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Abstract

Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis

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Objectives: To determine the effects of a policy of using acupuncture, compared with a policy of avoiding acupuncture, on headache in primary care patients with chronic headache disorders. The effects of acupuncture on medication use, quality of life, resource use and days off sick in this population and the cost-effectiveness of acupuncture were also examined.
Design: Randomised, controlled trial.
Setting: General practices in England and Wales.
Participants: The study included 401 patients with chronic headache disorder, predominantly migraine.
Interventions: Patients were randomly allocated to receive up to 12 acupuncture treatments over 3 months or to a control intervention offering usual care.
Main outcome measures: Outcome measures included headache score; assessment of Short Form 36 (SF-36) health status and use of medication at baseline, 3 months and 12 months; assessment of use of resources every 3 months; and assessment of incremental cost per quality-adjusted life-year (QALY) gained.
Results: Headache score at 12 months, the primary end-point, was lower in the acupuncture group than in controls. The adjusted difference between means was 4.6. This result was robust to sensitivity analysis incorporating imputation for missing data. Patients in the acupuncture group experienced the equivalent of 22 fewer days of headache per year. SF-36 data favoured acupuncture, although differences reached significance only for physical role functioning, energy and change in health. Compared with controls, patients randomised to acupuncture used 15% less medication, made 25% fewer visits to GPs and took 15% fewer days off sick. Total costs during the 1-year period of the study were on average higher for the acupuncture group than for controls because of the acupuncture practitioners' costs. The mean health gain from acupuncture during the year of the trial was 0.021 QALYs, leading to a base-case estimate of £9180 per QALY gained. This result was robust to sensitivity analysis. Cost per QALY dropped substantially when the analysis incorporated likely QALY differences for the years after the trial.
Conclusions: The study suggests that acupuncture leads to persisting, clinically relevant benefits for primary care patients with chronic headache, particularly migraine. It is relatively cost-effective compared with a number of other interventions provided by the NHS. Further studies could examine the duration of acupuncture effects beyond 1 year and the relative benefit to patients with migraine with compared to tension-type headache. Trials are also warranted examining the effectiveness and cost-effectiveness of acupuncture in patients with headache receiving more aggressive pharmacological management.

Contents

List of abbreviations

AACP	Acupuncture Association of Chartered Physiotherapists
AE	adverse event
ANCOVA	analysis of covariance
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
HRQoL	health-related quality of life
ICD	International Statistical Classification of Diseases and Related Health Problems
IHS	International Headache Society
MQS	Medication Quantification Scale
NICE	National Institute for Clinical Excellence
QALY	quality-adjusted life-year
SD	standard deviation
SF-36	Short Form 36
SPSS	Statistical Package for the Social Sciences

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 at the end of the table.

Executive summary

Objectives

The primary objective was to determine the effects of a policy of 'use acupuncture', compared with a policy of 'avoid acupuncture', on headache in primary care patients with chronic headache disorders. Secondary objectives were to determine the effects of using acupuncture compared with avoiding acupuncture on medication use, quality of life, resource use and days off sick in this population and to determine the cost-effectiveness of acupuncture.

Methods

Design

This study was conducted as a randomised, controlled trial.

Setting

General practices in England and Wales.

Participants

The study included 401 patients with chronic headache disorder, predominantly migraine.

Interventions

Patients were randomly allocated to receive up to 12 acupuncture treatments over 3 months or to a control intervention offering usual care.

Main outcome measures

The outcome measures included headache score, assessment of Short Form 36 (SF-36) health status and use of medication at baseline, 3 months and 12 months; use of resources was assessed every 3 months; and assessment of incremental cost per quality-adjusted life-year (QALY) gained for the purposes of economic evaluation.

Results

Headache score at 12 months, the primary end-point, was lower in the acupuncture group (mean 16.2, SD 13.7, $n = 161$, 34% reduction from baseline) than in controls (22.3, SD 17.0, $n = 140$, 16% reduction from baseline). The adjusted difference between means was 4.6 (95% confidence interval 2.2 to 7.0, $p = 0.0002$). This result is robust to sensitivity analysis incorporating imputation for missing data. Patients in the acupuncture group experienced the equivalent of 22 fewer days of headache per year (8 to 38). SF-36 data favoured acupuncture, although differences reached significance only for physical role functioning, energy and change in health. Compared with controls, patients randomised to acupuncture used 15% less medication ($p = 0.02$), made 25% fewer visits to GPs ($p = 0.10$) and took 15% fewer days off sick ($p = 0.2$). Total costs during the 1-year period of the study were on average higher for the acupuncture group (£403, $768, €598) than for controls (£217) because of the acupuncture practitioners' costs. The mean health gain from acupuncture during the year of the trial was 0.021 QALYs, leading to a base-case estimate of £9180 per QALY gained. This result was robust to sensitivity analysis. Cost per QALY dropped substantially when the analysis incorporated likely QALY differences for the years after the trial.

Conclusions

Implications for healthcare

The results of the study suggest that acupuncture leads to persisting, clinically relevant benefits for primary care patients with chronic headache, particularly migraine. It is relatively cost-effective compared with a number of other interventions provided by the NHS.

Implications for research

The optimal methods of acupuncture remain unknown and require systematic research. Further studies could examine the duration of acupuncture effects beyond 1 year and the relative benefit to patients with migraine compared with tension-type headache. Trials are also warranted examining the effectiveness and cost-effectiveness of acupuncture in patients with headache receiving more aggressive pharmacological management.

Chapter 1
Introduction

Migraine and tension-type headache give rise to significant health,[1,2] economic[2] and social costs.[2,3] Despite the undoubted benefits of medication,[4] many patients continue to experience significant distress and social disruption. This leads patients to try and health professionals to recommend non-pharmacological approaches to headache care. One of the most popular approaches appears to be acupuncture. Each week, approximately 10% of GPs in England either refer patients to acupuncture or practise it themselves[5] and chronic headache disorder is one of the most commonly treated conditions.[6]

A Cochrane Collaboration review of 26 randomised trials of acupuncture for headache concluded that although "existing evidence supports the value of acupuncture … the quality and amount of evidence are not fully convincing. There is an urgent need for well-planned, large-scale studies to assess the effectiveness and cost-effectiveness of acupuncture under real-life conditions."[7] This report describes a trial that set out to meet this challenge (ISRCTN96537534).

The major design concern was whether to incorporate placebo control. The present authors have previously discussed the methodological issues in using placebo controls in randomised trials both in general[8] and for acupuncture trials in particular.[9] A decision was made to avoid placebo and compare acupuncture with no treatment control, for the following reasons.

First, the intention was to reflect real-world decisions: those made by GPs when managing the care of headache patients, those made by patients when considering treatment options and those made by NHS entities when commissioning health services. The questions that need to be answered to inform these decision include: 'what effects would an acupuncture referral have on a headache patient's pain?' and 'Will he or she use less medication as a result?' rather than 'What is the relevant contribution of the acupuncture and acupuncturist to treatment effects?' The decision made in clinical practice is not that between referring to acupuncture or referring to placebo acupuncture, but between referring or not referring to acupuncture. It is thus to these two possibilities that patients were randomised.

Second, the investigators wanted to investigate the cost-effectiveness of acupuncture. Costs depend on behaviour and, importantly, behaviour depends on knowledge. It is reasonable to assume that a patient who knew that he or she was receiving true acupuncture might act differently to a patient unsure as to whether they were receiving a true or placebo technique. For example, a patient receiving acupuncture might forgo or delay other measures, such as a specialist visit or a change in medication, until the effects of treatment became apparent. A patient in the true acupuncture arm of a placebo-controlled trial may be less willing to do so, on the grounds that they might not be receiving effective treatment. As such, a placebo-controlled trial may not reflect the true costs of acupuncture, were it to be implemented on the NHS.

Third, it is likely that recruitment and patient compliance will be lower in a placebo-controlled trial. Patients do not generally like receiving placebo techniques, especially when, as is the case with acupuncture, several sessions of treatment are required over the course of many weeks. There is evidence that placebo groups may lower recruitment to randomised trials.[10]

Fourth, placebo-controlled trials have power disadvantages compared with those with no treatment control. If one assumes that placebo explains, for example, half of the effect of acupuncture, a trial comparing acupuncture with placebo would require four times as many patients (sample size is proportional to the square of the effect size). The sample size for the current trial was 400 patients, suggesting that 1600 would be required for a placebo-controlled trial. The feasibility of such a trial is questionable.

Fifth, there is reasonable evidence that acupuncture is not a placebo in migraine and excellent evidence that it is not a placebo in general. The Cochrane review[7] included a total of 11 trials comparing acupuncture with placebo acupuncture with patients with migraine. Two found no effects over sham acupuncture, three

showed trends in favour of acupuncture and five trials reported that patients in the acupuncture group did significantly better than those in the sham acupuncture group. The final trial reported a positive trend, but was judged to be uninterpretable owing to the high dropout rate. As an example of one of these trials, Vincent randomised 30 migraine patients to true acupuncture or to a sham technique, in which needles were inserted just under the skin, rather than to the traditional depth of 1 cm or so, and sited a few millimetres away from true acupuncture points. Importantly, Vincent carefully assessed the credibility of the placebo technique by administering a credibility questionnaire to all patients and comparing results between active and placebo groups. Pain scores in the acupuncture group fell by 43% after treatment, an improvement that was maintained at 1-year follow-up; there were no comparable differences in the placebo group and differences between groups were statistically significant.[11] A study that is not part of the Cochrane review provides further 'proof of principle' of an effect of acupuncture against migraine. Patients experiencing the first signs of a migraine attack were randomised to receive acupuncture, sumatriptan or a placebo injection. A full migraine attack was prevented in an approximately similar proportion of patients in the acupuncture and sumatriptan groups, with statistically significant differences between acupuncture and placebo.[12] This evidence is complemented by clinical trials showing differences between acupuncture and placebo for shoulder and neck pain,[13–16] pain after dental surgery[17] and postoperative vomiting.[18]

Finally, although a lack of placebo control may introduce bias, careful identification of the potential biases, attempts to reduce the identified bias (see Chapter 2, Introductory remarks) and appropriate statistical analysis can help to determine an unbiased estimate of the difference between acupuncture and control in this trial.

The type of trial proposed here has been termed 'pragmatic' and has been discussed at some length in the methodological literature.[19]

A second design decision concerned whether to limit the patient group to one specific type of chronic headache disorder. The decision was made to combine chronic tension-type headache and migraine in one study on the grounds that practitioners of acupuncture do not make a distinction between these conditions in their treatment and believe that they can treat both with equal effectiveness. There are several examples of trials in the headache literature that included both patients with tension-type headache and those with migraine. These typically involve treatments, such as behaviour therapies[20,21] or simple analgesics,[22] the effects of which are not likely to be specific to particular types of headache. It may be argued that a disadvantage of combining patients with both diagnoses would be if acupuncture has differential effectiveness for migraine and non-migraine headache. However, this may be seen as a positive advantage of the design: accruing a heterogeneous population and conducting appropriate subgroup analyses is an excellent way of testing whether the effects of acupuncture are diagnosis dependent.

The objective of the trial was as follows. An acupuncture service was established in primary care, then the study sought to determine the effects of a policy of 'use acupuncture' on headache, health status, days off sick and use of resources in patients with chronic headache disorders compared with a policy of 'avoid acupuncture'.

Chapter 2
Methods

Introductory remarks

In designing this study, the authors generally followed the first edition of the 'Guidelines for controlled trials of drugs in migraine', which were developed by the International Headache Society (IHS) Committee on Clinical Trials on Migraine.[23] Departures from these guidelines were largely related to this study's inclusion of patients with both migraine and tension-type headache and the use of an experimental intervention that is not pharmacological. In addition, as the IHS guidelines are "principally for explanatory trials" (meaning those concerned with the pharmacological efficacy of a drug), they were sometimes not suitable for this more pragmatically orientated study.

One important departure from the IHS guidelines concerned the choice of primary end-point. The IHS recommendation is to use number of days with headache per 28 days, whereas a headache score was used in this study. The main argument against using headache days as the principal outcome measure is that some trials of acupuncture have found significant differences in intensity and/or duration of headache, but not in incidence. For example, Lenhard and Waite found that acupuncture reduced the number of migraine headaches per month only from about 4.5 to about 3.5.[24] The effect on duration of headaches was, however, much greater, involving a halving of the average duration. Vincent reported large and statistically significant differences in pain score when assessed using the method proposed in the current trial, but there was no difference between groups for number of days with headache.[11] If only days with headache are measured, it is possible that a clinically relevant reduction in headache duration or severity may be missed. Reporting both a headache score and number of headache days will allow examination of whether acupuncture does indeed affect both the severity and the incidence of headache.

Performance and response bias were identified as the two most important potential sources of bias in the current study design. Performance bias means differential treatment of patients depending on the group assignment. For example, GPs may give a patient receiving acupuncture different medication to one in the control group, perhaps because it was felt that the control patient would need stronger therapy. This would bias the comparison for medication use. Response bias means that patients may modify their answers to questions about pain (and other outcomes) depending on how they believe this response would be interpreted by caregivers. For example, a patient may give an overoptimistic assessment of acupuncture to please the acupuncturist with whom a personal relationship had developed.

An attempt was made to control for performance bias by organising acupuncture treatment such that the GP did not know treatment allocation. In addition, patients were asked not to discuss their treatment allocation with their GP. As it is possible that GPs may learn this information inadvertently, they were explicitly asked not to make decisions based on group allocation in the trial, but on the clinical presentation of the patient. An attempt was made to control for response bias by explicitly and repeatedly informing patients that their responses on outcome assessments were confidential and could not be traced by their caregivers; moreover, that they should 'consciously try to avoid changing their answers depending on how they think others, such as their doctor, might react'. Two other features of the trial reduce the impact of response bias. First, all contact with the study team was by telephone, reducing the impact of social pressure. Second, the end-point was a diary completed several times a day over several weeks. It seems reasonable that response bias is more likely for a single questionnaire than for one repeated many times.

Recruitment

An initial pilot recruitment was conducted in two practices with list sizes of 11,000 and 6500 registered patients. The results suggested that 1.8–2.7% of the practice population would be potentially eligible for the study (aged 18–65 years, consulted for migraine or headache and/or receiving a prescription for migraine). The sample size calculation for the trial (see below) suggested that 400 patients would need to be

randomised. Allowing for attrition and ineligible patients, it was calculated that letters should be sent to approximately 4630 patients, which equates to 31 five-partner GP practices, assuming an average list size of 1500 per partner.

Full members of the Acupuncture Association of Chartered Physiotherapists (AACP) were approached to provide treatments for the study. Each member of the AACP who agreed to participate constituted a 'regional study centre'. Once the treating physiotherapists had been enrolled, nearby GP practices were approached with a request to participate. A list of GP practices in each regional study centre's locality was sent to the physiotherapist.

All practices deemed by the physiotherapist to be within easy travelling distance and with three or more partners were approached. Practices were offered a small honorarium to take part. They were asked to undertake a database search, give consent to contact the patients identified and provide access to enrolled patients' records at 1-year follow-up. Information given to the GPs highlighted a number of points about the trial which encouraged GPs to participate in research. These included the relevance of the research question, the minimal impact on practice workload, the benefits to a number of practice patients and no interference with the patient–physician relationship.

The trial was prospective, but patient identification was retrospective. Searches were conducted on practice databases using either repeat prescriptions alone or repeat prescriptions plus diagnostic terms. Practices were given a list of specific migraine drugs (a search on analgesic prescriptions would be too non-specific and so was not used), and for those practices able to conduct a diagnostic term search, Read terms and International Classification of Diseases (ICD) codes for migraine and tension-type headache. In general, the practices applied the trial age limits to the search criteria. The aim of the searches was to identify a high proportion of potentially eligible individuals, even though many were eventually found to be ineligible.

Potentially eligible patients identified by the search were mailed information about the study and acupuncture. Importantly, this mailing came from the practice – the covering letter was on practice-headed notepaper, signed by the senior partner, and the envelope had a local postmark – so that the trial was introduced by the patient's GP. Interested patients were requested to contact the study co-ordinating centre directly if they wanted further information.

The study finally included 12 separate sites consisting of a single acupuncture practice and two to five local general practices. Study sites were located in Merseyside, London and surrounding counties, Wales, and the north and south-west of England.

Accrual of patients

Practices searched their databases to identify potential participants. GPs then sent letters to suitable patients, providing information about the trial. A researcher at the study centre conducted recruitment interviews, eligibility screening and baseline assessment by telephone. Patients' conditions were diagnosed as migraine or tension-type headache, following the criteria of the IHS.[25] Patients aged 18–65 years and who reported an average of at least two headaches per month were eligible. Patients were excluded for any of the following: onset of headache disorder less than 1 year before or at age 50 years or older, pregnancy malignancy, cluster headache (IHS code 3), suspicion that the headache disorder had specific aetiology (IHS code 5–11), cranial neuralgias (IHS code 12) and acupuncture treatment in the previous 12 months. Eligible patients completed a baseline headache diary for 4 weeks. Patients who provided written informed consent, had a mean weekly baseline headache score of 8.75 or more and completed at least 75% of the baseline diary, were randomised to a policy of 'use acupuncture' or 'avoid acupuncture'.

Sample size

A sample size calculation was undertaken using values adapted from Vincent's trial, which used the same outcome measure as the current trial at the same 1-year follow-up.[11] Anonymised, individual patient data were obtained from the author. Data for patients who would not have met the inclusion criteria for the current trial were ignored. It was assumed that the control group would experience a change in pain score as reported for the placebo group and that standard deviations would be inflated by 25% to reflect the wider inclusion criteria in this trial. A power of 90% and an alpha of 5% were used. It was estimated that the study would require 288 evaluable patients to detect a reduction in headache score of 35% in the

acupuncture group, compared with 20% in controls. A dropout rate of about 25% was assumed and the plan was to randomise 400 patients.

Informed consent and initial interview

Recruitment interviews took place over the telephone. They were conducted by a registered general nurse with experience of trial recruitment, or someone under their supervision. At the interview, a standard description of the trial was given. Subjects were told that their acupuncture treatment costs would be covered for the duration of the study. They were also asked not to receive acupuncture from anyone but the study physiotherapist during the trial. Patients were screened for eligibility using the study inclusion and exclusion criteria. Preliminary oral consent was sought, although subjects were informed that they did not have to make a decision immediately if they did not want to. Subjects were told to complete written consent and return this with the first week of diaries. The result of each patient's recruitment appointment (included, excluded, no consent) was recorded.

Having obtained consent, researchers instructed patients on the use of all study diaries and forms in an interactive manner. They also informed patients that the results of the study diaries and all other information returned to the study centre would remain confidential and would not be released to GPs or study physiotherapists. Patients were asked to try consciously to avoid modifying their responses on the diaries depending on how they thought others, such as their doctor, may react.

The interviewer recorded the patient's name, gender, date of birth and chronicity. Chronicity was assessed by asking the question: 'When did you first start having regular headaches?' The researcher also took contact details for a friend or relative to allow the study team to maintain follow-up with the patient if he or she moved home during the trial.

Diagnoses were in one of two categories: migraine (classification 1 of the IHS system) or tension-type headache (classification 2 of the IHS system). Diagnosis was made using a questionnaire that has been piloted in a large, prospective observational study by the Münchener Model project. It is derived from the standard IHS Classification System.[25]

Section A of the questionnaire asked the following five questions: '(1) Is the pain often one-sided? (2) Can the pain be described as pulsating or throbbing? (3) Do the headaches severely restrict everyday activities? (4) Are the headaches sometimes accompanied by sickness and/or vomiting? (5) Do you sometimes feel sensitive to light and/or noise during the headache attacks?'

If the patient answered 'yes' to two or more of these questions they were asked to complete a further three questions: '(6) Does the pain get worse when you are climbing stairs or when you do any other kind of physical exercise? (7) Have you suffered from at least five headaches of this kind? (8) If you do not treat this type of headache, does it normally last between 4 and 72 hours?'

For a diagnosis of migraine to be made the following criteria in section A had to be met: from questions 1, 2, 3 and 6 at least two should be answered 'yes', from questions 4 and 5 at least one should be answered 'yes', and questions 7 and 8 should both be answered 'yes'.

Section B asked four different questions: '(1) Do the headaches affect the whole head? (2) Can the headache be described as dull, pressing or pulling pain? (3) Is it true that your headache does not get worse during everyday activities such as going for a walk, climbing stairs? (4) Can you carry out your daily chores despite the headaches?'

If the patient answered 'yes' to two or more of these questions they were asked to fill in a further five questions: '(5) Are the headaches sometimes accompanied by sickness? (6) Do you sometimes have to vomit when you suffer from a headache? (7) Do you sometimes feel sensitive to light during a headache? (8) Do you sometimes feel sensitive to noise when you have a headache?'

For a diagnosis of chronic tension-type headache to be made the following criteria from section B had to be met: from questions 1, 2, 3 and 4 at least two should be answered 'yes', from questions 5, 7 and 8 at least two should be answered 'no', and question 6 should be answered 'no'. For a diagnosis of episodic tension-type headache to be made the following criteria from section B had to be met: from questions 1, 2, 3 and 4 at least two should be answered 'yes', questions 5 and 6 should both be answered 'no', and from questions 7 and 8 at least one should be answered 'yes'.

If all criteria for migraine were met, the patient was categorised as 'migraine'. If the criteria for

either chronic tension-type headache or episodic tension-type headache were met, and not all migraine criteria were met, the patient was categorised as 'non-migraine'. If neither diagnosis could be made from the scores given the following steps were taken. The scores from section A were checked and if only one criterion had not been met then a diagnosis of migraine was assumed. If more than one criterion had not been met then a non-migraine diagnosis was given.

Treatment allocation

When the first 4 weeks of data recording were completed a researcher at the study centre checked the subjects for inclusion (compliance and headache incidence).

Randomisation took place by a randomised, minimisation algorithm ('biased coin') using gender, age, chronicity, severity, diagnosis and number of patients per group as the minimised variables. The minimisation weighting for each variable was 10, 10, 10, 10, 15 and 20, respectively, added to a random integer between 0 and 100. Minimisation was stratified by site. The use of secure minimised randomisation ensured that those responsible for recruitment were unable to predict treatment allocation before entering a patient into the study or change allocation after registration.

The result of the randomisation was sent by post to the patient, the GP and the physiotherapist conducting the acupuncture. The patient letter thanked the patient for his or her participation, described the results of the randomisation and explained 'what will happen next' (e.g. a patient in acupuncture group will receive a call from the physiotherapist to arrange an appointment). Patients were told to see their GP if they needed to, but only if they would do so normally if they were not taking part in the trial. They were also given a telephone number to call if they had any enquiries. A copy of the patient letter was kept by the study centre as auditable proof of treatment allocation.

The letter to the GP gave details of the patient's name, contact details and, where appropriate, practice code number, but not the group to which the patient had been assigned. GPs were told that the letter was purely for information purposes and that they need take no action. The letter also stated that there was no need to treat patients differently depending on their treatment allocation, should this become apparent, and that GPs should make a conscious effort to disregard patient participation in the trial when making treatment decisions.

The letter to the study physiotherapist included a list of patients randomised to acupuncture with their contact details and a form on which treatment details were recorded.

Treatment

Patients randomised to acupuncture received, in addition to standard care from GPs, up to 12 treatments over 3 months from an advanced member of the AACP. All acupuncturists in the study had completed a minimum of 250 hours of postgraduate training in acupuncture, which included the theory and practice of traditional Chinese medicine; they had practised acupuncture for a median of 12 years and treated a median of 22 patients per week. The acupuncture point prescriptions used were individualised to each patient and were at the discretion of the acupuncturist. Patients randomised to 'avoid acupuncture' received usual care from their GP but were not referred to acupuncture.

The study physiotherapists recorded the date and approximate duration of each completed acupuncture treatment and were asked to record whether, in their opinion, the patient completed the course of acupuncture.

Outcome assessment

Patients completed a daily diary of headache and medication use for 4 weeks at baseline and then 3 months and 1 year after randomisation. Before each follow-up, patients were contacted by telephone. This was an opportunity to warn patients that a pack was in the post and to confirm address details. The diary recorded headache severity and medication use. Severity of headache was recorded four times a day on a six-point Likert scale (box) and the total summed to give a headache score. Medication use was assessed by asking patients to describe the exact proprietary name of the drugs that they were taking and the number of doses of each. The diary contained reminders that the information in the diary was confidential and could not be traced back to the patient by the study physiotherapists or a patient's GP. It also reminded patients that they should consciously try to avoid changing their answers

depending on how they thought others, such as their doctor, may react.

Patients were instructed to send the weekly diary to the study centre at the end of each week using a reply-paid envelope. A researcher at the study centre checked each diary and contacted patients directly if there were any missing, inconsistent or illegible data. In addition, a researcher at the study centre telephoned patients after the first week of baseline recording to ask them whether they had any questions about how to fill in the diaries. After receipt of each week of each patient's study diary and resolution of any ambiguities, appropriate details were added to the study database.

The SF-36 health status questionnaire was completed at baseline, 3 months and 1 year. Every 3 months after randomisation, patients completed additional questionnaires that monitored use of headache treatments and days sick from work or other usual activity.

Every 3 months following randomisation, patients completed two forms that monitored use of other therapies and time taken sick from work or other usual activity.

The adjunctive therapies form asked: 'What have you done to treat your HEADACHE in the PAST THREE MONTHS?' The associated checkboxes were: visited your GP, visited a specialist at a hospital, taken non-prescription medication bought from a shop, taken homoeopathic or herbal remedies bought from a shop, received acupuncture, received treatment from a physiotherapist other than the trial acupuncturist, received treatment from an osteopath or chiropractor, received treatment from a homoeopath, received treatment from a herbal medicine practitioner, received treatment from a hypnotherapist, received treatment from a counsellor or psychotherapist, attended yoga or meditation classes, and received treatment from another type of health practitioner (please describe). For each response where treatment was received from a practitioner, the number of treatment sessions was recorded. The response for received acupuncture included the options: 'received from trial acupuncturist', 'received from other practitioner'. Patients were asked whether treatment was provided on the NHS or whether they paid for treatment and, if so, how much they paid for the last consultation. For each over-the-counter remedy, patients were asked to estimate how much they spent. The survey instrument was similar to one developed (with appropriate piloting) for use in a large survey of the use of complementary therapies by women with breast cancer.[25]

The days-off sick form asked: 'On about how many days IN THE PAST THREE MONTHS have you been kept from your usual activities (such as work, school or housework) because of headaches?'

Withdrawals were contacted by telephone and asked whether their withdrawal was due to one of the following reasons: ineffectiveness of treatment, treatment too much of a hassle, adverse effects, moved, intercurrent illness, consent withdrawal, and other.

While the study was under way an additional end-point was added. Patients were contacted 1 year after randomisation and asked to give a global estimate of current and baseline headache severity on a scale of 0–10. In this way, data could be obtained from patients who were unwilling to complete diaries, for use in sensitivity analysis.

Likert scale of headache severity

0 no headache
1 I notice the headache only when I pay attention to it
2 Mild headache that can be ignored at times
3 Headache is painful, but I can do my job or usual tasks
4 Very severe headache; I find it difficult to concentrate and can do only undemanding tasks
5 Intense, incapacitating headache

Data entry

Data entry was conducted blind to treatment allocation. Complete double-entry of data was undertaken using automated consistency and logical checks. Confidentiality was ensured by appropriate security software. Errors and inconsistencies were resolved by reference to the original patient records.

Missing or ambiguous data were treated as follows:

- **chronicity**: rounded to the nearest year; if a range was given, the higher number was taken
- **severity**: if two tickboxes were marked, the higher was taken
- missing data for **headache severity**: within a week, the average of the two scores either side, rounded up; whole week missing, treat as missing
- **missing data for pills**: assumed none taken

- **missing data for use of other therapies for headache**: assumed no use if the 'yes/no' box was not checked; assumed private payment for any visits to practitioners of complementary therapy or over-the-counter treatment, and NHS payment for visits to practitioners of conventional therapy; if no response was given to number of visits or cost, this was treated as missing data (i.e. number of observations was reduced accordingly)
- **missing data for days off sick**: treated as missing data
- **missing data for the Short Form 36 (SF-36)**: treated as missing data.

Scaled medication scores were computed automatically using a version of the Medication Quantification Scale (MQS).[27] This has been shown to be a reliable, valid and sensitive method of assessing medication use in patients with chronic pain. The basic methodology is that drugs are scaled relative to their recommended daily doses. Prophylactic and treatment drugs were scaled separately. No multiplication factor was used for prophylactic drugs.

Data monitoring and adverse effects

No interim analyses of headache outcome were planned.

Adverse events (AEs) were monitored by enclosing a coded, Freepost postcard in the informational materials given at baseline. Patients were instructed to complete a card each time they experienced an AE that they have not previously reported to the study centre.

On receipt of an AE card at the study centre that detailed an acupuncture AE, a doctor called the subject for further information. The doctor recorded details as to the nature of the AE, date and time of occurrence, duration of the AE, intensity and severity, clinical course, necessary therapeutic measures and likely causality.

Causality was assessed as follows. The AE was described as 'probable' if all of the following applied: there was a rational relationship between the occurrence of the AE and the time of treatment, the AE had already been described as an AE of acupuncture according to the largest survey of acupuncture AEs at the time the trial was opened (the Tromsø study[28]), regression or disappearance of the AE after discontinuation of treatment or dose reduction, reappearance of the AE after repeated exposure, and the AE could not be plausibly explained in terms of other causal factors. The AE was described as 'possible' if all of the following applied: there was a rational relationship to the time of treatment administration, the AE had already been described as an AE of acupuncture according to the Tromsø study, and the AE could be explained by numerous other factors. The AE was described as 'improbable' if all of the following applied: there was a rational relationship to the time of treatment administration, the AE had not been reported so far as a side-effect of the treatment according to the Tromsø study, the AE persisted after discontinuation of the treatment or dose reduction, repeated exposure does not lead to reappearance of the AE, and the AE could be explained by numerous other factors. The AE was described as 'no relationship' if both of the following applied: there was no rational relationship to the time of treatment administration, and the AE was evidently caused by other factors (e.g. a symptom of a concomitant disease). The AE was described as 'unable to evaluate' if the amount and content of data did not permit a judgement of the relationship to the treatment. Whether the AE was described as probable, possible, improbable, no relationship or unable to evaluate was at the discretion of a single researcher.

Stopping rule

The stopping rule was as follows: once 400 subjects had been randomised, any recruitment interviews that had been arranged were honoured. Subjects yet to be contacted, as well as those subsequently expressing an interest in the trial, were sent a letter thanking them for their interest, but explaining that the trial was now closed.

Statistical considerations

The primary outcome measure was headache score at the 1-year follow-up. Secondary outcome measures included headache score at 3 months, days with headache, use of medication scored with the MQS, the SF-36, use of resources and days off usual activities. The statistical plan was revised to use adjusted rather than unadjusted analyses after publication of the initial protocol but before any analyses had been conducted. Data were analysed on Stata 8 software (Stata Corporation, College Station, Texas, USA) using analysis of covariance (ANCOVA) for continuous end-points,

χ^2 for binary data and negative binomial regression for count data such as number of days of sick leave. Randomisation strata were entered into regression models as covariates. Data were analysed according to allocation, regardless of the treatment received.

Economic analysis

For the purposes of this evaluation it was assumed that the acupuncture intervention was to be provided in the community by the NHS; hence, costs were measured from both an NHS perspective and a societal perspective. Effectiveness was measured in terms of the quality-adjusted life-years (QALYs) gained. For the base case, a conservative approach was taken by excluding savings in productivity costs and adopting a time horizon of 12 months, the length of the trial follow-up. Given the time horizon, no need arose to discount costs or effects. Costs were measured in UK prices (£) for 2002/03. The SF-6D algorithm devised by Brazier and colleagues,[29] a single index measure of health-related quality of life (HRQoL), was used to calculate data for each patient at baseline, 3 months and 12 months from patients' responses to the SF-36 at each of these time-points.

The patients reported unit costs associated with non-prescription drugs and private healthcare visits. The health component of the harmonised index of consumer prices was used to inflate these costs to 2003 levels.[30] *Table 1* details other unit costs. Standard NHS costs for a specific service were used if these had been published.[31] For NHS visits to practitioners of complementary or alternative medicine the mean cost of a private visit, as recorded in the trial, was used. Drug prescriptions were recorded for a subgroup of patients (n = 71) from the database of their GP.

To estimate the cost of the study intervention, the standard cost (including overheads, capital and training) for an NHS community physiotherapist[31] was multiplied by the contact time for each individual patient with the physiotherapist trained in acupuncture. The cost of needles and other consumables were not included, as these are negligible compared with staff time.[35] It was assumed that acupuncture sessions on the NHS, but not by a study acupuncturist, had a duration equal to the mean duration of a study session, 31 minutes.

Linear regression (ANCOVA) with the randomisation strata and baseline SF-6D as covariates was used to estimate differences between groups for cost and effectiveness on the intention-to-treat principle. Exact methods for estimating confidence intervals for incremental cost-effectiveness ratios are not possible, and therefore the net benefit approach was used to estimate parametric cost-effectiveness acceptability curves (CEACs)[36,37] Net benefit analysis usually requires any gain in outcome (e.g. QALYs) from an intervention to be valued by using the ceiling ratio, λ, defined as the decision-makers' willingness to pay for an additional unit of health outcome, and from this any additional costs are subtracted. A λ equal to £30,000 per QALY is a threshold of cost-effectiveness consistent with decisions that have been taken by the National Institute for Clinical Excellence (NICE).[38] The CEACs show the probability that the incremental cost-effectiveness is below λ, for a range of values of λ. SPSS for Windows, version 11.0.0, was used to perform statistical analysis and Microsoft Excel 2002 SP2 was used for the calculation of CEACs.

For the base case no imputation was done for cases missing HRQoL data; therefore, the cost-effectiveness analysis sample was those patients who reported SF-36 completely in all three questionnaires and for whom QALYs could thus be calculated. Data on use of resources and cost were available for a larger sample of cases, and for these variables statistics are reported for all responding patients.

Economic evaluation is subject to uncertainty not just because of sample variation but also because of assumptions made and generalisability issues.[39] Therefore, sensitivity analyses were conducted to test the robustness of the results to changes in the base-case assumptions. The staff time and grade associated with acupuncture treatment were varied, and different strategies used for missing data. Productivity costs were added by multiplying the number of days sick from work or other usual activity, as reported by the study patients, by the average earnings per day in England and Wales[33] inflated to 2003 prices.[34] The base-case analysis does not project beyond the 12 months of observation. It is improbable that the difference in HRQoL observed at 12 months would disappear immediately. In the sensitivity analysis it was assumed that, although the study acupuncture intervention was delivered as a one-off package and not taken up again in subsequent years, the difference in costs (excluding acupuncture) and effectiveness would gradually subside at the same rate over varying periods. Costs were discounted at 6% and QALYs at 1.5%, in keeping with the conventions of UK central government.

TABLE 1 *Unit costs*

Cost component	Unit cost (£)	Source of unit cost	Details[a]
Acupuncture			
Study acupuncture visit (per hour)	43.00	Netten and Curtis 2002[31]	Clinic visit to community physiotherapist
Non-study NHS acupuncture visit	22.28	Netten and Curtis 2002,[31] trial data	£0.72 × 31 minutes
Private acupuncture visit	Various	Trial data	Patients reported individual costs
NHS visits			
GP	27.00	Netten and Curtis 2002[31]	Cost per clinic consultation
Outpatient	82.00	Netten and Curtis 2002[31]	Generic cost per outpatient attendance
Counsellor or psychotherapist	35.75	Netten and Curtis 2002[31]	Clinic visit to community-based counsellor
Physiotherapy	17.00	Netten and Curtis 2002[31]	Clinic visit to community physiotherapist
Chiropractor or osteopath	25.38	Trial data	Mean cost of a private visit
Medical herbalist	18.17	Trial data	Mean cost of a private visit
Homoeopath	31.46	Trial data	Mean cost of a private visit
Hypnotherapist	38.75	Trial data	Mean cost of a private visit
Relaxation therapy	6.92	Trial data	Mean cost of a private visit
Other costs (base case)			
Private healthcare visits	Various	Trial data	Patients reported individual costs
Over-the-counter medication	Various	Trial data	Patients reported individual costs
Other costs (sensitivity analysis)			
GP cost per hour	118.00	Netten and Curtis 2002[31]	Cost per hour of patient contact
Private acupuncture	28.38	Trial data	Mean cost of a private visit
Prescription drugs	Various	BNF, September 2002[32]	Specified by dosage and pack size
Cost of a day off sick	88.05	Office for National Statistics[33]	Average earnings per hour × average working hours = £11.74[33] × 7.5[34]

[a] All NHS visit costs include salary, on-costs, qualifications, overheads and capital overheads.
BNF, British National formulary.

Chapter 3
Results

Recruitment took place between November 1999 and January 2001. *Figure 1* shows the flow of participants through the trial. Compliance of patients was good: only three patients in the control group reported receiving acupuncture outside the study.

Acupuncture patients received a median of nine (interquartile range 6–11) treatments, with a median of one treatment per week. The dropout rate was close to that expected and approximately balanced between groups. Patients who dropped out were similar to completers in terms of gender, diagnosis and chronicity, but they were slightly younger (43 versus 46 years, $p = 0.01$) and had higher headache score at baseline (29.3 versus 25.6, $p = 0.04$). *Table 2* shows baseline characteristics by group for completers and non-completers. Thirty-one of the patients who withdrew provided 3-month data and an additional 45 provided a global assessment. Only 6% of patients (12 in each group) provided no data for headache after randomisation.

Table 3 shows results for medical outcomes for patients completing the 12-month follow-up. In the primary analysis mean headache scores were significantly lower in the acupuncture group. Scores fell by 34% in the acupuncture group compared with 16% in controls ($p = 0.0002$). When the prespecified cut-off of 35% was used as a clinically significant reduction in headache score, 22% more acupuncture patients improved than controls, equivalent to a number needed to treat of 4.6 [95% confidence interval (CI) 9.1 to 3.0]. The difference in days with headache of 1.8 days per 4 weeks is equivalent to 22 fewer days of headache per year (95% CI 8 to 38). The effects of acupuncture seem to be long lasting; although few patients continued to receive acupuncture after the initial 3-month treatment period (25, ten, and six patients received treatment after 3, 6, and 9, months, respectively), headache scores were lower at 12 months than at the follow-up after treatment.

Medication scores at follow-up were lower in the acupuncture group, although differences between groups did not reach statistical significance for all end-points. Analysis of the patient questionnaires revealed many instances in which drugs used to treat acute attacks, such as a triptan, had been defined by the patient as a drug to prevent a migraine. In an unplanned analysis, therefore, the scores for prophylactic and treatment medication were combined and groups were compared with adjustment for baseline scores (see last row of *Table 3*). Looking at total medication taken by patients after randomisation, weekly use fell by 23% in controls, but by 37% in the acupuncture group (adjusted difference between groups 15%, 95% CI 3 to 27%, $p = 0.01$).

'Days with headache' was defined very liberally as days on which a patient recorded headache severity of at least 1 out of 5 for at least one time-point. The mean number of days with headache reported here is accordingly larger than that seen in other trials. Therefore, the analyses were repeated using more conservative definitions of days with headache, for example, defining a headache day as one on which moderate or severe headache was reported. The results shown in *Table 4* show that differences between groups are not sensitive to the definition of headache day.

SF-36 data generally favoured acupuncture (*Table 5*), although differences reached statistical significance only for physical role functioning, energy and change in health.

Interaction analyses were conducted to determine which patients responded best to acupuncture. Although improvements in mean headache score over control were much larger for migraine patients (4.9, 95% CI 2.4 to 7.5, $n = 284$) than for patients who did not meet the criteria for migraine (1.1, 95% CI –2.4 to 4.5, $n = 17$), the small numbers of patients with tension-type headache preclude the exclusion of an effect of acupuncture in this population. The interaction term for baseline score and group was positive and significant ($p = 0.004$), indicating larger effects of treatment on patients with more severe symptoms, even after controlling for regression to the mean. Predicted improvements in headache score for each quartile of baseline score in acupuncture patients are 22%, 26%, 35% and 38%; *Figure 2* shows comparable data for days with headache. The results of acupuncture treatment were not influenced by age, chronicity or gender.

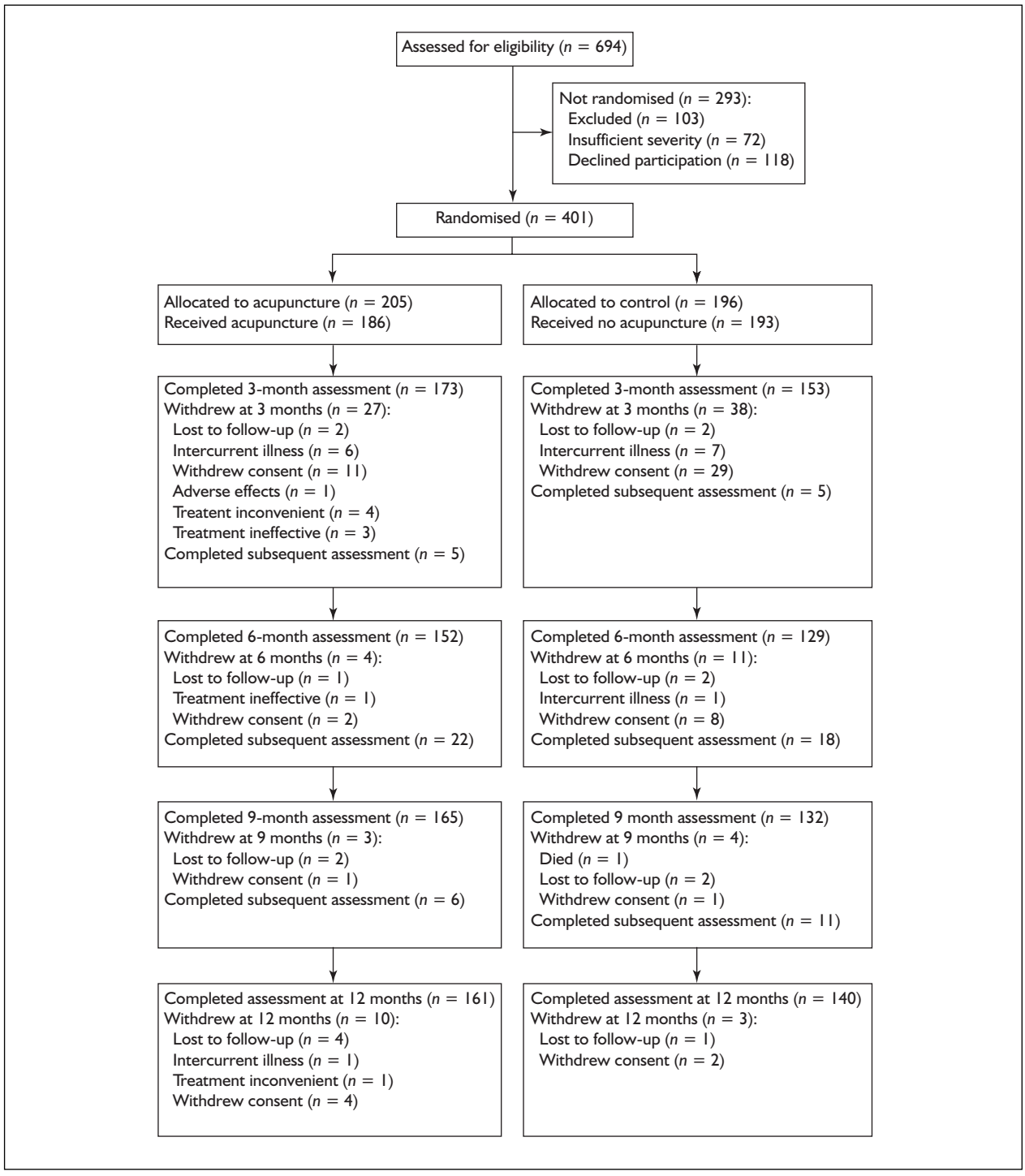

FIGURE 1 *Flow of participants through the trial*

Table 6 shows data on use of resources. Patients in the acupuncture group made fewer visits to GPs and complementary practitioners than those not receiving acupuncture and took fewer days off sick. Confirming the excellent safety profile of acupuncture,[40,41] the only adverse event reported was five cases of headache after treatment in four subjects.

Sensitivity analysis

The basis of the sensitivity analyses was the imputation of missing data using linear regression. In brief, a regression model provides a prediction of every patient's 1-year headache score on the basis of baseline headache score and the randomisation strata (age, gender, chronicity,

TABLE 2 *Baseline characteristics*

	Completers			Non-completers		
	Acupuncture (*n* = 161)	**Control (*n* = 140)**	**Total (*n* = 301)**	**Acupuncture (*n* = 44)**	**Control (*n* = 56)**	**Total (*n* = 100)**
Mean age in years (SD)	46.4 (10.0)	46.2 (10.8)	46.3 (10.4)	43.1 (12.5)	43.1 (12.8)	43.1 (12.6)
Female gender	133 (83)	120 (86)	253 (84)	45 (80)	39 (89)	84 (84)
Migraine diagnosis	152 (94)	132 (94)	284 (94)	51 (91)	42 (95)	93 (93)
Mean chronicity in years (SD)	21.3 (14.5)	21.9 (13.3)	21.6 (14.0)	21.5 (13.6)	20.7 (13.1)	21.0 (13.3)
Baseline score (SD)	24.6 (14.1)	26.7 (16.8)	25.6 (15.4)	29.4 (19.4)	29.3 (17.0)	29.3 (18.0)

Values are numbers (percentages) of participants unless otherwise indicated.

TABLE 3 *Headache and medication outcomes*

	Baseline		After treatment (at 3 months after randomisation)					At 12 months				
End-point	**Acupuncture (*n* = 161)**	**Controls (*n* = 140)**	**Acupuncture (*n* = 159)**	**Controls (*n* = 136)**	**Difference[c]**	**95% CI**	***p***	**Acupuncture (*n* = 161)**	**Controls (*n* = 140)**	**Difference[c]**	**95% CI**	***p***
Weekly headache score	24.6 (14.1)	26.7 (16.8)	18.0 (14.8)	23.7 (16.8)	3.9	1.6 to 6.3	0.001	16.2 (13.7)	22.3 (17.0)	4.6	2.2 to 7.0	0.0002
Days of headache in 28 days	15.6 (6.6)	16.2 (6.7)	12.1 (7.2)	14.3 (7.3)	1.8	0.7 to 2.9	0.002	11.4 (7.5)	13.6 (7.5)	1.8	0.6 to 2.9	0.003
Clinically relevant improvement in score[a]	–	–	65 (41%)	37 (27%)	14%	3 to 24%	0.014	87 (54%)	45 (32%)	22%	11 to 33%	0.0001
Clinically relevant improvement in frequency[b]	–	–	36 (23%)	17 (13%)	10%	2 to 19%	0.024	49 (30%)	21 (15%)	15%	6 to 25%	0.002
Scaled pain medication (weekly)	16.5 (18.1)	14.3 (17.6)	11.0 (13.6)	11.4 (14.1)	1.6	–0.7 to 3.9	0.16	8.5 (12.2)	8.7 (12.6)	1.2	–0.6 to 3.1	0.19
Scaled prophylactic medication (weekly)	9.0 (17.8)	13.3 (22.2)	7.9 (17.6)	11.5 (21.3)	0.7	–2.4 to 3.8	0.7	5.0 (14.4)	11.1 (21.3)	3.9	0.5 to 7.4	0.026
Use of any prophylactic medication in 28 days	40 (25%)	45 (32%)	34 (21%)	39 (29%)	7%	–3 to 17%	0.15	22 (14%)	37 (26%)	13%	4 to 22%	0.005
Total scaled medication (weekly)	25.4 (25.1)	27.6 (28.8)	18.9 (21.7)	22.9 (24.8)	2.9	–1 to 6.7	0.14	13.4 (18.2)	19.8 (24.4)	5.2	5.3 to 9.2	0.009

Values are means (SD) unless otherwise indicated.
Higher scores indicate greater severity of headache and increased use of medication.
Differences between groups were calculated by ANCOVA.
[a] As defined in study protocol: ≥ 35% improvement in headache score from baseline.
[b] IHS definition: ≥ 50% reduction in days with headache.[23]
[c] Adjusted difference: positive favours acupuncture.

TABLE 4 *Outcome for number of days with headache per 28 days given different criteria for 'headache day'*

	Baseline		At 12 months					Improvement[a]				
Criterion	**Acupuncture (*n* = 161)**	**Controls (*n* = 140)**	**Acupuncture (*n* = 159)**	**Controls (*n* = 136)**	**Difference[b]**	**95% CI**	***p***	**Acupuncture (*n* = 159)**	**Controls (*n* = 136)**	**Difference[b]**	**95% CI**	***p***
Any headache (original analysis)	15.6 (6.6)	16.2 (6.7)	11.4 (7.5)	13.6 (7.5)	1.8	0.6 to 2.9	0.003	49 (30%)	21 (15%)	15%	6 to 25%	0.002
At least mild headache	13.5 (6.3)	13.8 (6.5)	9.1 (6.5)	10.9 (6.6)	1.6	0.5 to 2.6	0.004	56/161 (35%)	25/140 (18%)	17%	7 to 27%	0.001
Moderate or severe headache	8.5 (5.0)	8.9 (5.7)	5.4 (4.8)	6.9 (5.6)	1.2	0.4 to 2.1	0.006	63/161 (39%)	37/140 (26%)	13%	2 to 23%	0.02

[a] IHS definition: ≥ 50% reduction in days with headache.[23]
[b] Adjusted difference: positive favours acupuncture.

TABLE 5 *Health status as scored on the SF-36*

	Baseline		After treatment (3 months after randomisation)					At 12 months				
End-point	**Acupuncture**	**Controls**	**Acupuncture**	**Controls**	**Difference[a]**	**95% CI**	***p***	**Acupuncture**	**Controls**	**Difference[a]**	**95% CI**	***p***
Physical functioning	*n* = 161: 81.9 (21.1)	*n* = 139: 85.3 (18.4)	*n* = 156: 82.6 (20.7)	*n* = 134: 81.7 (21.3)	3.0	–0.2 to 6.2	0.07	*n* = 157: 82.6 (23.3)	*n* = 138: 82.3 (20.2)	2.7	–0.7 to 6.0	0.12
Role functioning – physical	*n* = 161: 60.4 (40.2)	*n* = 139: 59.4 (38.6)	*n* = 154: 63.5 (41.4)	*n* = 134: 56.7 (40.8)	5.0	–3.6 to 13.5	0.3	*n* = 156: 70.0 (39.2)	*n* = 137: 60.3 (41.3)	8.8	0.6 to 17.0	0.036
Role functioning – emotional	*n* = 160: 73.2 (36.6)	*n* = 140: 69.6 (39.4)	*n* = 155: 72.4 (39.7)	*n* = 130: 74.7 (36.3)	–5.1	–13 to 2.9	0.2	*n* = 154: 76.0 (37.0)	*n* = 136: 70.1 (39.2)	4.9	–3.5 to 13.4	0.3
Energy or fatigue	*n* = 161: 47.9 (19.9)	*n* = 140: 52.2 (20.2)	*n* = 154: 51.3 (21.6)	*n* = 134: 51.8 (20.8)	1.9	–1.8 to 5.7	0.3	*n* = 158: 55.4 (20.7)	*n* = 139: 54.2 (20.7)	4.2	0.6 to 7.7	0.02
Emotional well-being	*n* = 161: 66.0 (15.0)	*n* = 140: 67.0 (14.1)	*n* = 156: 66.6 (15.3)	*n* = 134: 67.8 (14.0)	–0.9	–3.8 to 2.0	0.5	*n* = 158: 68.3 (15.4)	*n* = 139: 68.9 (14.7)	0.0	–2.9 to 2.9	1
Social functioning	*n* = 161: 71.0 (24.9)	*n* = 140: 73.6 (21.6)	*n* = 156: 73.6 (24.8)	*n* = 134: 75.4 (22.6)	–0.8	–5.6 to 4.1	0.8	*n* = 158: 77.9 (25.2)	*n* = 138: 74.8 (23.2)	4.2	–0.8 to 9.2	0.10
Pain	*n* = 160: 59.8 (23.3)	*n* = 140: 66.3 (21.3)	*n* = 156: 64.3 (23.6)	*n* = 134: 64.6 (23.5)	2.4	–2.5 to 7.3	0.3	*n* = 158: 65.0 (24.5)	*n* = 139: 63.7 (22.2)	4.4	–0.2 to 9.0	0.063
General health	*n* = 161: 60.2 (21.1)	*n* = 140: 64.0 (21.8)	*n* = 156: 61.1 (21.1)	*n* = 134: 61.8 (22.1)	2.1	–1.0 to 5.3	0.2	*n* = 158: 61.9 (22.5)	*n* = 139: 62.5 (22.9)	3.0	–0.4 to 6.5	0.09
Health change	*n* = 161: 52.5 (15.4)	*n* = 140: 53.4 (17.0)	*n* = 154: 58.0 (18.9)	*n* = 133: 50.6 (18.3)	7.7	3.5 to 12.0	0.0004	*n* = 158: 62.8 (20.1)	*n* = 137: 55.5 (18.4)	7.9	3.5 to 12.3	0.0004

Values are means (SD). Higher scores indicate better quality of life.
Differences between groups were calculated by ANCOVA.
[a] Adjusted difference: positive favours acupuncture.

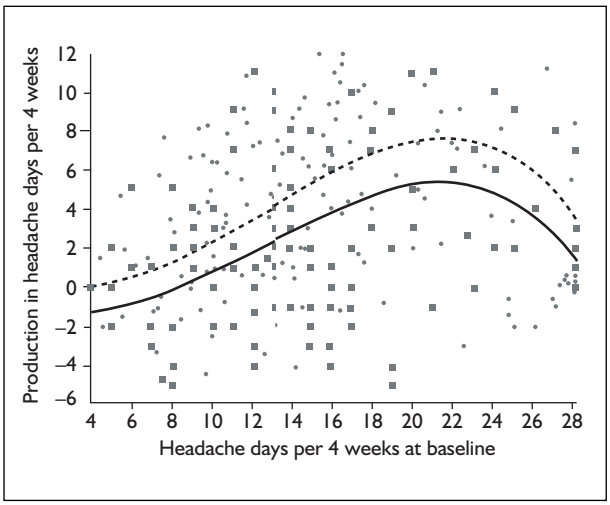

FIGURE 2 *Frequency of headache at baseline and after treatment. Dots are actual values for patients in the acupuncture group; squares are for controls. The curved lines are regression lines (upper dashed line for acupuncture, lower solid line for controls) that can be used as predictions. Some outliers have been removed. Days of headache are defined as days with any headache pain, even if mild.*

diagnosis, site). Additional variables (such as post-treatment score) were used in the prediction for the different analyses; however, treatment group (acupuncture or control) was deliberately excluded from the model as a conservative measure. The difference between a patient's true and predicted headache score is called a residual, and the distribution of residuals can be calculated for any particular regression model. For patients with missing data for headache score, the headache score predicted by the regression model was imputed, but a randomly drawn residual was added. Imputed and non-missing data were then combined and analysed by ANCOVA as described in Chapter 2. The process was repeated 100 times and the difference between groups with associated standard error recorded for each iteration. The results for headache score were then combined following Rubin's rules[42] using NORM statistical software;[43] the results for difference in response (i.e. the proportion improving by ≥ 35%) were combined by simple averaging.

The imputations were conducted as shown in *Table 7*. Sensitivity analyses (*Table 8*) were conducted hierarchically, so that, for example, sensitivity analysis 2 used the data from the complete cases and the imputations for groups 1 and 2; sensitivity analysis 3 included all patients. Two additional sensitivity analyses were conducted: sensitivity analysis 4 was the same as sensitivity analysis 3, with the exception of one patient who provided no follow-up data and who gave ineffectiveness of acupuncture as a reason for withdrawal. For this patient, change from baseline was fixed at the fifth centile (close to the worst possible result). In the final sensitivity analysis, an unadjusted *t*-test was used to compare change between baseline and follow-up, as planned in the original protocol.

It has been argued that the coefficients for the linear prediction should be randomly sampled from a plausible distribution.[41] This was attempted using NORM, but the imputation had poor properties: the data augmentation algorithm did not converge unambiguously and some imputations led to implausible results, such as the mean change in headache scores being a 20-point increase in both groups. Nonetheless, both the estimate for the difference between groups and the *p*-value obtained from this method were close to those reported in *Table 8* (3.66, $p = 0.001$).

TABLE 6 *Use of resources*

Resource	Acupuncture	Controls	Difference between groups[a]	95% CI	*p*-Value
No. of visits to:					
GP	1.7 (2.5)	2.3 (3.6)	0.77	0.56 to 1.06	0.10
Specialist	0.22 (0.9)	0.14 (0.6)	1.13	0.34 to 3.73	0.8
Complementary therapist	2.0 (7.1)	2.3 (6.8)	0.56	0.18 to 1.72	0.3
No. of days off sick	12.6 (18.9)	13.8 (16.2)	0.84	0.64 to 1.09	0.2

Values are means (SD).
Visits to acupuncturists and physiotherapists are excluded.
[a] Adjusted difference between groups. Results are expressed as an incident rate ratio: the proportion of events in the acupuncture group compared with controls. Values < 1 indicate fewer events in the acupuncture group, e.g. the value of 0.77 for visits to GPs means that acupuncture patients made 23% fewer visits.

TABLE 7 *Data used in the imputations*

Group	Patient group	*n*	Data used
Complete cases	Patients providing follow-up score at 1 year	301	Actual follow-up score
1	Patients providing post-treatment score but no score at 1 year	31	Imputed from randomisation strata and post-treatment score
2	Patients providing global score but no follow-up diaries	45	Imputed from randomisation strata and change in global estimate of headache severity
3	Patients providing no follow-up data	24	Imputed from randomisation strata and whether patient completed the post-treatment or 1-year follow-up diaries

TABLE 8 *Results of the sensitivity analyses*

		Difference between groups	
Sensitivity analysis	**Total no.**	**Headache score**	**Response**
Principal analysis	301	4.60 (p = 0.0002)	21.9%
Sensitivity analysis 1	332	4.42 (p = 0.0004)	20.8%
Sensitivity analysis 2	377	4.16 (p = 0.0007)	19.1%
Sensitivity analysis 3	401	3.91 (p = 0.001)	18.2%
Sensitivity analysis 4	401	3.85 (p = 0.002)	18.0%
Sensitivity analysis 5	301	3.96 (p = 0.004)	21.9%

Economic analysis: missing data

There were essentially two types of missing data: (1) where patients completed the cost questionnaire generally but did not report one or more items, and (2) where patients did not respond to any of the cost questionnaires.

Missing data on private expenditure

On some occasions, subjects reported visiting a private practitioner but did not report the cost of these visits. As the number of such visits across the entire sample was small, the simple mean cost across all such visits was used to impute missing values.

Missing data on number of GP visits

On some occasions, subjects reported visiting a GP during the 3 months but did not report the number of visits. The number of such visits was large enough to facilitate a multiple regression approach. Negative binomial regression was used to impute GP visits using the randomisation strata. Negative binomial regression is an extension of the Poisson regression model which allows the variance of the process to differ from the mean. In addition to the baseline covariates, the number of GP visits in one of the other first 3-month periods was used as a covariate.

Missing data on number of healthcare visits (other than GP visits)

On some occasions, subjects reported visiting a healthcare practitioner during the previous 3 months but did not report the number of visits. As the number of such visits across the entire sample was small, the simple mean number of visits for all those who had at least one visit was used to impute missing values. However, if the patient had reported the number of visits in one of the other 3-month cost questionnaires then this was used instead. The same approach was used when patients reported purchasing over-the-counter medication but did not report the number of packets.

Missing data on number of acupuncture sessions

Data on the number of study acupuncture sessions came from a separate questionnaire completed by the study acupuncturists. This was largely complete; however, two of the patients reported that they had sessions, although no equivalent session was recorded by the acupuncturist. In these cases, the patient cost questionnaire was used to impute the missing number of sessions. For one case, the participant reported attending the study acupuncturist but the number of sessions was unknown; this was imputed using the mean

number of sessions (8.7 sessions). For non-study acupuncture sessions the patient cost questionnaires were used. Where the patient stated that they had acupuncture but did not state whether it was with the study acupuncturist, it was assumed that it was with the study acupuncturist for the post-treatment follow-up and with an outside acupuncturist otherwise.

Data on the duration of study acupuncture sessions were reported by the study acupuncturists. Sometimes the duration was only reported for the first few sessions. In these cases, the duration was assumed to be the same as for the previous sessions. Where no duration ($n = 14$) was given for any session, linear regression was used to impute total acupuncture duration. For this regression, number of treatment sessions was used as a covariate.

Missing questionnaires

When patients did not complete the SF-36 on all three occasions, QALYs could not be calculated. These patients were consequently left out of the base-case analysis. For the sensitivity analysis QALYs were imputed using linear regression analysis, and for a subset of these patients their cost was also missing and was also imputed using linear regression. The covariates in these regressions were the randomisation strata and the SF-6D score at baseline. All imputed values for QALYs were plausible (i.e. between zero and one). Imputed values for costs were negative in a few cases. For this reason a second imputation was carried out, this time using a logarithmic transformation on cost.

The results of all the imputation regressions are summarised in *Table 9*.

Economic analysis: results

Table 10 shows the baseline characteristics for the patients who completed the SF-36 on all three occasions. This group forms the sample for the base-case analysis of cost-effectiveness. *Tables 11* and *12* show resource use, HRQoL and cost; for these tables the results from all responding individuals are reported.

Patients in the acupuncture arm had on average 4.2 hours of contact with a study acupuncturist (*Table 11*). Two patients in the control arm were treated by one of the study acupuncturists, and 18 patients in the acupuncture arm did not attend for acupuncture. Some patients (30 in the acupuncture arm and two in the control arm) visited an acupuncturist for further acupuncture (either NHS or private). Hence, the cost of the study acupuncture sessions was augmented by the cost of additional acupuncture sessions (*Table 12*).

There were small reductions in expenditure on visits to GPs and complementary or alternative medications (*Table 12*). Differences in other cost components did not reach significance. Costs for prescription drugs were obtained from a subsample of 71 patients, and it had been hoped that results could be extrapolated from these patients to the full study sample. However, regression models of these costs had poor properties: linear regression was heteroscedastic, and results differed depending on the various alternative regression methods used. Therefore, prescription drug costs were excluded from the cost-effectiveness analyses. As differences between groups were small (<£50 per patient) and tended to favour the acupuncture group, exclusion of the costs of prescription drugs is a conservative measure that is unlikely to have an important influence on cost-effectiveness estimates.

Table 11 reports HRQoL as measured by the SF-6D. The mean health gain was estimated to be 0.021 QALYs, equivalent to 8 quality-adjusted days (*Table 13*).

The mean incremental cost of the acupuncture intervention to the NHS was estimated to be £205 per patient, excluding the impact on prescription drugs (*Table 13*). This was offset slightly by a small reduction in direct patient costs (over-the-counter medication and visits to practitioners of complementary and alternative medicine). Overall, this equates to an additional cost of £9180 per QALY gained, including patient costs.

Figures 3 and *4* show the probability that the intervention is cost-effective for a range of cost-effectiveness ceilings. At a ceiling of £30,000 per QALY gained (a threshold of cost-effectiveness consistent with decisions that have been taken by NICE[38]) the probability that acupuncture is cost-effective is 92%. The figures also show how cost-effectiveness changes for several different scenarios (details and further scenarios in *Table 14*). Given the relative value of a GP's time, acupuncture by physiotherapists represents better value for money. Even if a GP manages to treat four patients in an hour this is still less cost-effective than a physiotherapist treating two per hour (the base-case scenario).

TABLE 9 *Summary of imputation regression models for missing economic data*

Dependent variable	Type	Condition[a]	Adjusted *n*	Adjusted R^{2b}	Covariates	Statistically significant covariates	Residual mean square error
GPVISQ1	Negative binomial	GPVISQ1 > 0	93	0.08	GPVISQ3 + baseline covariates	GPVISQ3	NA
GPVISQ2	Negative binomial	GPVISQ2 > 0	68	0.06	GPVISQ3 + baseline covariates	GPVISQ3	NA
GPVISQ4	Negative binomial	GPVISQ3 > 0	85	0.03	GPVISQ3 + baseline covariates	(None)	NA
QALY	Linear	None	255	0.55	SF6DBASE + baseline covariates	SF6DBASE	0.006
QALY[c]	Linear	None	255	0.05	Baseline covariates	SITE, SEVBASE	0.013
COST	Linear	None	334	0.25	Baseline covariates	SITE	125 985
COST	Log transformation	None	334	0.03	Baseline covariates	(None)	1.906
PDCOST	Linear	None	61	0.08	COST + baseline covariates	CHRONICITY	175 324
PDCOST[c]	Linear	None	71	0.07	Baseline covariates	CHRONICITY, GENDER	168 572

[a] None means that all cases without missing values are used.
[b] Pseudo R^2 for negative binomial regressions.
[c] There were two imputation regressions for QALYs, one to impute values for the subsample that responded to SF-6D at baseline and one for those patients who did not respond. The same method was used to predict PDCOST with respect to COST.
Definitions of variables:
CHRONICITY, number of years of headache disorder; COST, total cost of migraine treatment for the year (including direct patient costs but excluding prescription drug costs); GPVISQ1, etc., number of visits to the GP in the first quarter of the year; PDCOST, prescription drug costs for 1 year; SEVBASE, headache severity score at baseline; SF6DBASE, SF-6D score at baseline; SITE, geographical location.

TABLE 10 *Characteristics of patients for whom QALYs could be calculated*

	Acupuncture arm	Control arm
Mean age in years (SD)	46.7 (9.7)	46.0 (11.0)
No. of female participants (%)	111 (82%)	102 (85%)
Mean chronicity in years (SD)	22.1 (14.8)	21.8 (13.3)
Mean headache severity score at baseline (SD)	24.1 (14.0)	27.0 (16.9)
No. of participants with migraine (%)	128 (94%)	113 (95%)
Sample size: acupuncture = 136, control = 119.		

TABLE 11 *Use of resources and HRQoL*

	Acupuncture arm		Control arm	
Resource	**Mean (SD)**	***n***	**Mean (SD)**	***n***
No. of acupuncture visits				
Acupuncture, study	7.92 (3.76)	205	0.10 (1.03)	196
Study hours of contact	4.24 (2.31)	205	0.06 (0.59)	196
Acupuncture, other NHS	0.79 (2.31)	177	0.01 (0.08)	157
Acupuncture, private	0.34 (1.45)	177	0.01 (0.16)	157
No. of other healthcare visits				
GP	1.72 (2.54)	177	2.65 (3.79)	157
Outpatient	0.26 (0.93)	177	0.15 (0.65)	157
Other, NHS	0.10 (0.64)	177	0.27 (1.57)	157
Other, private	2.77 (8.70)	177	2.71 (7.52)	157
HRQoL (SF-6D, score out of 100)				
Baseline	69.3 (13.2)	197	70.6 (12.8)	189
At 3 months	71.2 (13.6)	157	70.3 (13.1)	143
At 12 months	73.9 (14.3)	150	70.7 (13.3)	133

TABLE 12 *Costs in pounds*

	Acupuncture arm		Control arm		
Cost	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Difference[a] mean (95% CI)**
Acupuncture					
Acupuncture, study	201.49 (89.62)	177	3.02 (28.60)	157	198.97 (185.72 to 212.22)
Acupuncture, other NHS	17.54 (51.55)	177	0.14 (1.78)	157	17.76 (9.65 to 25.86)
Acupuncture, private	10.68 (46.27)	177	0.38 (4.79)	157	10.48 (3.08 to 17.89)
Other visits					
GP	46.40 (68.48)	177	71.67 (102.34)	157	–21.38 (–39.89 to –2.87)
Outpatient	21.68 (76.49)	177	12.10 (53.32)	157	10.24 (–4.15 to 24.63)
Other, NHS	2.59 (18.80)	177	6.63 (39.61)	157	–3.48 (–9.59 to 2.63)
Other, private	73.15 (262.04)	177	68.38 (369.97)	157	5.00 (–62.61 to 52.61)
Medication					
Over-the counter-drugs	39.07 (60.97)	177	39.42 (50.67)	157	0.00 (–11.87 to 11.87)
Complementary or alternative medication	1.72 (10.00)	177	5.68 (17.82)	157	–4.01 (–7.13 to –0.88)
Prescription drugs[b]	160.98 (365.77)	36	211.51 (484.15)	35	–32.04 (–231.27 to 167.18)

[a] Adjusted for baseline variables.
[b] Subsample only.

TABLE 13 *Cost-effectiveness*

	Acupuncture arm *n* = 136	Control arm *n* = 119	Mean difference[c] (95% CI)
NHS cost (£)[a]	289.65 (165.86)	88.65 (130.28)	205.34 (169.33 to 241.35)
Patient cost (£)	113.75 (258.24)	128.56 (426.56)	–15.91 (–86.24 to 54.42)
Total cost (£)[b]	403.40 (356.69)	217.20 (486.00)	189.42 (102.24 to 276.61)
QALYs	0.727 (0.119)	0.708 (0.112)	0.021 (0.001 to 0.040)

Values are means (SD) unless otherwise indicated.
Incremental cost per QALY gained: £9951 (NHS cost); £9180 (total cost).
[a] Excluding prescription drug costs.
[b] Total cost (£) = NHS cost + patient cost.
[c] Adjusted for baseline variables.

TABLE 14 *Sensitivity analysis*

	Sample size	Incremental cost (£)	QALYs gained	Incremental cost per QALY gained (£)
Base case (see *Table 5*)	255	189.42	0.021	9,180
Alternative unit costs associated with acupuncture[a]				
Using average cost of a private acupuncture session	255	234.72	0.021	11,375
Physiotherapist can treat three patients per hour	255	117.64	0.021	5,701
GP instead of physiotherapist (treating four patients per hour)	255	254.50	0.021	12,333
Strategy for handling of missing values				
Include only patients completing all cost questionnaires	220	201.52	0.018	11,474
Imputation of QALYs and cost[b]	401	164.59	0.015	10,836
Inclusion of additional cost component				
Productivity costs (days off sick)	255	67.34	0.021	3,263
Projection of results into the future				
Trial arms converge by 2 years	255	183.33	0.039	4,730
Trial arms converge by 5 years	255	166.39	0.092	1,807
Trial arms converge by 10 years	255	142.10	0.177	801

All analyses adjusted for baseline variables.
[a] Assumes same health outcome as the base case.
[b] Using linear regression to predict missing values from baseline parameters.

There was a marked improvement in cost-effectiveness associated with the inclusion of productivity costs. However, this represents an underestimate of the cost per QALY since the quality of life measure will in part reflect this improved productivity, especially with respect to increased leisure time. Estimated cost-effectiveness was also improved by the projection of effects beyond 1 year and the assumption that acupuncturists could improve their throughput by dealing with patients simultaneously. Cost-effectiveness was not markedly different when private acupuncture costs were used. Similarly, imputing values for cases with missing data did not greatly influence the results, although the explanatory power of the imputation regressions was weak. Under none of the scenarios did the central estimate of cost indicate overall cost savings.

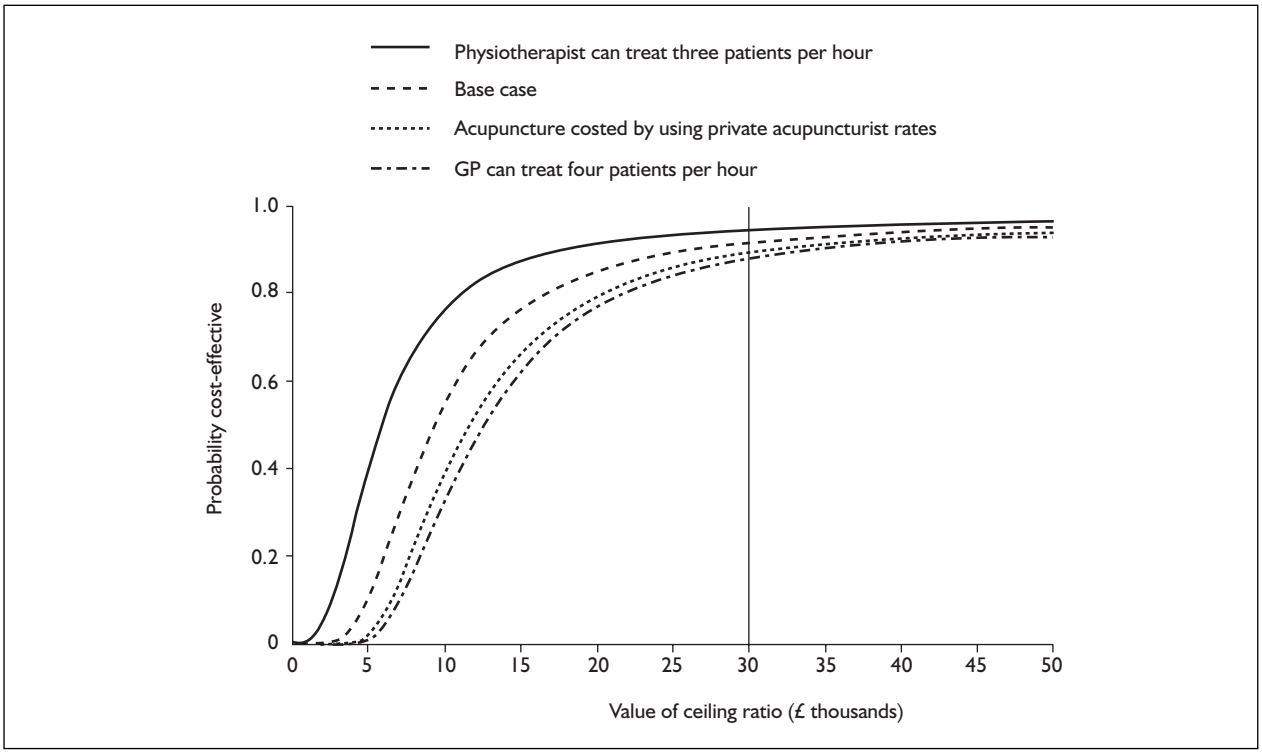

FIGURE 3 *CEAC with sensitivity analysis for acupuncture unit cost*

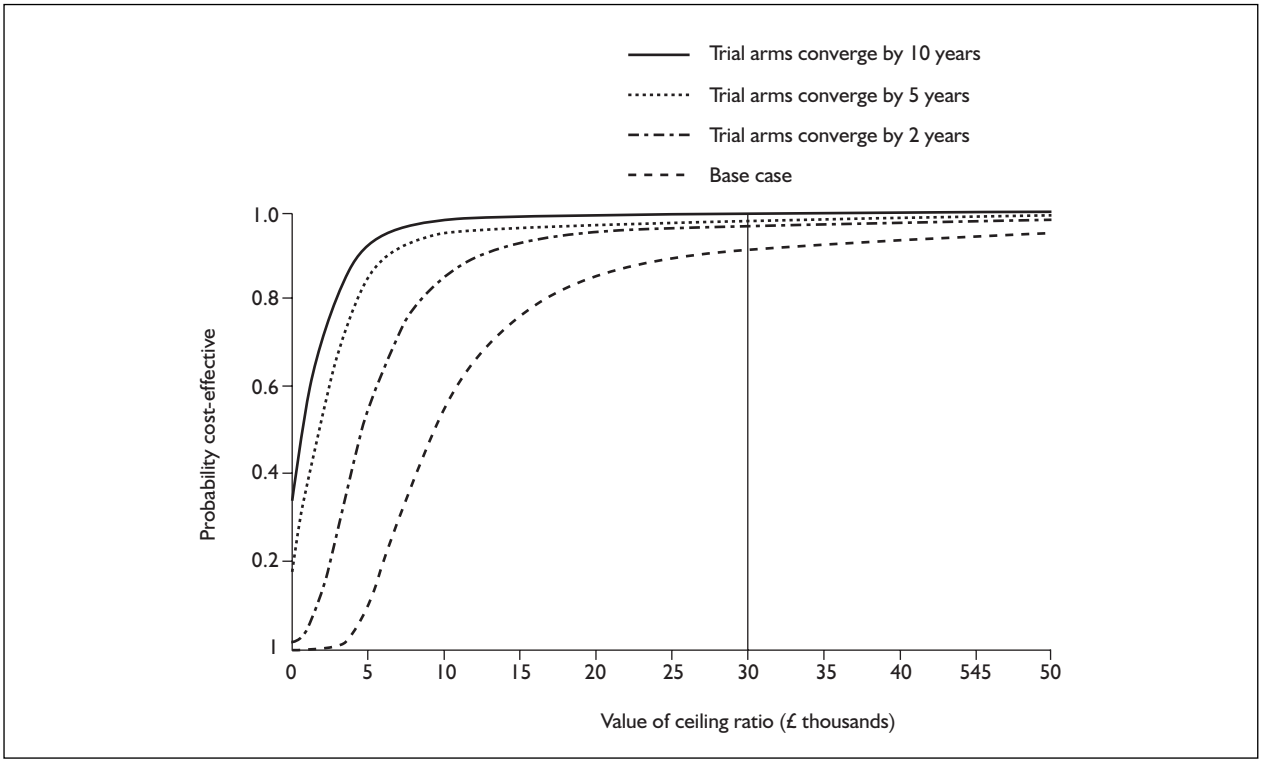

FIGURE 4 *CEAC with sensitivity analysis for duration of effect*

Chapter 4
Discussion

Main findings

The results of the study suggest that acupuncture in addition to standard care results in persisting, clinically relevant benefits for primary care patients with chronic headache disorders, particularly migraine, compared with controls. The study also found improvements in quality of life, decreases in use of medication and visits to GPs, and reductions in sick leave. Methodological strengths of the study include a large sample size, concealed randomisation and careful follow-up, with careful modelling for missing data. The practical value of the trial was maximised by comparing the effects of clinically relevant alternatives on a diverse group of patients recruited directly from primary care.[19]

Limitations

Control patients did not receive a sham acupuncture intervention. One hypothesis might be that the effects seen in the acupuncture group resulted not from the physiological action of needle insertion, but from the 'placebo effect'. Such an argument is not relevant to an assessment of the clinical effectiveness of acupuncture because in everyday practice, patients benefit from placebo effects. Nonetheless, good evidence from randomised trials shows that acupuncture is superior to placebo in the treatment of migraine.[7,12] Furthermore, this study was modelled on Vincent's earlier double-blind, placebo-controlled trial in migraine,[11] which makes direct comparison possible. Raw data were obtained from the author and results compared directly between trials. Vincent was unable to provide 1-year data, so the post-treatment follow-up was used as the end-point. If placebo explained the activity of acupuncture in the present study, one would expect patients in the control group, who received no treatment, to experience smaller improvements than Vincent's placebo-treated controls, leading to a larger difference between groups. However, improvements in the present controls (7.1% from a baseline headache score of 26.7) were similar to those in Vincent's trial (10.5% from 27.2) and differences between groups are non-significantly smaller in the current trial (4.1 versus 8.1). This implies that these findings perhaps cannot be explained purely in terms of the placebo effect. That said, such an explanation cannot be ruled out, given the lack of placebo control.

Patients in the trial were not blinded and may therefore have given biased assessments of their headache scores. Measures to minimise bias included minimum contact between trial participants and the study team, extended periods of anonymised diary completion and coaching patients about bias. The difference between groups is far larger (odds ratio for response 2.5) than empirical estimates of bias from failure to blind (odds ratio 1.2).[44] The similarity of the current results to those of the prior blinded study provides further evidence that bias does not completely explain the apparent effects of acupuncture.

An additional consideration is that, if bias explained the results of this trial, it is unclear why this would be differentially expressed between end-points. For example, differences between groups for SF-36 pain or physical functioning are considerably smaller than for headache score. This is relatively easy to explain if the differences are attributed to a treatment effect: improvements on a general domain, such as physical functioning, are generally smaller than improvement on a specific symptom, such as headache score, because the symptom is only one factor influencing the general domain, that is, patients' physical functioning may be reduced by symptoms other than headache. It is unclear, however, why patients would be more biased about reporting headache than physical functioning. It is also unclear why, if bias explained the results, differences between groups for medication use, an objective end-point, were similar to those for the subjective end-point of headache score: the difference between groups for headache score was 4.6 from a mean baseline of 25.6; the comparable figures for medication use were a difference of 5.2 from a baseline of 26.5.

Patients recorded all treatments for headache during the course of the study. Use of medication and other therapies (such as chiropractic) was lower in patients assigned to acupuncture, indicating that the superior results in this group were not due to confounding by off-study interventions.

Comparison with other studies

A strength of the current trial is that its results are congruent with much of the prior literature on acupuncture for headache. Effects found in this study that have been previously reported include: differences between acupuncture and control for migraine[7,12,45] that increased between post-treatment and 1-year follow-up,[11] unconvincing effects for tension-type headache,[46–49] improvements in severity and frequency,[24] and increased benefit in patients with greater headache severity.[11]

Economic analysis

Acupuncture led to increases in both QALYs and health service costs. The incremental cost-effectiveness was estimated to be £9180 per QALY gained. The estimated improvement in quality of life correlates with the observed reductions in headache severity and frequency.

The base case is likely to be conservative as it excludes cost savings associated with prescription drugs and productivity gains. More importantly, the base-case analysis considers only the 12 months of the trial. The effects of acupuncture appear to be persistent as differences between groups were slightly larger at 1 year than immediately post-treatment. If likely QALY differences for subsequent years are included, then acupuncture appears even better value for money.

Acupuncture by medical GPs, (as well as by specialist physiotherapists) appears to be reasonably cost-effective compared with usual care; however, given the relative value of a GP's time, acupuncture by physiotherapists represents better value for money, unless GPs can achieve substantially better outcomes or much shorter contact times, or both.

The probability that the programme is cost-effective at a ceiling of £30,000 was estimated to be 92% for the base case. This does not take into account the uncertainty due to imputing missing values, which means that this probability is a slight overestimate. When only complete responders are included in the analysis the probability falls to 84%, but this estimate is biased conservatively. This study, like most economic evaluations,[50] was not powered to detect a difference in cost-effectiveness and therefore the lack of statistical significance at the 5% level should not be interpreted as evidence of non-cost-effectiveness: few if any economic evaluations attain conventional levels of statistical significance.

To the authors' knowledge, this is the first rigorous economic evaluation of acupuncture. Prior economic studies on acupuncture for pain have typically been conducted by acupuncture advocates and have used questionable methods. For example, studies have claimed cost savings on the basis of hypothetical interventions that would have been necessary had acupuncture not been administered.[35,51] Other studies have used before and after comparisons[52] or non-randomised controls.[53] Cost savings have been shown by retrospective studies of acupuncture for other conditions, but similar methodological problems have been described.[54]

The present study, with a relatively large sample size, a randomised comparison arm and prospective evaluation of costs, has not found such overall cost savings for headache patients: it seems fairly certain from the results that acupuncture adds to health service costs for these patients. Therefore, the pertinent question is whether this additional cost is justified by the associated health gains. Even when using the conservative base-case estimate of £9180 per QALY gained, acupuncture for migraine seems to be better value for money than several interventions that have been recommended by NICE.[38,54] To the authors' knowledge, a cost per QALY analysis has only been performed for one other antimigraine intervention (sumatriptan compared with oral caffeine and ergotamine), which had a cost per QALY of Can$29,366 (£16,000).[55] Acupuncture therefore compares favourably with this.

Chapter 5

Implications for the NHS

Headache treatment

The recruitment for this study revealed considerable headache morbidity in the population. It is estimated that about 1% of the entire population on the GPs' lists entered the trial and that approximately 1.5% would have been eligible (e.g. the researchers closed the trial before responding to all enquiries). Half of the patients were experiencing moderate to severe headache on at least 1 out of every 4 days, and one-quarter were experiencing moderate to severe headache for 12 or more days per calendar month. Given this extent of severe headache morbidity, it appears unlikely that patients in UK primary care are receiving optimal management, a conclusion also reached in a recent study analysing referrals to a specialist headache clinic.[56]

NHS clinicians

Referral to acupuncture for patients with poorly managed chronic headache disorders would appear to be worthy of consideration. Clinicians could use *Figure 2* to estimate the extent of likely benefit for an individual patient based on the number of days per 4 weeks on which they experience any headache pain. It would be important to take into account the patient's preferences and values when considering referral for acupuncture. This is perhaps particularly because recent research has indicated that the degree of benefit of acupuncture for low back pain correlates with patients' expectation of benefit.[57] A key problem is likely to remain the availability of suitably qualified practitioners. This study used physiotherapists as acupuncture providers, but the number of physiotherapists trained in acupuncture is inadequate to provide services throughout the NHS. This suggests that referrals may need to be made to doctor acupuncturists (registered by the British Medical Acupuncture Society) or acupuncturists who are without conventional clinical qualifications (registered by the British Acupuncture Council). Whether such referrals will be covered financially by the NHS, or will need to be paid 'out-of-pocket' is subject to large geographical variations.[5]

NHS commissioners

This study has shown that, contrary to claims made by some acupuncturists, increases in costs related to acupuncture services are larger than any decreases associated with reduced use of medication and other NHS resources. Although acupuncture appears relatively cost-effective compared with other NHS interventions, expanding the availability of acupuncture in the NHS can only be achieved at the expense of other new or existing investment options.

Chapter 6

Recommendations for further research

A large, randomised trial of the sort often described as 'Phase III' has been conducted. Many interventions go through considerable preclinical and early-phase clinical research before reaching Phase III. Such research is generally used to determine the optimal use of the intervention, for example, by establishing dose, frequency and concurrent treatments. Acupuncture has not gone through a systematic process of optimisation; rather, it has developed by unsystematic trial and error over many years. Accordingly, its practice is extremely diverse.[58] Even within the clinical trial literature one can find pain treated by an enormous variety of different techniques, including traditional Chinese deep needling;[16] shallow needling, of body points,[59] insertion of thick, semipermanent studs in the ear,[60] insertion of thick, semipermanent studs in the body,[61] insertion of thin, semipermanent needles in the body,[62] brief needling of trigger points,[63] laser stimulation[64] and electroacupuncture.[65] There is also great diversity as to the total number and frequency of treatment sessions. The acupuncture points used also vary not only from style to style, but even from practitioner to practitioner.[66,67] Furthermore, practitioners differ in their use of co-interventions such as massage or moxibustion. Such diversity suggests the following research questions.

- Does heterogeneity of practice lead to heterogeneity of results? This question could be answered by a large, prospective, single-arm study involving a limited number of practitioners, perhaps ten to 20. Each practitioner would treat several hundred patients, each of whom would record baseline and post-treatment severity on a simple scale (such as a numerical rating scale). The results for each practitioner would be adjusted for case-mix and the degree of remaining heterogeneity in outcomes estimated. This type of research could be extended to determine whether the results of acupuncture as implemented in this trial, in the context of a physiotherapy intervention, differ when given in a different context, such as a traditional Chinese medicine consultation.
- What types of acupuncture treatment are associated with better response? The authors believe that it would be feasible for the acupuncture community to conduct a large, randomised trial comparing different acupuncture treatment strategies at relatively low cost. Patients meeting a very general eligibility criterion would be asked to provide simple baseline data (such as a numerical rating scale of symptom severity) and give informed consent. Treatment allocation could be performed online, with patients randomised to one of several different strategies with follow-up symptom assessment at the final treatment. Such a trial should have good acceptability to both patients and practitioners and be relatively inexpensive.
- It is likely that different treatment strategies compared in the randomised trial described above would be selected from those currently used by practitioners. There remains the possibility, however, that treatments could be rationally developed on the basis of an understanding of acupuncture mechanisms. Currently, most research into acupuncture mechanisms, be this studies of neurotransmitters in rats[68] or functional magnetic resonance imaging studies in humans,[69] has had a basic science, rather than a translational, orientation. Those studying the mechanisms of acupuncture could be encouraged to conduct research that can inform clinical practice.

With respect to the results of this study in particular, further research could address several hypotheses suggested by the data.

- There are two lines of evidence suggesting that acupuncture may be less effective in patients with tension-type headache than in those with migraine. First, the effect size in the tension-type headache subgroup was considerably smaller than in the migraine subgroup. Second, there was evidence of decreasing effectiveness with increasing number of headache days (see *Figure 2*). Simple guidelines were used to place patients in the diagnostic categories of migraine or non-migraine headache. This was done on the basis that more complex algorithms are unlikely to be implemented in primary care. However, it seems that many of the patients

who were categorised as 'migraine', and who undoubtedly suffered at least some migraine headaches, also experienced important morbidity from tension-type headache. For example, approximately 20% of migraine patients in the study suffered at least some headache on 6 or more days a week. Even if the definition of a 'headache day' is restricted to one on which at least moderate pain was reported, about 15% of migraine patients experienced a headache on at least half of all days. This is in contradistinction to the typical course of migraine as attacks lasting for 4–72 hours interspersed with periods without headache. Therefore, future researchers could explore strategies for determining which patients with chronic headache disorder are most likely to respond to acupuncture. Ideally, these could be combined in a simple prognostic algorithm that was strongly predictive of outcome.

- The persistence of acupuncture effects could not be estimated in this study as improvements were entirely maintained (indeed, increased) between post-treatment and 1-year follow-up. A single-arm study with follow-up over several years could determine the likely persistence of treatment effects.
- It appears likely that the patients in this study were not receiving optimal pharmacological management. Comparable to other studies,[56] a minority of patients were receiving prophylactic medication, and only about one in five used a triptan during the 28-day baseline. This raises questions concerning both the effectiveness and the cost-effectiveness of acupuncture in patients receiving more aggressive management. It is likely that the effect size of acupuncture would be smaller, as an interaction was found between baseline severity and improvements on acupuncture. However, it is also possible that acupuncture would be much more cost-effective in this setting: if the reductions in medication use observed were generalised to more expensive drugs, then it is plausible that total health costs would be lower in patients receiving acupuncture. Although a randomised trial in optimally treated patients would be ideal, this would need to be large (given the anticipated smaller effect size). An alternative may be a single-arm study comparing medication use in the year before and after a course of acupuncture treatment.

One additional recommendation for research may be made.

- This article has reported a 'positive' trial with encouraging findings. Patients receiving the experimental intervention experienced an average of 22 fewer days with headache per year. It does not take a headache expert to understand the impact that this has on a patient's quality of life. However, at the end of the trial, patients in the treatment group were still highly morbid, experiencing moderate to severe headache on about 7 days in each calendar month. Acupuncture is far from a cure for chronic headache disorders and the extent of morbidity uncovered during recruitment gives no room for complacency. The authors therefore strongly support further basic, translational and therapeutic research on chronic headache disorders, as well as research to evaluate different methods of providing services to this chronically ill population.

Conclusion

A policy of using a local acupuncture service in addition to standard care resulted in persisting, clinically relevant benefits for primary care patients with chronic headache disorders, particularly migraine. Effects were achieved at relatively low cost, giving an estimate of cost-effectiveness that is within the range considered to represent acceptable value for money within the NHS.

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Contributions of authors

All authors listed below were involved in either the conception and design of the study or its analysis and interpretation. All were involved in the drafting of the report and approved the final version. Andrew J Vickers conceived and designed the study and is its overall guarantor; he also analysed the medical outcomes of the study and advised on statistical aspects of the economic analyses; Rebecca W Rees, Catherine E Zollman, Claire M Smith and Nadia Ellis contributed to the original design, with particular contributions to outcome assessment (RWR, CMS), patients and treatment (CEZ), and acupuncture treatment (NE). Rob McCarney contributed to the design of resource outcome assessment; RM, Robbert Van Haselen and Peter Fisher contributed to development of data collection methods for sensitivity analysis; David Wonderling undertook the economic analyses and is the guarantor of the economic aspects of the paper; and Richard Grieve advised on the economic analyses.

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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