
Social cost – cycle 4	0.00 (0.00)	53.37 (286.99)	18.48 (143.18)
Total social cost	148.60 (925.90)	466.87 (1490.27)	91.38 (472.80)
Total societal costs (social cost + health-care costs)	219.26 (983.56)	578.00 (1557.79)	253.30 (760.40)

calculations. Independent sample *t*-tests indicated that the changes in EQ-5D score over time were not statistically significant.

Statistical tests indicated that there were no significant differences between EQ-5D scores at baseline for the three treatment arms. This being the case, baseline adjustments were not required. At baseline 10.0% (7/70) of the missing EQ-5D values were excluded as a result of one missing response on the questionnaire; 3.6% (5/140) of the missing values in cycle 1 were due to missing one response, 1.6% (3/192) in cycle 2 were missing one response, 0.9% (2/229) in cycle 3 were missing one response and 0.3% (1/313) in cycle 4 were missing one response.

TABLE 38 Mean EQ-5D scores: full-case scenario

Time point		Acupressure	Standard care	Sham acupressure
EQ-5D baseline	Mean (SD) EQ-5D score	0.764 (0.226)	0.775 (0.210)	0.774 (0.246)
	n valid (missing)	133 (24)	126 (20)	121 (26)
EQ-5D cycle 1	Mean (SD) EQ-5D score	0.778 (0.215)	0.784 (0.244)	0.788 (0.254)
	n valid (missing)	110 (47)	101 (45)	99 (48)
EQ-5D cycle 2	Mean (SD) EQ-5D score	0.788 (0.190)	0.764 (0.253)	0.799 (0.209)
	n valid (missing)	93 (64)	89 (57)	76 (71)
EQ-5D cycle 3	Mean (SD) EQ-5D score	0.732 (0.334)	0.748 (0.237)	0.806 (0.249)
	n valid (missing)	79 (78)	72 (74)	70 (77)
EQ-5D cycle 4	Mean (SD) EQ-5D score	0.806 (0.176)	0.752 (0.255)	0.820 (0.266)
	n valid (missing)	53 (104)	40 (106)	44 (103)

TABLE 39 Mean EQ-5D scores: LOCF imputed values

Time point		Acupressure	Standard care	Sham acupressure
EQ-5D baseline	Mean (SD) EQ-5D score	0.764 (0.226)	0.775 (0.210)	0.774 (0.246)
	n valid (missing)	133 (24)	126 (20)	121 (26)
EQ-5D cycle 1	Mean (SD) EQ-5D score	0.748 (0.244)	0.765 (0.244)	0.785 (0.265)
	n valid (missing)	148 (9)	141 (5)	138 (9)
EQ-5D cycle 2	Mean (SD) EQ-5D score	0.776 (0.217)	0.763 (0.252)	0.779 (0.255)
	n valid (missing)	111 (46)	103 (43)	104 (43)
EQ-5D cycle 3	Mean (SD) EQ-5D score	0.735 (0.314)	0.746 (0.249)	0.797 (0.258)
	n valid (missing)	96 (61)	92 (54)	77 (70)
EQ-5D cycle 4	Mean(SD)	0.763 (0.291)	0.749 (0.245)	0.806 (0.246)
	n valid (missing)	81 (76)	73 (73)	71 (76)

TABLE 40 Mean EQ-5D change between baseline and follow-up points for the three arms of the trial

Time point		Acupressure[a]	Standard care[a]	Sham acupressure[a]
Baseline to cycle 1	Mean	–0.0086	–0.0113	0.0209
	n	133	126	121
Baseline to cycle 2	Mean	–0.0186	–0.0503	0.0170
	n	96	88	86
Baseline to cycle 3	Mean	–0.0639	–0.0637	–0.0144
	n	85	79	66
Baseline to cycle 4	Mean	–0.0401	–0.0649	0.0050
	n	74	63	60

a A negative value is a deterioration in quality of life.

Economic evaluation results regarding quality-adjusted life-year gains

Table 41 shows the total costs and QALY gains for each of the three treatment arms. Differences in QALY gains between groups were minimal and suggest only negligible health benefits of acupressure over standard care. The sham acupressure group had the highest QALY gains over the trial period with the standard care group having the lowest. The mean total cost was highest for the sham acupressure group and lowest for the acupressure group. The high SDs for the cost estimates indicate the presence of a few outlying individuals who incurred significant health service costs.

Table 42 provides the cost-effectiveness results, showing the incremental costs and benefits as well as the ICERs for each arm of the trial. Interpretation should be tempered by considering the high level of uncertainty surrounding the cost estimates and the negligible between-group differences observed in QALY gains. The standard care group was dominated by acupressure as it had higher costs and lower QALY gains. The results suggest that acupressure might be cost saving compared with standard care alone. The acupressure group had lower costs than the sham acupressure group; however, the sham group had higher, albeit negligible, QALY gains.

Table 43 shows the sensitivity analyses that were carried out as well as the results from the non-parametric bootstrapping. The analysis adding 20% to the costs supports the base-case analysis as acupressure still dominates the standard care group. Subgroup analyses by emetogenic risk group were not possible as a very small proportion of patients was rated as high or low emetogenic risk and a large majority was rated as moderate.

Including only patients who had completed EQ-5D scores at every time point did not significantly change the ICER. The mean cost and QALY gain estimates from the bootstrapping yield similar ICER results to those of the deterministic base-case scenario. Acupressure still dominates standard care only and is cheaper but marginally less effective than sham acupressure. Excluding cost outliers or including societal costs does not alter the outcome of the key comparisons.

Figures 9 and *10* are cost-effectiveness planes for acupressure compared with standard care and acupressure compared with sham acupressure respectively. For acupressure compared with standard care (see *Figure 9*), the 1000 sample estimates are spread mainly in the south-east and south-west quadrants, suggesting that acupressure is likely to be cost saving. A high proportion of iteration results are in the south-east quadrant suggesting that acupressure is also likely to lead to a higher quality of life; however, QALY gains are minimal. For acupressure compared with sham acupressure (see *Figure 10*), most of the

TABLE 41 Total costs and QALY gains by treatment arm

	Acupressure, mean (SD)	Standard care, mean (SD)	Sham acupressure, mean (SD)
n	72	62	60
Total QALY gain	0.270 (0.062)	0.265 (0.072)	0.283 (0.058)
Total cost (£)	70.66 (129.75)	111.13 (262.68)	161.92 (604.57)

TABLE 42 Cost-effectiveness results

Analysis	Incremental cost (£)	Incremental QALY gain	ICER (£)
Acupressure vs standard care	–40.47	0.005	–7494.44 (acupressure dominates)
Acupressure vs sham acupressure	–91.26	–0.012	7359.68
Sham acupressure vs standard care	50.79	0.018	2853.37

TABLE 43 Sensitivity analyses

Analysis	Incremental cost (£)	Incremental QALY gain	ICER (£)
+20% of costs			
Acupressure vs standard care	–48.56	0.005	–8993.33 (acupressure dominates)
Acupressure vs sham acupressure	–109.51	–0.012	8831.61
Sham acupressure vs standard care	60.95	0.018	3424.04
–20% of costs			
Acupressure vs standard care	–32.38	0.005	–5995.56 (acupressure dominates)
Acupressure vs sham acupressure	–73.01	–0.012	5887.74
Sham acupressure vs standard care	40.63	0.018	2282.70
EQ-5D full-case scenario			
Acupressure vs standard care	–111.51	0.009	–12,319.31 (acupressure dominates)
Acupressure vs sham acupressure	–153.92	–0.018	8538.87
Sham acupressure vs standard care	42.41	0.027	1566.25
Excluding cost outliers			
Acupressure vs standard care	–7.58	0.005	–1403.70
Acupressure vs sham acupressure	–9.68	–0.012	780.65
Sham acupressure vs standard care	2.10	0.018	117.98
Societal cost perspective			
Acupressure vs standard care	–358.74	0.005	–66,433.33 (acupressure dominates)
Acupressure vs sham acupressure	–34.04	–0.012	2745.16
Sham acupressure vs standard care	–324.70	0.018	–18,241.57 (sham acupressure dominates)
Bootstrapping			
Acupressure vs standard care	–40.64	0.005	–9025.53 (acupressure dominates)
Acupressure vs sham acupressure	–90.26	–0.013	7163.27

sample iterations lie in the south-west quadrant, suggesting that acupressure is less effective (leads to reduced quality of life) than sham acupressure but leads to cost savings.

Figures 11 and *12* are the cost-effectiveness acceptability curves showing the probability that each treatment is a cost-effective choice given a range of cost-effectiveness willingness-to-pay thresholds. *Figure 11* compares standard care with acupressure. Using the NICE threshold of £20,000 the probability that acupressure is cost-effective is 0.70 compared with standard care. *Figure 12* compares all three treatments. At the NICE threshold of £20,000, sham acupressure appears more likely to be the cost-effective option ($p = 0.71$) than acupressure ($p = 0.20$). Only at low willingness-to-pay thresholds (< £7000) does acupressure become the most likely option to be cost-effective. However, considering the negligible QALY gains observed in the study, the low levels of resource use, the low median health-care costs and the leverage of a few high-cost outliers, any results must be treated with caution. It is difficult to make robust claims about the comparative cost-effectiveness of any of the therapy arms.

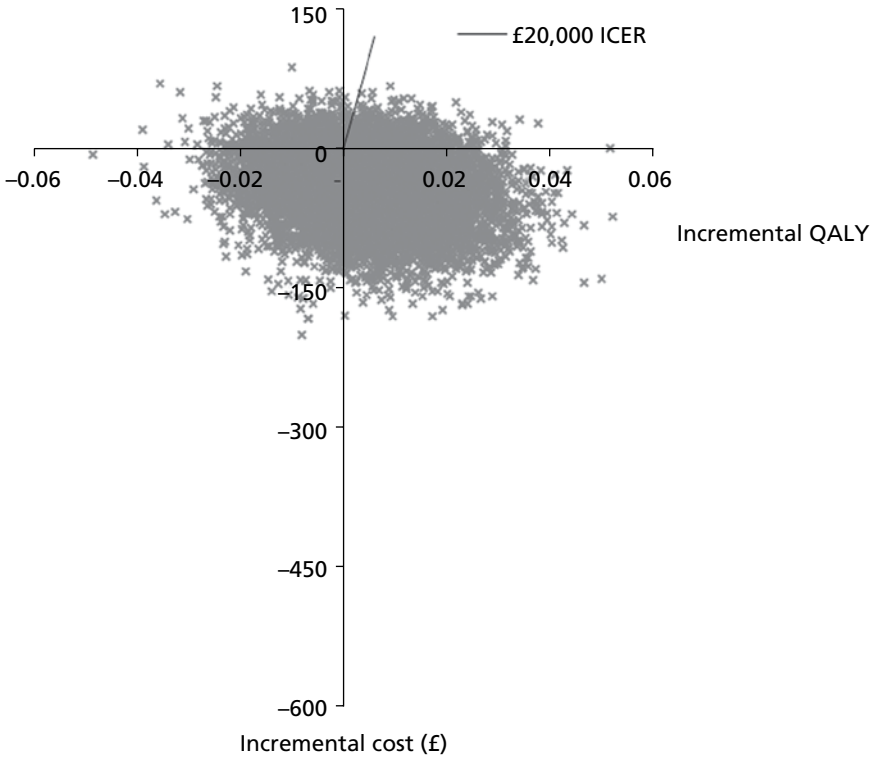

FIGURE 9 Cost-effectiveness plane for acupressure compared with standard care.

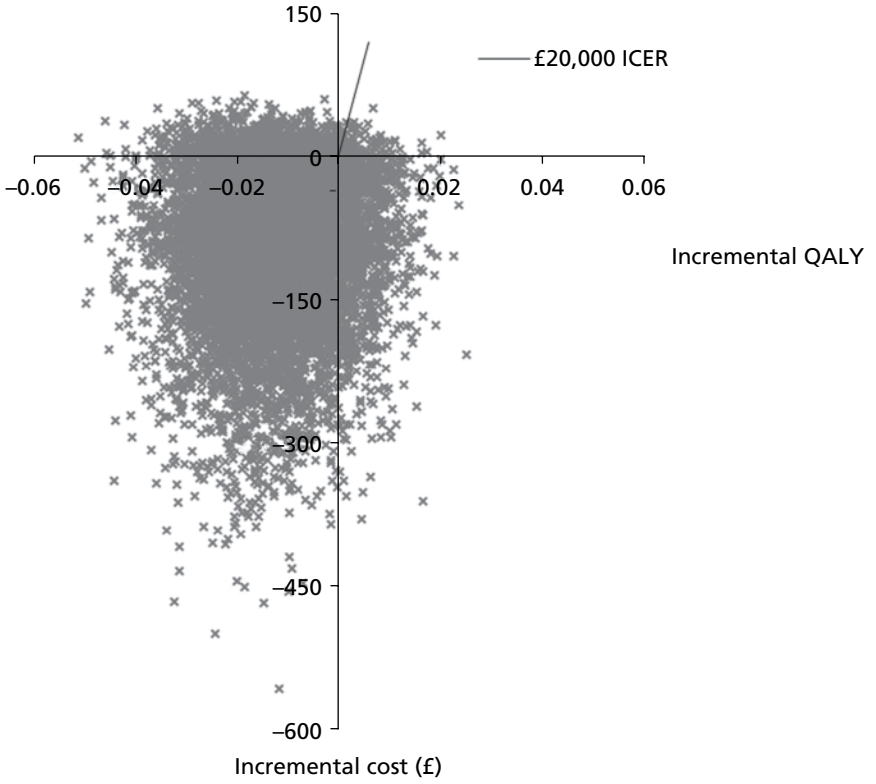

FIGURE 10 Cost-effectiveness plane for acupressure compared with sham acupressure.

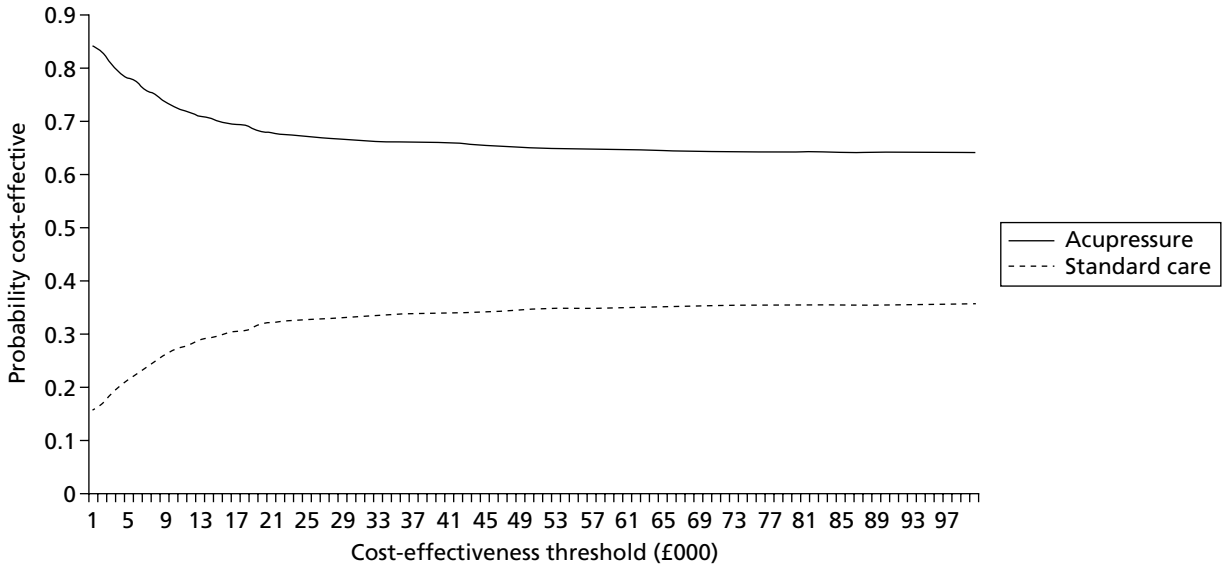

FIGURE 11 Cost-effectiveness acceptability curves for acupressure compared with standard care.

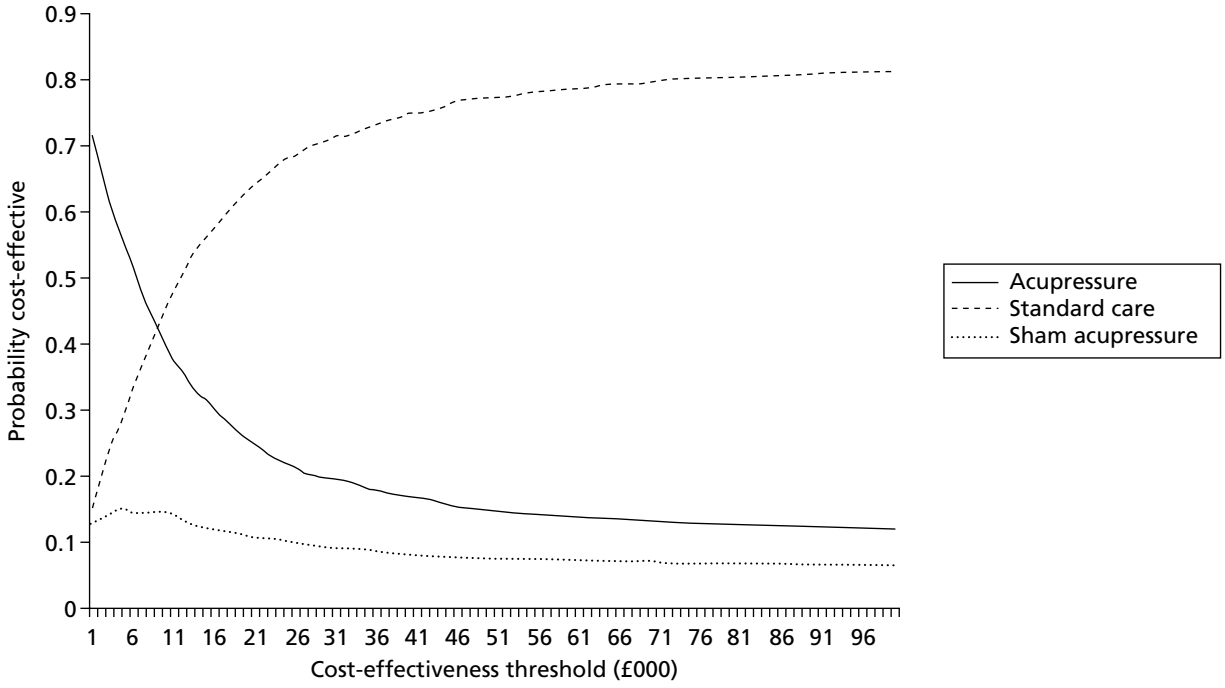

FIGURE 12 Cost-effectiveness acceptability curves for all three treatments.

Net monetary benefit

Net monetary benefit was calculated for each patient and was found to be generally positive. NMB means (SD) were 5333 (1288), 5184 (1521) and 5489 (1261) for acupressure, standard care and sham acupressure respectively. Univariate ANOVA and linear regression models using age group, gender, emetogenic risk group, treatment allocation and baseline EQ-5D scores as covariates and independent variables were run to predict NMB.

Treatment allocation was not found to be a significant predictor of NMB. Only baseline EQ-5D score was found to be a significant contributor to the models. This is unsurprising as NMB is based partially on QALY values derived from the EQ-5D.

Chapter 6 Qualitative data

Objectives

- To outline patients' experiences of using acupressure wristbands.
- To outline the reasons why patients consent to take part in a clinical trial of acupressure wristbands.
- To outline patients' experiences of taking part in a randomised controlled trial of acupressure wristbands.

Findings

Sample

A total of 26 patients participated. Nine patients were recruited from Greater Manchester, nine from Merseyside and eight from Plymouth; in total, 10 patients had received true acupressure, nine had received sham acupressure and seven had not received any acupressure. The age range of the patients was 35–79 years (mean 55 years) and seven were male and 19 were female. Nine of the sample were classified as receiving chemotherapy of high emetogenic potential, 12 as receiving chemotherapy of medium emetogenic potential and five as receiving chemotherapy of low emetogenic potential. How much nausea participants expected to experience during their chemotherapy treatment ranged from 0 to 10 (mean 5.8), with 0 being 'not at all' and 10 being 'very frequently'; participants' belief that the acupressure wristbands would help manage their sickness ranged from 2 to 10 (mean 6.9), with 0 being 'not at all' and 10 being 'will help me a lot'.

Themes

Deciding to participate

The majority of patients indicated that, after the initial approach by members of the research team, the decision to participate was immediate. In the time before consenting to take part (24+ hours), most did, however, discuss their intention to participate with significant others, typically partners and close family. Interestingly, patients attending one hospital appear to have been informed that if they participated in clinical trials it generated additional funds for the hospital, which appears to have influenced some patients to participate.

> *Well part of it he [consultant] did say that obviously it would be useful but also at the same time he did explain that obviously the more people that took part then you know it helped their side of things as well, like it got funded or something.*
>
> *P318*

> *I didn't hesitate.*
>
> *P382*

Patients identified a range of factors influencing their decision to participate in the trial of acupressure wristbands. Undoubtedly the main motivational factor influencing patients was a desire to 'give something back'. Almost all participants expressed an awareness of the fact that, without the willingness of patients to engage in research studies, it would be impossible for cancer care treatments and services to advance. In particular, it was the altruistic act of attempting to improve the care of future cancer patients that motivated patients to assist in evaluating whether or not acupressure wristbands are effective for chemotherapy-related nausea and vomiting.

> *My reasons were as I'd had various treatments obviously associated with the diagnosis I'd had earlier that year it was partly that each time I had treatment I did reflect on people that had gone before me who from their experience and their participation in possible research that that perhaps made things easier for me in my experience. So it was a small way of trying to help for the future. That was kind of in my head, that I just wanted to try and be part of this and hopefully that would help people like me in the future.*
>
> *P358*

> *Well I thought if it helps somebody else in the future that is the only way they are going to find out the answers.*
>
> *P411*

Patients were aware that chemotherapy treatment is associated with a number of adverse side effects, including nausea and vomiting. A desire to limit their own experience of nausea and vomiting during their chemotherapy treatment was also a strong motivational factor for almost all patients. Of key importance was the fact that those patients participating in the trial may receive wristbands in addition to the antiemetic medication they would have received as part of their conventional care.

> *I just thought if I was to be going to be sick then it might be helpful.*
>
> *P318*

> *Because I could see all the list of things that you have . . . the after effects, you get tummy upsets and stuff like that. Then I thought, well, if that's going to help me I don't want to keep being sick, if it does help me I'll have a go.*
>
> *P351*

A minority of patients indicated that the lack of any perceived risk of adverse effects from taking part in the trial was also a motivational factor when deciding to participate. Some of these patients elaborated, comparing participating in the trial of acupressure wristbands with participating in a pharmaceutical trial – specifically that the decision to participate would likely have been more considered if the trial had been for a new drug as opposed to a 'natural' remedy because of a perceived greater likelihood of adverse effects.

> *There would be no side effects, there would be nothing, there was, it was no detriment really . . . . I know you have got to help with these things, I think possibly yes [if pharmaceutical trial] I would have done but I would have had to know a lot more about it and a lot more in depth about it.*
>
> *P280*

Perceptions and experiences of complementary therapies

As part of the interview process participants were asked about their views and experiences of complementary and alternative medicine. Most patients had only limited personal experience of complementary and alternative medicine treatments before taking part in the trial; however, a number indicated that they had received additional complementary and alternative medicine treatments during their cancer treatment, such as reflexology, massage and reiki.

Some patients were aware of the current lack of an evidence base underpinning many complementary and alternative medicine treatments. Despite this patients frequently described themselves as 'open-minded' with regards to complementary and alternative medicine treatments and their effectiveness, often citing the successful treatment of family/friends or the long history of some of the treatments, with comments such as 'it's been around for years, so there must be something in it' being common. Complementary and alternative medicine treatments were also perceived as being 'natural', 'safe' treatments associated with fewer side effects than conventional medicine. However, some patients, often those who had used complementary and alternative medicine treatments previously, held preconceived beliefs that many complementary and alternative medicine interventions were beneficial to patients whereas others held

an opinion that complementary and alternative medicine treatments were of little or no benefit to patients. For some, particularly those with a belief in the effectiveness and value of complementary and alternative medicine treatments, these preconceptions were identified as a further motivational factor when deciding to participate. Interestingly, some patients indicated that their involvement in the trial, or use of complementary and alternative medicine during chemotherapy, had altered their perception of complementary and alternative medicine; typically, their personal experiences of using complementary and alternative medicine made them more accepting of its potential value to patients.

> *I think a lot of people don't realise that it's beneficial and it helps. So yeah I think if more people realised and realised what help it does, you think oh complementary therapy it's neither here nor there, but actually it does help you relax and you can forget about your troubles and what you've gone through and it's just, it's so relaxing and so nice. You just feel as though you could, you are just a million miles away.*
>
> *P280*

> *I can't say whether it totally worked for me but for some people it must really assist them. Not it's the way we have got to go, if it can save taking drugs, save ailments and acupuncture has been going on for quite a few years now [laughs] there must be something in it, for it to still keep going you know and so I have never experienced the needles or anything like that, but I understand and appreciate it must work because it is still going after what hundreds of years?*
>
> *P334*

Most patients saw the role of complementary and alternative medicine as being in combination with conventional medicine. Indeed, some patients indicated that they would be accepting of complementary and alternative medicine only if it was provided within the NHS, or if they were advised to use it by a treating conventional health-care practitioner. Irrespective of previously held views or experiences of complementary and alternative medicine interventions, participants were near unanimous in the importance they placed on research into complementary and alternative medicine, highlighting the importance of establishing whether or not treatments are effective for patients to use. There was also a view among some that there should be a greater integration of complementary and alternative medicine therapies and conventional therapies provided within the NHS but that this increasing integration should be underpinned by an emerging evidence base.

> *Yes I think any alternative therapy should be looked into, or to run not necessarily on its own but to run alongside you know, medicine.*
>
> *P219*

> *I think it's very important [research into complementary and alternative medicine]. Yes. Because I see complementary medicine as being non-invasive, as being an aid to conventional medicines, or an add-on to conventional medicines. Yes.*
>
> *P302*

Experience of taking part in the trial

Only a couple of participants had any previous experience of taking part in research before agreeing to take part in the trial of acupressure wristbands. Interviewed patients typically indicated that they felt that they had a good understanding of the study before consenting to participate, with many recounting the written and verbal information they had received before consenting.

> *Yes I knew what it entailed and it was explained to me quite well.*
>
> *P411*

Part of this was being given information on the randomisation process to receive wristbands A, wristbands B or treatment as normal. Patients were typically pragmatic in their perception of the process, exemplified

by P280 who commented: 'you are either going to be lucky if you get the wristbands and it might help, you are unlucky you don't get anything and you just carry on as you would do if you wasn't on the trial'.

However, despite this pragmatic approach, many allocated to treatment as normal still indicated that they felt 'disappointment' at not receiving wristbands.

Many participants expressed feeling daunted on initially receiving the paperwork for the trial. As one participant stated, 'I thought oh crumbs [laughter]. I thought oh God every day.' However, these feelings typically subsided once patients familiarised themselves with the forms and realised that forms were extensively duplicated. Participants generally felt that the included questionnaires were easy to follow, with comments such as 'pretty straightforward' being common. Although the questionnaires were easy to complete, a few patients felt that they were a little onerous, making comments such as 'they were perhaps, perhaps a little bit too lengthy maybe'. Patients were asked to complete forms for the first 7 days following chemotherapy and on day 10. Some indicated that they failed to complete all of the paperwork on the designated days, in particular that lapses in memory, or poor health, led to forms sometimes being completed retrospectively. In some instances this could involve forms being completed up to 1 week after the date on which they were supposed to be completed. It was the difficulty of completing the paperwork when experiencing the adverse effects of chemotherapy that most patients felt resulted in some patients dropping out of the trial.

> *Some of the days when I was really, really poorly with the chemo I couldn't even get out of bed to even fill it in I'll be honest, but I knew each day how bad I was, how sick I was. So, you know, was able to fill it in accurately because I knew that at the beginning I was so poorly and so sick and by the end of it you are kind of coming round, so I knew from as soon as I come round and I was out of bed I filled it in.*
>
> *P280*

A number of patients felt that they had experienced positive outcomes as a result of taking part in the trial. Linked to patients' motivations for taking part, most frequent was a sense of well-being as a result of feeling that they had completed an altruistic act and helped others. In addition, some patients felt that the process of completing the trial paperwork had been of benefit to them, specifically that it provided them with some control at a time when they felt a lack of control over their cancer experience or that they gained benefit from being able to reflect on how their symptoms had improved during previous cycles of chemotherapy. In contrast, some patients indicated that they had experienced some negative effects from completing the paperwork, chiefly that reading and rating their level of nausea and vomiting at a time when they were feeling nauseous had at times worsened their experience.

> *I think taking part in the trial is quite, it makes you feel better actually because it is a useful tool and it's going to be of use for other people in the future . . . . Yes because it makes you feel better doesn't it if you feel you are contributing something.*
>
> *P250*

> *I just completed the forms as requested and it was no hassle at all. And actually it helped because it was something positive to do, on certain days and ticking the boxes and all that sort of thing, I felt because I think part of having cancer is you lose control, and I am quite, the sort of person that likes to be in control and this is enabling me a little bit of control back, so that part I quite enjoyed actually.*
>
> *P317*

> *I know this sounds silly, funny almost, but some of the questions actually don't help you when you're not feeling well. You actually go oh, I feel sick reading out how many cups sort of, you know, sick.*
>
> *P358*

Experience of using the wristbands

Those patients who were allocated to receive either true or sham wristbands during the trial were asked about their experiences of using them. Almost all patients interviewed appeared to have worn the wristbands as instructed, keeping them on for at least 7 days following chemotherapy and removing them only when washing or bathing. Indeed, some patients continued using the wristbands after the 7-day period, and many also continued using the wristbands after the four chemotherapy cycles included in the trial. Patients were asked to demonstrate how they wore the bands, with most of those interviewed apparently wearing the wristbands in the correct position. The exceptions were two patients allocated to receive sham wristbands, who were found to have worn them inappropriately. One patient wore the wristbands inside out (meaning that slight pressure would have been applied to the point) and the other patient indicated that he had manually applied pressure to acupoint P6.

Many of the patients interviewed indicated that they had experienced only mild nausea or vomiting during the trial. A number of patients were pragmatic about the extent to which the wristbands were responsible for this, highlighting the fact that there could be a number of other reasons, including their antiemetic medication, basic constitution or just luck. However, many patients, including some sham-treated patients, believed the wristbands to have had a positive impact on their nausea and vomiting. There was a perception and belief that the wristbands were, at least in part, responsible for the lack of nausea and vomiting they had experienced. In some cases this resulted from the patients' experiences during the trial, such as noticing that nausea was greater when the wristbands were not worn. The wristbands were not seen as being any more or less effective at different times of the day or at different points in the patients' chemotherapy treatment. There were also no additional benefits reported from wearing the wristbands beyond the alleviation of nausea and vomiting.

> *Until the trial is complete you can't really say whether it helped you or not can you . . . . I wore them, yes I wore them each time I had treatment yes. And erm . . . yes I feel as though I benefited from them, and I think I possibly would have been more sick than what I was. I felt the bands did help in that respect. Yes.*
>
> *P219*

> *I must say I think, having learnt that I didn't used to wear them for the first 2 weeks at first, but then I would be feeling a bit sick and I would think goodness me, why am I feeling so sick and then I would put them on and it would improve and one day I was feeling sick with them on, but they weren't in the right place (laughs) I was looking at them and they weren't in the right place, so there is a reason you know, this is why I have got such belief in them now.*
>
> *P334*

Patients reported that they had not experienced any restrictions from wearing the wristbands in terms of everyday activities, other than showering/bathing/washing dishes. As P297 commented, 'I don't have many household chores, but no not at all, not at all. I just, take them off when I have a bath or a shower, other than that no they are not intrusive at all'. For most patients the wristbands were seen as comfortable to wear, although a few patients reported that they had experienced minor irritations, such as the wristbands feeling tight or painful, or the wrists becoming itchy. All reported adverse side effects were generally deemed minor and acceptable.

> *I find sometimes my, it gets, my skin gets quite red, and they rub and I am sure it's because they are so badly made inside, I think that is the contributing factor.*
>
> *P318*

> *I did find the bobble that went into your arm painful a few times, and I sort of had to wriggle it around just sort of release the pressure on my arm just for a few minutes, rub my arm and then put it back in again.*
>
> *P334*

A number of patients highlighted the fact that they had been questioned by others, both known to them and not, regarding their wearing of the trial wristbands. Many were unconcerned by the views of others. As P210 commented, 'if they don't like it, that's their problem . . . didn't influence me whatsoever'. However, a few patients highlighted that they had inhibitions about wearing them in the company of others or had received negative responses from others to their wearing of the wristbands. When asked about this, some compared the minor impact of wearing wristbands with such things as having to wear a headscarf or have surgical pointers on their body.

> *It's a, it's a silly point but they are there all the time, so you do sort of start pulling your sleeves down because you don't want people to see them, you know it looks rather strange walking round with two wristbands on . . . Well everybody knew about them, because I, you know you chat to people and people ask you, and so, I would just tell people but if you went for a meal or if you were out somewhere socially where people didn't know you, you would feel slightly embarrassed. These two bands, that look as though you should be in the gym.*
>
> *P302*

Irrespective of perceptions of effectiveness, almost all patients indicated that they would recommend the wristbands to other chemotherapy patients, or to patients experiencing nausea and vomiting from other causes. This related to the fact that, irrespective of whether or not the wristbands were of benefit for nausea and vomiting, they were not associated with any negative or adverse effects.

> *There isn't a reason not to wear them. Personally yes. So, yes I would recommend them yes.*
>
> *P194*

Chapter 7 Discussion

Key quantitative findings

Despite the higher proportion of patients showing no nausea in the acupressure group, the results of the trial show that there were no statistically significant differences between the three trial arms in relation to nausea experience. Patients in both wristbands arms had a higher OR for improving their nausea experience than those in the standard care arm, with the sham arm having a higher OR than the acupressure arm. There was a significant gender effect with women in both wristband groups showing significant improvements compared with men. Health-care utilisation was lower in the wristband arms than in the standard care only arm.

Other trials in the past have also shown no significant effects from the use of acupressure in relation to nausea and vomiting management during chemotherapy administration. A review by Lee and Frazier[74] examined the results of seven trials of acupressure, with four having positive results and three negative, highlighting that the overall effect of acupressure is strongly suggestive but not conclusive. No significant differences were reported in another trial of 160 women with regards to acute nausea and vomiting, although significant differences were reported with regards to delayed nausea and vomiting.[75] In the largest trial of its kind ($n = 739$), Roscoe *et al.*[24] showed that patients experienced less nausea in the first day of chemotherapy in the acupressure arms but there were no significant differences in relation to delayed symptoms. Also, the authors identified a strong gender effect, with men in an acustimulation arm improving but not women, which is in contrast to the results of the current trial. Roscoe *et al.*[17] also showed, in a small sample of 27 patients (25 women and two men), no statistically significant differences in average severity of nausea between acustimulation of the P6 point, sham acustimulation and standard care; however, the data showed a difference close to statistical significance in the severity of delayed nausea between active acustimulation and no acustimulation ($p = 0.06$). In addition, patients took fewer antinausea pills during the active acustimulation cycle of this experiment than during the no acustimulation phase ($p < 0.05$). Negative results have been shown in relation to acupressure and nausea/vomiting symptoms in a large trial of 340 women during labour and delivery.[76] In a trial of acupuncture compared with sham acupuncture during radiotherapy,[77] the authors showed less nausea and vomiting in both the real and the sham acupuncture arms than in the standard care arm and justified this as due to non-specific effects of general care or high patient expectancy, which may partly explain our results too.

Key issues in most of the past studies showing positive results include the lack of standardised antiemetic use in the trial participants and inclusion of only or mostly female subjects. If our trial had included only the female subsample, the results would have also been positive. Also, it seems that the vast majority of positive studies in the literature include small sample sizes (< 100 participants), whereas the negative studies (or partly negative) have much larger sample sizes; this suggests that effects observed in methodologically weaker studies cannot always be sustained when larger and more robust trials are carried out. Furthermore, other studies in the past have shown that expectancy,[24,78] age and anxiety[28,29] together with the antiemetic potential of the chemotherapy are important predictors of, and can affect, the outcome of acupressure, but in our trial, although unidimensionally these were also important, in a multivariate model only gender showed a significant effect.

Our findings suggest a placebo or non-specific effect of the intervention arms. Placebo effects are viewed as a form of interpersonal healing, distinct from spontaneous natural healing or technological healing that depends on physiologically active pharmacological products or procedures.[79] Alkaissi *et al.*[80] have suggested that acupressure does indeed have a placebo effect in relation to nausea after 24 hours, although correct stimulation of the P6 point is needed to observe decreased rescue antiemetic use and decreased vomiting. Research also suggests that there are different placebo responses, each of which may

be influenced by different psychological and neurobiological mechanisms depending on the context in which the placebo is given.[81] The literature also shows that placebos have actual biological effects on the brain and body and are more than response biases. The review by Price *et al.*[81] concludes that placebo effects reflect mind–brain–body relationships and as such we should not 'resort to eliminative materialism or forms of dualism that completely divide the mind from the body' (p. 586).

Trials of acupressure pose a specific problem with regards to the blinding and the choice of placebo, particularly when outcome measures are subjective. We have chosen to use the same wristbands in both the real and the sham groups so that they look identical, with the real acupressure group instructed to have the button pressing the P6 point and the sham group instructed to have the button pointing away from the P6 point on the other side of the arm. We observed during the interviews that some patients in the sham acupressure group (two out of nine) used the wristbands as in the acupressure group because they had looked on the internet or saw others wearing them properly. This may have contaminated our results. It was not possible to create a wristband that would look identical to the real one but which would not have a button or which would exert no pressure. These bands were elastic bands and, as reported by Sinha *et al.*[76] (through observations from their colleagues in the Department of Industrial and Manufacturing Engineering, Penn State University, PA, USA), elastic bands result in some pressure. This suggests that the pressure of the band in the area proximal to the P6 point, irrespective of the presence of a button pressing the P6 point, may have produced some positive results.

Our sample had generally low levels of nausea and/or vomiting. This may be due to the fact that we have standardised antiemetic use in our study and an inclusion criterion was receiving antiemetics as per MASCC antiemetic guidelines. This low level of experienced symptoms may be a reason for not showing significant differences in the current trial, as we have shown in another observational study of nearly 1000 patients that use of antiemetics during chemotherapy according to MASCC guidelines is associated with significantly improved nausea/vomiting symptoms.[52]

A limitation of the trial may be the missing data for the primary outcome. However, the proportion of cases missing the primary outcome (28%) is of a similar order to that anticipated at the design stage (33%). Originally 90% power had been planned for a standardised difference in means of around 0.48. For pragmatic reasons the study power was reduced to 80% so that it could complete in a reasonable time frame. The attained power that the final sample size with complete data for the primary outcome ($n = 361$) delivered was 80% for a standardised difference in means of 0.46. Also, another limitation that needs to be carefully considered in future trials is the choice of sham wristbands, which in our case may not have been the most optimal design.

Health-care utilisation data

Although there was no statistically significant effect of acupressure over sham acupressure and no acupressure, the health economics part of the trial was run concurrently with the effectiveness part of the trial. Through health economic analyses in negative trials it is possible that intervention benefits that are not apparent in traditional efficacy end points may register in QALYs, as this is a different composite outcome. Current thinking in respect of economic analyses in cases in which there is no clear differential effect/effectiveness of the intervention being assessed is that a full cost-effectiveness analysis is undertaken and uncertainty accounted for. Even given that the EQ-5D changes were below those levels that are minimally important and were not significant, and the QALY gains were minimal (for acupressure vs standard care), one cannot evaluate the cost-effectiveness without considering costs.[82,83]

Mean costs resulting from NHS resource use were consistently higher for the standard care only group than for the acupressure group; this finding was relatively robust to sensitivity analyses. However, because very little resource use was recorded in the study and the results may have been unduly influenced by outliers with high costs, this finding is relatively uncertain and must be treated with caution. The results

from the EQ-5D score analysis revealed no significant differences in utility changes over time between treatment arms and QALY gains throughout the study were negligible.

The acupressure bands group appears to have reduced health-care resource use while realising negligible improvements in quality of life compared with standard care alone. A rapid review of the literature found no studies including costs of chemotherapy-induced nausea and vomiting to the NHS, precluding comparison with previous research. Neither did the review yield any previous studies reporting EQ-5D scores for this patient group. In the present study the EQ-5D analysis showed no differences in utility between groups. There also appeared to be little overall impact of chemotherapy as no utility score changes between any cycle exceeded (or came close to exceeding) the minimal important difference identified for the measure. EQ-5D scores for older patients at the final chemotherapy cycle were similar to the population norm,[84] but younger patients appeared to experience a greater utility decrement relative to norms. The mean utility for both the 25–50 and ≥50 age groups was 0.77 after cycle 4 compared with population norms of 0.90 for the 25–54 age group and 0.79 for the 55–74 age group. It is possible that the EQ-5D is not a sensitive enough measure to capture quality-of-life benefits that may be experienced as a result of reduced chemotherapy-induced nausea and vomiting, although a cancer-specific quality-of-life measure (FACT-G) also failed to detect any between-group differences. There is also a non-significant baseline difference in utility scores between groups, which may explain differential QALY gains over the trial period.

There were several limitations of this economic evaluation. We made assumptions regarding drug doses and antiemetics drug type because of missing data and also made assumptions regarding length of hospital stay. Assumptions were also necessary regarding the standard care of each of the patients, relying on expert opinion and assuming that care was the same across centres. It is possible that more expensive (branded) antiemetic treatments may have been used but not captured as not all prescribing information was available. Different sites may have different protocols relating to antiemetic prescription as a standard therapy. However, the ICERs and the resulting conclusions regarding the cost-effectiveness of acupressure were robust to sensitivity analyses and stochastic bootstrapping.

When calculating the EQ-5D missing data we employed the LOCF approach; this method assumes that the participant's EQ-5D response would have been stable between each cycle, rather than declining or improving. It also assumes that missing values are 'missing completely at random' (i.e. that the probability of dropout is not related to variables such as disease severity, symptoms or drug side effects). As such, the LOCF method may lead to bias in the results. However, assumptions about both costs and utilities were tested in the sensitivity analyses. Finally, as stated above, it is possible that the EQ-5D is an inappropriate measure to capture health benefits incurred as a result of reduced nausea and that a cancer-specific measure may be more suitable.[85] However, cost–utility analyses and the EQ-5D are compliant with the NICE reference case. Future research should consider cancer-specific utility measurement and comparisons with generic utility values. As the occurrence and impact of chemotherapy-induced nausea and vomiting varies over time in relation to chemotherapy receipt, quality-of-life impact depends on the time of measure completion during the cycle. Thus, research exploring patients' health status on a daily basis throughout the course of a chemotherapy cycle may be warranted. Given the influence of high-cost outliers in the analyses, greater exploration of what is driving these costs and indeed whether or not they relate to chemotherapy-induced nausea and vomiting may be worthwhile; this may involve qualitative follow-up of high-resource-use individuals.

Qualitative data

The nested qualitative study aimed to explore patients' reasons for taking part in a clinical trial of acupressure wristbands and their experiences of using acupressure wristbands and taking part in the trial of acupressure wristbands. The key findings from these data suggest that patients in the wristband arms perceived the bands to be effective and felt more in control of their nausea and vomiting experience.

The motivations that patients identified for participating in the trial are congruent with the findings of previous research. Paterson *et al.*[86] conducted a nested qualitative study exploring the experiences of patients with migraines receiving acupuncture within a randomised controlled trial. Similar to the present study, they found that patients felt that acupuncture was 'worth a try', with patients being eager for symptom relief and having a desire to help with research for altruistic motives, although the theme 'giving something back' appears to be much more prevalent within the present study. This may be a consequence of the greater morbidity associated with cancer, although further research would need to be conducted to confirm whether or not this is the case.

Patients were largely satisfied with the organisation and running of the trial. The process of recruitment was generally perceived as straightforward and to have been adequately described. Interestingly, the completion of trial paperwork was seen as being of benefit by some patients, a finding again consistent with previous research.[86] Where the current study findings appear to differ from previous research is in the explicit feeling of 'well-being' that many patients experienced as a direct result of knowing that their participation in the trial might lead to the improvement of care for future cancer patients.

Previous qualitative research exploring the experiences of patients receiving treatment with acupuncture suggests that patients experience a range of benefits beyond the alleviation of their presenting condition, including improvements in overall well-being, sleep pattern and energy levels.[54–56] A number of patients who received wristbands in the present study indicated that they had experienced only minor levels of nausea and vomiting during their chemotherapy. Some patients – those receiving both true and sham wristbands – attributed the wristbands as having had a positive impact on the level of nausea and vomiting experienced. However, none of the patients who participated in interviews associated the acupressure wristbands with eliciting benefits beyond the relief of chemotherapy-related nausea and vomiting. This may suggest that a greater stimulation of acupuncture points is required to elicit these effects or that the contextual factors within the acupuncture consultation, such as the interaction between the practitioner and the patient or consultation setting, may work in conjunction with the stimulation of acupuncture points to elicit these expanded effects of care.

The wristbands were not associated with any significant adverse effects and patients found them easy to wear and to be associated only with limited social inhibitions. Importantly, patients appear to have worn the wristbands in the correct location and for the period of time instructed. However, the data revealed that two of the nine sham acupressure group patients had worn their wristbands inappropriately (based on their trial arm allocation), either wearing them inside out or applying pressure manually to the acupoint. Also of importance is the apparent delay in some patients completing the trial paperwork, relying on memory to fill in the forms. Both of these may represent confounding variables, which if generalisable to other patients in the trial could have serious implications for the results of the trial.

Conclusions and research recommendations

Despite several acupressure antiemetic trials suggesting a beneficial effect, the trial heterogeneity and inconsistent findings prevented any definitive conclusions being drawn. Our study, using a strong methodological design and standardisation of antiemetics, showed no significant differences between acupressure and sham acupressure wristbands for the management of nausea and vomiting during chemotherapy. Nevertheless, the somewhat improved, albeit not statistically significant, levels of nausea in both wristband arms needs some attention, although, as minimally important differences in relation to chemotherapy-related nausea and vomiting are currently not established, some caution is necessary here. The use of wristbands led to lower health-care utilisation (although this did not reach statistical significance). Bands are well accepted and are low cost and safe additions to antiemetic drugs, but the ethical aspects of suggesting the use of potentially non-effective interventions that lead to lower health-care costs and health-care utilisation need some careful consideration. There is a sufficiently encouraging signal and a suggestion of potential health resource-use benefits to justify exploration of acupressure

in further trials using both no intervention and sham acupressure controls. Questions that need to be answered in the future include whether or not other forms of acupressure such as regular finger acupressure or Korean hand acupressure could be more effective than wristband acupressure. A meta-analysis of existing data on acupressure wristbands may be an appropriate way to provide a more concrete answer to the question of whether or not acupressure wristbands are effective in managing nausea and/or vomiting during chemotherapy.

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Professor Alex Molassiotis (Professor of Cancer and Supportive Care, University of Manchester) conceived and designed the initial plan of the study, had overall responsibility for the study, analysed the data together with **David Ryder** (Senior Statistician, Christie NHS Foundation Trust, who led on the statistical analysis) and drafted the final report. **Dr Wanda Russell** (Clinical Trials Manager, University of Manchester) was responsible for the day-to-day operationalisation and management of the study, liaison with the study sites, recruitment at the Manchester sites, quality assurance, producing reports and preparing for meetings and liaising with the National Cancer Research Network (NCRN) database. **Dr John Hughes** (Research Associate, University of Liverpool) and **Dr Matt Breckons** (Research Associate, University of Plymouth) were responsible for recruitment and trial management at the Liverpool and Plymouth sites respectively. **Dr John Hughes** also carried out the qualitative interviews (together with

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Appendix 1 Study scales: Rhodes Index of Nausea, Vomiting and Retching

Instructions:

Please mark the box for each question that most clearly corresponds to your experience. Please do not miss out a question and place only one **X** in a box for each question. *e.g.* ☒ The ____ in statements represents the selected phrase.

Day before chemotherapy ☐
Day of chemotherapy ☐
Day 1 after chemotherapy ☐
Day 2 after chemotherapy ☐
Day 3 after chemotherapy ☐
Day 4 after chemotherapy ☐
Day 5 after chemotherapy ☐
Day 6 after chemotherapy ☐

1. In the last 12 hours I threw up ____ times:

7 or more ☐
5-6 ☐
3-4 ☐
1-2 ☐
I did not throw up ☐

2. In the last 12 hours, from retching and dry heaves, I have felt ____ distress:

no ☐
mild ☐
moderate ☐
great ☐
severe ☐

3. In the last 12 hours, from vomiting or throwing up, I have felt ____ distress:

severe ☐
great ☐
moderate ☐
mild ☐
no ☐

4. In the last 12 hours, I have felt nauseated or sick to my stomach:

not at all ☐
1 hour or less ☐
2-3 hours ☐
4-6 hours ☐
more than 6 hours ☐

5. In the last 12 hours, from nausea/sickness to my stomach, I have felt ____ distress:

no ☐
mild ☐
moderate ☐
great ☐
severe ☐

6. In the last 12 hours, each time I threw up I produced a ____ amount:

very large (3 cups or more) ☐
large (2-3 cups) ☐
moderate (1/2-2 cups) ☐
small (up to 1/2 cup) ☐
I did not throw up ☐

7. In the last 12 hours, I have felt nauseated or sick to my stomach ____ times:

7 or more ☐
5-6 ☐
3-4 ☐
1-2 ☐
no ☐

8. In the last 12 hours, I have had periods of retching or dry heaves without bringing anything up ____ times:

no ☐
1-2 ☐
3-4 ☐
5-6 ☐
7 or more ☐

Date completed d d / m m / y y y y

Signed _____

Appendix 2 Study scales: Multinational Association of Supportive Care in Cancer Antiemesis Tool

MASCC Antiemesis Tool (MAT): Acute

Information and instructions:

Definitions:
Vomiting: The bringing up of stomach contents.
Nausea: The feeling that you might vomit.

Please place a firm cross *e.g.* ☒ in a single box per row. For question 2 and for the completion of dates please use leading zeros if necessary e.g. 01/03/2008.

Nausea and Vomiting during the first 24 hours after chemotherapy (Please fill this section out the day after chemotherapy)

This section refers to the **first 24 hours** following chemotherapy:

1) in the 24 hours since chemotherapy, did you have any vomiting? No ☐ Yes ☐

2) If you vomited in the 24 hours since chemotherapy, how many times did it happen? ☐☐
(Please use a leading zero if required e.g. 04)

3) in the 24 hours since chemotherapy, did you have any nausea? No ☐ Yes ☐

4) If you had nausea, please enter the number that most closely resembles your experience.
How much nausea did you have in the last 24 hours?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

None As much as possible

Date completed d d / m m / y y y y Signed _____

MASCC Antiemesis Tool (MAT): Delayed

Information and instructions:

Definitions:
Vomiting: The bringing up of stomach contents.
Nausea: The feeling that you might vomit.

Please place a firm cross *e.g.* ☒ in a single box per row. For the completion of dates please use leading zeros if necessary e.g. 01/03/2008.

Delayed Nausea and Vomiting
(Please fill this section out 4 days after chemotherapy)

This section asks about the period from the day after to 4 days after chemotherapy.
So it asks about the time **after** the first 24 hours:

5) Did you vomit 24 hours or more after chemotherapy? No ☐ Yes ☐

6) If you vomited during this period, on how many days did it happen? 1 ☐ 2 ☐ 3 ☐ 4 ☐

7) Did you have any nausea 24 hours or more after chemotherapy? No ☐ Yes ☐

8) If you had nausea, please enter the number that most closely resembles your experience.
How much nausea did you have over this time period?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

None As much as possible

Date completed d d / m m / y y y y Signed _____

Appendix 3 Study scales: Functional Assessment of Cancer Treatment – General scale

Instructions:

Below is a list of statements that other people with your illness have said are important. **By placing a firm cross in one box per line, please indicate how true each statement has been for you during the past 7 days**. *e.g.* ☒

PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have a lack of energy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I have nausea	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Because of my physical condition, I have trouble meeting the needs of my family	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I have pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am bothered by side effects of treatment	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I feel ill	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am forced to spend time in bed	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I feel close to my friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I get emotional support from my family	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I get support from my friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
My family has accepted my illness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am satisfied with family communication about my illness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I feel close to my partner (or the person who is my main support)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
I am satisfied with my sex life	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I feel sad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am satisfied with how I am coping with my illness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am losing hope in the fight against my illness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I feel nervous	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I worry about dying	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I worry that my condition will get worse	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PLEASE TURN OVER

Instructions:

By placing a firm cross in one box per line, please indicate how true each statement has been for you during the past 7 days. *e.g.* ☒

FUNCTIONAL WELL-BEING

	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (include work at home)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
My work (include work at home) is fulfilling	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am able to enjoy life	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I have accepted my illness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am sleeping well	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am enjoying the things I usually do for fun	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I am content with the quality of my life right now	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PLEASE MAKE SURE YOU HAVE COMPLETED BOTH SIDES, THANK YOU

Date completed d d / m m / y y y y

Signed _____

Appendix 4 Study scales: Hospital Anxiety and Depression Scale

Instructions:

This questionnaire is designed to help us know how you feel. Read each item and place a firm cross in the box opposite the reply which comes closest to how you have been feeling in the past week. *e.g.* ☒

Don't take too long over your replies; your immediate reaction will probably be more accurate than a long thought out response. Please do not miss out a statement and place only one **X** in a box for each statement.

I feel tense or 'wound up':
- Most of the time ☐
- A lot of the time ☐
- From time to time, occassionally ☐
- Not at all ☐

I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not too often ☐
- Only occasionally ☐

I feel cheerful:
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

I feel restless as if I have been on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

I can enjoy a good book or radio or TV programme
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Date completed d d / m m / y y y y

Signed _____

Appendix 5 Study scales: expectations and complementary therapy questionnaire

Instructions:

Please place a firm cross *e.g.* ☒ in a single box per row. A number of items are on a 0 to 10 scale with the meaning of the extremes of the scale stated in words (please choose a value between 0 and 10 that best represents your view).

Have you used complementary therapies in the past? No ☐ Yes ☐

How much nausea (the feeling of being sick) do you think you will experience during your chemotherapy treatment?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Not at all Very frequently

How much vomiting (being sick) do you think you will experience during your chemotherapy treatment?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Not at all Very frequently

How much do you believe that the acupressure method if allocated will help you manage your sickness better?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Not at all Will help me a lot

How much faith do you have in complementary therapies in general?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

None at all Complete faith

Date completed d d / m m / y y y y Signed _____

Appendix 6 Study scales: sociodemographic characteristics questionnaire

Instructions: For choice fields please place a firm cross e.g. ☒ in a single box per item. For all numeric responses (including dates) please complete all the boxes with leading zeros as required e.g. 0 5 All dates are in dd/mm/yyyy format.

Initials ☐☐☐☐ **Date of birth** d d / m m / y y y y ☐☐ / ☐☐ / ☐☐☐☐

Gender
- Male ☐
- Female ☐

Marital status
- Single ☐
- Married ☐
- Divorced or separated ☐
- Widowed ☐

Educational attainment
- Primary school ☐
- Secondary school ☐
- College/Diploma ☐
- University/Degree ☐
- Postgraduate ☐

Ethnic origin
- Caucasian ☐
- Black ☐
- Asian/Chinese ☐
- Mixed ☐

Religious affiliation
- Christian ☐
- Muslim ☐
- Hindu ☐
- None ☐
- Prefers not to say ☐
- Other ☐

Occupational group
- Professional ☐
- Managerial & technical ☐
- Skilled non manual ☐
- Skilled manual ☐
- Unskilled ☐
- Not applicable ☐

Occupational status
- Employed full-time ☐
- Employed part-time ☐
- Retired ☐
- Unemployed ☐
- Casual worker ☐
- Not working due to ill health ☐
- Housewife ☐
- Other ☐

Smoking history
- Never ☐
- Previously ☐
- Current ☐

Date completed d d / m m / y y y y ☐☐ / ☐☐ / ☐☐☐☐ Signed _____

Appendix 7 Study scales: acupressure wristband compliance questionnaire

Instructions:

Please mark the box for each listed day of this cycle of chemotherapy that most clearly corresponds to the length of time that you have worn your wristbands. Please do not miss out a day and place only one **X** in a box for each day *e.g.* ☒

	None of the time	A little of the time	Most or all of the time
Day of chemotherapy	☐	☐	☐
Day 1 after chemotherapy	☐	☐	☐
Day 2 after chemotherapy	☐	☐	☐
Day 3 after chemotherapy	☐	☐	☐
Day 4 after chemotherapy	☐	☐	☐
Day 5 after chemotherapy	☐	☐	☐
Day 6 after chemotherapy	☐	☐	☐

Signed _____

Appendix 8 Wristband audit observation log

ACUPRESSURE FOR CHEMOTHERAPY-RELATED NAUSEA : ANCHoR Trial

Wristband audit

Please use this sheet to log whether participants in the ANCHoR trial who attend for chemotherapy appointments, and who have been allocated wristbands, are wearing their wristbands correctly. Once you have completed this information for a minimum number of 15 patient/cycle observations (i.e. the same patient may be included more than once at different cycles), please return this sheet to Wanda Russell.

ANCHoR Trial Site & Code (e.g. 'The Christie, '01'): _____

Patient trial no.	Date of observation	Chemo cycle? (1/2/3/4)	Is wristband correctly worn on right wrist? (Y/N)	Is wristband correctly worn on left wrist? (Y/N)	Comments: 1) If wristband(s) incorrectly worn, please state why (e.g. too high/low on wrist, acupressure button not positioned between tendons). 2) Please state if wristband is in good/bad condition.	Observer's initials

Contd. Overleaf….

Patient trial no.	Date of observation	Chemo cycle? (1/2/3/4)	Is wristband correctly worn on right wrist? (Y/N)	Is wristband correctly worn on left wrist? (Y/N)	Comments: 1) If wristband(s) incorrectly worn, please state why (e.g. too high/low on wrist, acupressure button not positioned between tendons). 2) Please state if wristband is in good/bad condition.	Observer's initials

Any additional comments/observations:

Appendix 9 Health economics baseline questionnaire

Health Economics Baseline Questionnaire

Use of health care services, medication and expenses incurred as a result of nausea or vomiting before chemotherapy

Instructions: Over the next few weeks we will need to ask you some questions about the health care services you have used and anything you have had to buy because of any nausea or vomiting you may have experienced following chemotherapy. We are doing this to find out the costs of the different approaches to treatment. This first questionnaire asks about any services used or anything you have had to buy because of any nausea or vomiting you have experienced in the last three weeks. Some questions will seem more relevant to you than others, but please try to answer all the questions so that we can compare the costs of the treatments fairly.

Your date of birth:

Hospital:

1. Please complete today's date ☐☐ ☐☐ ☐☐☐☐
DAY MONTH YEAR

2. Please tick one box for the category that describes your present employment status.

Employment Status	Tick one category that best describes your employment now *(please tick one box only)*
a. Employee, full time (more than 30 hours/week)	☐
b. Employee, part time (less than 30 hours/week)	☐
c. Self-employed	☐
d. Government-supported training	☐
e. Other training or education	☐
f. Employee on sick leave	☐
g. Not in paid employment due to retirement	☐
h. Not in paid employment for other reasons	☐

If you are in paid work please tells us the number of days you have been away from work due to nausea or vomiting in the last three weeks.

No of days ☐ Not applicable ☐

Please estimate the earnings lost by to absence from work due to nausea or vomiting in the last three weeks? (bring home earnings).

Earnings lost £☐☐☐☐☐ Not applicable ☐

3. Have you used any health care services following nausea or because of vomiting in the last three weeks?

Type of service	**Which services you have used in the last three weeks as a result of nausea or vomiting**		**Total number of face to face contacts**	**Total number of contacts you had by telephone or e-mail**
GP surgery visit	Yes ☐	No ☐		
GP home visit	Yes ☐	No ☐		
District nurse,	Yes ☐	No ☐		
Contact with oncology hotline for advice	Yes ☐	No ☐		
Contact with hospital oncology nurse clinician for advice	Yes ☐	No ☐		
Contact with hospital oncology clinic for advice	Yes ☐	No ☐		
Hospital inpatient stay	Yes ☐	No ☐		
Hospital accident and emergency department	Yes ☐	No ☐		
Hospital general outpatient clinic	Yes ☐	No ☐		
Other services. *Please specify in the boxes and for each service also provide number of contacts.*	1.		1.	1.
	2.		2.	2.
	3.		3.	3.

4. Were you prescribed any medication for nausea or vomiting following use of any of the above services?

Type of service	Medication prescribed for nausea or vomiting?		Name of the medication	No. of times dose to be taken per day	Total No. of days medication prescribed	Cost to you
GP surgery visit	Yes ☐	No ☐				
GP home visit	Yes ☐	No ☐				
District nurse,	Yes ☐	No ☐				
Contact with oncology hotline for advice	Yes ☐	No ☐				
Contact with hospital oncology nurse clinician for advice	Yes ☐	No ☐				
Contact with hospital oncology clinic for advice	Yes ☐	No ☐				
Hospital inpatient stay	Yes ☐	No ☐				
Hospital accident and emergency department	Yes ☐	No ☐				
Hospital general outpatient clinic	Yes ☐	No ☐				
Other services. *Please specify in the boxes and for each service also provide number of contacts.*	Yes ☐	No ☐				

5. Did you incur any other expenses in the last three weeks due to nausea or vomiting?

Yes ☐

No ☐

6. If you have ticked 'Yes' to the previous question, please also describe the expenses that you have had to meet (for example, travel expenses, special diet or complementary therapy) in the table below.

Brief description of item	Cost to you (£'s)
	£ ☐☐☐☐
	£ ☐☐☐☐
	£ ☐☐☐☐
	£ ☐☐☐☐

7. For each of the five sets of statements below, please tick the one box that best describes your own health state today.

(i). Mobility

I have no problems in walking about…..…….…… ☐
I have some problems in walking about ……..…… ☐
I am confined to bed ……..…… ☐

(ii). Self-care

I have no problems with self-care…….……... ☐
I have some problems washing and dressing myself…….…….. ☐
I am unable to wash or dress myself…….…….. ☐

(iii). Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities……... ☐
I have some problems with performing my usual activities……..... ☐
I am unable to perform my usual activities…… ☐

(iv). Pain/discomfort

I have no pain or discomfort…… ☐
I have moderate pain or discomfort……..…… ☐
I have extreme pain or discomfort…….. ☐

(v). Anxiety/depression

I am not anxious or depressed…… ☐
I am moderately anxious or depressed……..…… ☐
I am extremely anxious or depressed……..... ☐

Appendix 10 Health economics questionnaire

Health Economics Questionnaire

Use of health care services, medication and expenses incurred as a result of nausea or vomiting following chemotherapy

Instructions: We need to ask you some questions about the health care services you have used and anything you have had to buy because of any nausea or vomiting you may have experienced following your last cycle of chemotherapy. We are doing this to find out the costs of the different approaches to treatment. Some questions will seem more relevant to you than others, but please try to answer all the questions so that we can compare the costs of the treatments fairly.

Your date of birth:

Hospital:

1. Please complete today's date ☐☐ ☐☐ ☐☐☐☐
DAY MONTH YEAR

2. Please tick one box for the category that describes your present employment status.

Employment Status	Tick one category that best describes your employment now *(please tick one box only)*
a. Employee, full time (more than 30 hours/week)	☐
b. Employee, part time (less than 30 hours/week)	☐
c. Self-employed	☐
d. Government-supported training	☐
e. Other training or education	☐
f. Employee on sick leave	☐
g. Not in paid employment due to retirement	☐
h. Not in paid employment for other reasons	☐

If you are in paid work please tell us the number of days you have been away from work due to nausea or vomiting following your last cycle of chemotherapy?

No of days ☐ Not applicable ☐

Please estimate the earnings lost by to absence from work due to nausea or vomiting following your last cycle of chemotherapy? (bring home earnings).

Earnings lost £☐☐☐☐☐ Not applicable ☐

3. Have you used any health care services following your last cycle of chemotherapy as a result of feeling nauseous or because of vomiting (please only include services used *after* leaving the hospital following chemotherapy)?

Type of service	**Which services you have used in the last three weeks as a result of nausea or vomiting**		**Total number of face to face contacts**	**Total number of contacts you had by telephone or e-mail**
GP surgery visit	Yes ☐	No ☐		
GP home visit	Yes ☐	No ☐		
District nurse,	Yes ☐	No ☐		
Contact with oncology hotline for advice	Yes ☐	No ☐		
Contact with hospital oncology nurse clinician for advice	Yes ☐	No ☐		
Contact with hospital oncology clinic for advice	Yes ☐	No ☐		
Hospital inpatient stay	Yes ☐	No ☐		
Hospital accident and emergency department	Yes ☐	No ☐		
Hospital general outpatient clinic	Yes ☐	No ☐		
Other services. *Please specify in the boxes and for each service also provide number of contacts.*	1.		1.	1.
	2.		2.	2.
	3.		3.	3.

4. Were you prescribed any medication for nausea or vomiting following use of any of the above services?

Type of service	Medication prescribed for nausea or vomiting?		Name of the medication	No. of times dose to be taken per day	Total No. of days medication prescribed	Cost to you
GP surgery visit	Yes ☐	No ☐				
GP home visit	Yes ☐	No ☐				
District nurse,	Yes ☐	No ☐				
Contact with oncology hotline for advice	Yes ☐	No ☐				
Contact with hospital oncology nurse clinician for advice	Yes ☐	No ☐				
Contact with hospital oncology clinic for advice	Yes ☐	No ☐				
Hospital inpatient stay	Yes ☐	No ☐				
Hospital accident and emergency department	Yes ☐	No ☐				
Hospital general outpatient clinic	Yes ☐	No ☐				
Other services. *Please specify in the boxes and for each service also provide number of contacts.*	Yes ☐	No ☐				

5. Did you incur any other expenses due to nausea or vomiting following your last cycle of chemotherapy?

Yes ☐

No ☐

6. If you have ticked 'Yes' to the previous question, please also describe the expenses that you have had to meet (for example, travel expenses, special diet or complementary therapy) in the table below.

Brief description of item	Cost to you (£'s)
	£ ☐☐☐☐
	£ ☐☐☐☐
	£ ☐☐☐☐
	£ ☐☐☐☐

7. For each of the five sets of statements below, please tick the one box that best describes your own health state today.

(i). Mobility

I have no problems in walking about…….…… ☐
I have some problems in walking about …….…… ☐
I am confined to bed ……..…… ☐

(ii). Self-care

I have no problems with self-care.…….…….... ☐
I have some problems washing and dressing myself…….…….. ☐
I am unable to wash or dress myself.…….…….. ☐

(iii). Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities.……... ☐
I have some problems with performing my usual activities.……..... ☐
I am unable to perform my usual activities.…… ☐

(iv). Pain/discomfort

I have no pain or discomfort.…… ☐
I have moderate pain or discomfort.……..…… ☐
I have extreme pain or discomfort.…….. ☐

(v). Anxiety/depression

I am not anxious or depressed…… ☐
I am moderately anxious or depressed.……..…… ☐
I am extremely anxious or depressed.……..... ☐

Appendix 11 Unit costs for the health economics analysis

Resource item	Face-to-face cost (£)	Telephone call cost (£)	Source
GP surgery visit/contact	36	22	Curtis and Netten[53] (p. 167) – with qualification, based on average visit time/telephone call
GP home visit	120	NA	Curtis and Netten[53] (p. 167) – with qualification, based on average time
District nurse	27	NA	Curtis and Netten[53] (p. 159) – per home visit including qualifications
Contact with oncology hotline for advice	N/A	8.50	Expert opinion
Contact with hospital oncology nurse clinician for advice	105	NA	Department of Health[87] – NHS trusts and PCTS combined – non-consultant led attendance non-admitted face to face
Contact with hospital oncology clinic for advice	129	NA	Department of Health[87] – NHS trusts and PCTS combined – consultant led attendance non-admitted face to face
Hospital inpatient stay	523	NA	Curtis and Netten[53] (p. 119) – non-elective (short)
Hospital accident and emergency department	37 (131[a])	NA	Curtis and Netten[53] (p. 119) – walk-in services leading to admitted (admitted/inpatient stay)
Hospital general outpatient clinic	136	NA	Curtis and Netten[53] (p. 119) – outpatient procedures, weighted average of all adult outpatient attendances

NA, not applicable.

a The cost of admission.

Appendix 12 Drug costs used for the health economic analysis

Antiemetic/drug	Dose	Cost	Source
Cyclizine (Valoid®, Amdipharm)	Orally – 50 mg three times a day for 7 days	50 mg, net price 100-tablet pack = £7.41	BNF[64]
Domperidone	Orally – 20 mg four times a day for 7 days	10-mg tablets/pack size 30 = £0.28; two packs = £0.56	eMIT[63]
Ondansetron	Intravenously – 8 mg on day of chemotherapy	8 mg/4 ml solution for injection ampoules/pack size 5 = £1.94 = £0.39 per injection	eMIT[63]
	Orally – 8 mg twice a day for 3 days	8-mg tablets/pack size 10 = £0.99	
Dexamethasone	Intravenously – 8 mg on day of chemotherapy	8 mg/2 ml solution for injection vials/pack size 5 = £8.37 = £1.67 per injection	eMIT[63]
	Orally – 8 mg 1 day, 4 mg 1 day, 2 mg 1 day	2-mg tablets/pack size 50 = £2.08	
Palonosetron (Aloxi®, IS Pharmaceuticals)	Intravenously – 250 μg on day of treatment	50 μg/ml, net price 5-ml ampoule = £55.89; five ampoules = £279.45	BNF[64]
Metoclopramide	Orally – 10 mg four times a day for 7 days	10 mg, net price 28-tablet pack = £0.17	eMIT[63]
Ondansetron (Zofran)	Orally – 8 mg 1–2 hours before treatment	4 mg, net price 30-tablet pack = £107.91	BNF[64]
Levomepromazine (Nozinan®, Sanofi-Aventis)	Orally – 12.5 mg daily for 7 days	25 mg, net price 84-tablet pack = £20.26	BNF[64]
Granisetron	Intravenously – 3 mg on day of chemotherapy	3 mg/3 ml solution for injection ampoules/pack size 5 = £7.95 = £1.59 per injection	eMIT[63]
	Orally – 2 mg daily for 3 days	2-mg tablets/pack size 5 = £5.88	
Aprepitant (Emend®, Merck, Sharp & Dohme)	Orally – 3-day pack, one pack per cycle	Day pack of one 125-mg capsule and two 80-mg capsules = £47.42	BNF[64]
Prochlorperazine (Buccastem®, Alliance/ Stemetil®, Sanofi-Aventis)	Orally – 2.5 mg daily for 7 days	3 mg, net price 5 × 10-tablet pack = £5.89	BNF[64]
Haloperidol	Orally – 1.5-mg tablets, one a day for 7 days	1.5-mg tablets/pack size 28 = £1.66	eMIT[63]
Lansoprazole	30 mg daily for 21 days	30-mg gastroresistant capsules/pack size 28 = £1.14	eMIT[63]

Appendix 13 Protocol

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.

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