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Abstract

Non-pharmacological educational and self-management interventions for people with chronic headache: the CHESS research programme including a RCT

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Background: Headaches are a leading cause of years lived with disability. For some people, headaches become chronic and disabling, with treatment options being primarily pharmaceutical. Non-pharmacological alternative treatment approaches are worthy of exploration.

Aim: To develop and test an educational and supportive self-management intervention for people with chronic headaches.

Objectives: To develop and evaluate a brief diagnostic interview to support diagnosis for people with chronic headaches, and then to develop and pilot an education and self-management support intervention for the management of common chronic headache disorders (the CHESS intervention). To select the most appropriate outcome measures for a randomised controlled trial of the CHESS intervention, and then to conduct a randomised controlled trial and economic evaluation of the CHESS intervention with an embedded process evaluation.

Design: Developmental and feasibility studies followed by a randomised controlled trial.

Setting: General practice and community settings in the Midlands and London, UK.

Participants: For our feasibility work, 14 general practices recruited 131 people with chronic headaches (headaches on ≥15 days per month for >3 months). People with chronic headaches and expert clinicians developed a telephone classification interview for chronic headache that we validated with 107 feasibility study participants. We piloted the CHESS intervention with 13 participants and refined the content and structure based on their feedback. People with chronic

headaches contributed to the decisions about our primary outcome and a core outcome set for chronic and episodic migraine. For the randomised controlled trial, we recruited adults with chronic migraine or chronic tension-type headache and episodic migraine, with or without medication overuse headache, from general practices and via self-referral. Our main analyses were on people with migraine.

Interventions: The CHESS intervention consisted of two 1-day group sessions focused on education and self-management to promote behaviour change and support learning strategies to manage chronic headaches. This was followed by a one-to-one nurse consultation and telephone support. The control intervention consisted of feedback from classification interviews, headache management leaflet and a relaxation compact disc.

Main outcome measures: The primary outcome was headache-related quality of life measured using the Headache Impact Test-6 at 12 months. The secondary outcomes included the Chronic Headache Quality of Life Questionnaire; headache days, duration and severity; EuroQol-5 Dimensions, five-level version; Short Form Questionnaire-12 items; Hospital Anxiety and Depression Scale; and Pain Self-Efficacy Questionnaire scores. We followed up participants at 4, 8 and 12 months.

Results: Between April 2017 and March 2019, we randomised 736 participants from 164 general practices. Nine participants (1%) had chronic tension-type headache only. Our main analyses were on the remaining 727 participants with migraine (376 in the intervention arm and 351 in the usual-care arm). Baseline characteristics were well matched. For the primary outcome we had analysable data from 579 participants (80%) at 12 months. There was no between-group difference in the Headache Impact Test-6 at 12 months, (adjusted mean difference −0.3, 95% confidence interval −1.23 to 0.67; $p = 0.56$). The limits of the 95% confidence interval effectively exclude the possibility of the intervention having a worthwhile benefit. At 4 months there was a difference favouring the CHESS self-management programme on the Headache Impact Test-6 (adjusted mean difference −1.0, 95% confidence interval −1.91 to −0.006; $p = 0.049$). However, the self-management group also reported 1.5 (95% confidence interval 0.48 to 2.56) more headache days in the previous 28 days. Apart from improved pain self-efficacy at 4 and 12 months, there were few other statistically significant between-group differences in the secondary outcomes. The CHESS intervention generated 0.031 (95% confidence interval −0.005 to 0.063) additional quality-adjusted life-years and increased NHS and Personal Social Services costs by £268 (95% confidence interval £176 to £377), on average, generating an incremental cost-effectiveness ratio of £8617 with an 83% chance of being cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year. The CHESS intervention was well received and fidelity was good. No process-related issues were identified that would explain why the intervention was ineffective.

Limitations: Only 288 out of 376 (77%) of those randomised to the CHESS intervention attended one or more of the intervention sessions.

Conclusions: This short, non-pharmacological, educational self-management intervention is unlikely to be effective for the treatment of people with chronic headaches and migraine.

Future work: There is a need to develop and test more sustained non-pharmacological interventions for people with chronic headache disorders.

Patient and public involvement: Substantial patient and public involvement went into the design, conduct and interpretation of the CHESS programme. This helped direct the research and ensured that the patient voice was embedded in our work.

Trial registration: This trial is registered as ISRCTN79708100.

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Contents

List of tables

List of figures

List of boxes

List of supplementary material

Report Supplementary Material 1 Nurse Classification Training Manual

Report Supplementary Material 2 Facilitators Training Manual

Report Supplementary Material 3 Nurse one to one consultation manual

Report Supplementary Material 4 COSH Delphi study

Report Supplementary Material 5 Protocol

Report Supplementary Material 6 Data management plan

Report Supplementary Material 7 Statistical analysis plan

Report Supplementary Material 8 Health economics analysis plan

Report Supplementary Material 9 Quality assurance protocol

Report Supplementary Material 10 Baseline questionnaire

Report Supplementary Material 11 Follow-up questionnaire at 4, 8 and 12 months

Report Supplementary Material 12 Statistical report

Report Supplementary Material 13 Analysis for all 736 participants

Report Supplementary Material 14 Health economic analysis report

Report Supplementary Material 15 Process evaluation report

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/PLJL1440).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
app	application
ASSIA	Applied Social Sciences Index and Abstracts
CACE	complier-average causal effect
CBT	cognitive–behavioural therapy
CD	compact disc
CGRP	calcitonin gene-related peptide
CHESS	Chronic Headache Education and Self-management Study
CHQLQ	Chronic Headache Quality of Life Questionnaire
CI	confidence interval
COSMIG	core outcome set for migraine
CRN	clinical research network
DVD	digital versatile disc
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
heiQ	Health Education Impact Questionnaire
HIT-6	Headache Impact Test-6
ICER	incremental cost-effectiveness ratio
ICHD-3	*International Classification of Headache Disorder*, third edition
IQR	interquartile range
LBP	low back pain
MSQ	Migraine-Specific Quality of Life Questionnaire
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMC	National Migraine Centre
PDG	Programme Development Grant
PGfAR	Programme Grants for Applied Research
PPI	patient and public involvement
PROM	patient-reported outcome measure
PSC	Programme Steering Committee
PSEQ	Pain Self-Efficacy Questionnaire
PSS	Personal Social Services
QALY	quality-adjusted life-year
QUADAS-2	Quality of Diagnostic Accuracy Studies
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
SIS	Social Integration Subscale
WP	work package

Plain language summary

What did we want to find out?

We wanted to find out if an education and self-management support programme for people with frequent headaches made these people feel better.

What did we do?

We first made sure that we could find people with frequent headaches, from general practice, who would want to take part in our study. We then trained nurses to do telephone interviews to find out what sort of headaches people had.

We looked at previous research and then, together with people with frequent headaches, designed a group education and self-management programme. It was run by a nurse and another health professional over 2 days, followed by a one-to-one session and telephone support with a nurse.

We worked with people with frequent headaches and health professionals specialising in headaches to agree how best to measure how headaches affect people's quality of life.

We then tested our self-management programme. We recruited 736 people with frequent headaches, of whom 727 had migraine. Using a computer, we allocated them at random either to attend the self-management programme or to receive a relaxation compact disc. Everyone was told their headache type. We asked participants to tell us about their headaches and headache quality of life after 4 months, 8 months and 12 months.

What did we find?

Our main results are for the 727 people with migraine. Our support programme did not help people in our study with frequent migraines to live better. There were also no important differences in the number of headaches people had each month or the amount of prescribed or over-the-counter medication they took for their headaches.

What does this mean?

Our short 2-day programme did not appear to improve headache-related quality of life or reduce the number of headache days. Other ways of helping people manage their chronic headaches are needed.

Scientific summary

Background

Headaches are second to low back pain as a global cause of years lived with disability. Headaches are the most common neurological disorder treated in primary care. They account for around 3% of general practitioner consultations. Seventy per cent of people with headaches seen by their general practitioner do not get a formal diagnosis. For some people headaches become a chronic disabling disorder. There is a need for more non-pharmacological treatments to help those living with headache disorders.

Our overarching aim was to develop and test a supportive education and self-management group intervention, implementable in primary care, for people with chronic headaches.

Objectives

The objectives of the programme were to:

- develop and test strategies for recruiting people with chronic headaches from primary care [work package (WP) 1]
- develop and evaluate a brief classification interview to support diagnosis for people with chronic headaches (WP2)
- develop and pilot an education and self-management support intervention for the management of common chronic headache disorders [the Chronic Headache Education and Self-management Study (CHESS) intervention] (WP3)
- select the most appropriate outcome measures for a randomised controlled trial of the CHESS intervention package (WP4)
- run a multicentre randomised controlled trial, including an economic evaluation, of the CHESS intervention package (WP5).

Methods and results

We used an epidemiological definition of chronic headaches: headaches on ≥15 days per month for >3 months. Phase 1 of our work, WPs 1–4, consisted of interlinked systematic reviews and a feasibility study.

Feasibility study (work package 1)

Fourteen general practices in the West Midlands recruited 131 people with chronic headaches by writing to people with recorded consultations for headaches and prescriptions for migraine-specific drugs (triptans and pizotifen). Eligibility was confirmed by a telephone call by the study team. This group was our sampling frame for WPs 2–4.

Classification interview (work package 2)

We wanted to identify the population of interest for the main trial but also to feel confident that those who had other headache types not suitable for our trial were appropriately identified and referred for relevant support. We first reviewed the literature on diagnostic tools and found 38 papers validating 30 tools. We did not find any tools that were suitable for our proposed trial. We therefore organised a consensus meeting to inform our thinking on the content of a new classification tool. This was attended

by neurologists with a specialist interest in headaches, general neurologists, headache specialist nurses, general practitioners with a specialist interest in headaches and people with chronic headaches. We established what we needed to know from a person to:

- exclude secondary headaches
- exclude primary headaches other than chronic migraine and tension-type headache
- distinguish between chronic tension-type headache and chronic migraine
- identify medication overuse headache.

We used this information to develop a classification logic model for use in a nurse-delivered classification interview. A research nurse and a doctor, with expertise in headaches, from the National Migraine Centre then independently interviewed 107 participants. We found a high level of agreement between the nurse and specialist. Over 90% of study participants were classified as having chronic migraine.

Intervention development (work package 3)

Three systematic reviews informed our intervention development.

Using a meta-ethnographic approach our systematic review of the lived experience of chronic headaches (*n* = 4 studies) we found three overarching themes:

- headache as a driver of behaviour
- the spectre of headache
- strained relationships.

In our systematic review of prognostic factors in chronic headache (*n* = 27 studies), we found moderate evidence for depression and anxiety, poor sleep, stress, medication overuse and poor self-efficacy predicting a poor outcome. We found inconclusive evidence for treatment expectations, age and age at onset, body mass index, employment and headache features predicting a poor outcome.

In our systematic review of the effectiveness, style and content of self-management interventions for chronic headache (*n* = 16 studies) we found beneficial effects of the interventions compared with usual care in pain intensity, headache-related disability and quality of life. Interventions including either education or mindfulness components, and delivered in a group format, showed greater reductions in pain intensity than interventions without these features. A greater beneficial effect on mood was observed in interventions that included a cognitive–behavioural approach component than in those without this.

We interviewed seven people living with chronic headaches recruited through our charity partners. We found that participants had tried a range of therapies and interventions, some of which were helpful and others less so. Access to education and peer support was deemed positive, as was learning new skills such as relaxation, mindfulness and stress management.

We then presented our findings to 18 people from clinical, academic and lay backgrounds at an intervention development day to agree the structure and content of our new intervention. We agreed on a modular group intervention for 8–10 people delivered by a nurse and a layperson with chronic headaches. It should include educational material, self-management material and medication advice, and include a digital versatile disc (DVD) suitable to share with friends and family. We included a single face-to-face session and up to 8 weeks of telephone support with a specially trained nurse. After piloting with 13 participants, we identified that it was difficult for lay facilitators to commit to the sessions because of the unpredictable nature of their headaches. We therefore changed to using allied health professionals as the second facilitator. The final format was two group days followed by a one-to-one

session with a nurse to discuss medication, lifestyle factors and goal-setting, followed by up to 8 weeks of telephone support (individually negotiated).

Clinical effectiveness and cost-effectiveness measures (work package 4)

In our systematic review of patient-reported outcomes (46 studies evaluating 23 patient measures) we found that for a 'headache' population only the Headache Impact Test-6 (HIT-6) had acceptable evidence for its validity and reliability for use in our trial. The Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) had relevance to our population. We modified this measure, changing the focus of each item from 'migraine' to 'headache' to produce the Chronic Headache Quality of Life Questionnaire (CHQLQ) and did a mixed-methods comparative evaluation of the CHQLQ and HIT-6.

Both the CHQLQ and the HIT-6 were well completed, had good psychometric properties and were relevant to the experience of headache. The CHQLQ captured the wide-ranging impact of chronic headache, in particular the emotional impact, to a greater extent than the HIT-6.

As this work was not complete before starting the main trial, we set HIT-6 as the primary outcome for the trial and the CHQLQ as a secondary outcome.

We developed three questions to capture headache frequency, duration and severity for use in a smartphone application (app) or in a paper diary. Eight feasibility participants tested the app over 11 weeks. Feedback was positive but completion rates varied. We included the app as part of the main trial.

From our work on outcome measures we identified the need for a core outcome set for migraine. This work took place after the design of the randomised controlled trial had been finalised. We identified >50 domains from our systematic reviews and our qualitative work. We did a modified, three-round electronic Delphi study with patients and professionals to identify which domains were most important. At a consensus day, when the aim was to ratify the core domains, a two-domain core outcome set was agreed for chronic and episodic migraine:

1. migraine-specific pain – to be assessed with an 11-point numerical pain rating scale, and frequency as the number of headache/migraine days over a specified period
2. migraine-specific quality of life to be assessed with the Migraine Functional Impact Questionnaire (MFIQ).

Professor Underwood, the chief investigator for this study, is a director and shareholder of Clinvivo Ltd, who provided the Delphi platform. He recused himself from any discussions related to the choice of Delphi platform for this study.

Phase 2: randomised controlled trial, work package 5

Phase 2 of the programme was a randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of the CHESS intervention package.

We identified people with chronic headaches from general practice records. Self-referral to the trial was also possible. We included adults with migraine or tension-type headache with or without medication overuse headache. People who appeared eligible after an initial telephone call were asked to provide consent and baseline measures. This was followed by a classification interview with a research nurse to confirm eligibility and identify people with suspected non-eligible headaches.

After the feasibility study we specified that if at least 85% of our participants had migraine our primary analysis would just be on the population with migraine, with sample size inflated, if necessary, to ensure adequate statistical power for this analysis.

The randomisation allocation ratio was 1 : 1.07 in favour of the intervention group to account for clustering in one arm. Randomisation was done using minimisation, stratifying by geographical locality (Midlands and Greater London) and headache type [definite chronic migraine, probable chronic migraine (i.e. episodic migraine plus chronic tension-type headache) and chronic tension-type headache only, with or without medication overuse headache].

Our primary outcome was the HIT-6 score at 1 year. We used the Migraine-Specific Quality of Life Questionnaire as the secondary headache disability outcome. We did follow-ups at 4, 8 and 12 months.

The sample size was based on testing the clinical effectiveness in the migraine population excluding participants with just tension-type headache (n = 689 participants: relaxation arm, n = 689; self-management arm, n = 356) provided 90% power to detect a between-group difference of 2 points (standard deviation 6.87 points, from the feasibility study) in HIT-6 score at 12 months for those with migraine using a two-sided test and a 5% significance level with a 20% loss to follow-up. Some over-run on sample size was expected to allow all groups to be adequately populated. We did a within-trial health economic analysis.

Between April 2017 and March 2019, staff at 164 general practices in the Midlands and London wrote to 31,026 people and we randomised 736 people, 727 (99%) with migraine: 54% (396/727) had chronic migraine and 56% (407/727) medication overuse headache. Despite reporting chronic headache when eligibility for the study was determined, after receiving informed consent at baseline, 38% (274/727) reported < 15 headache days in the preceding 4 weeks. Unless otherwise stated, analyses were on the 727 participants with migraine. Baseline characteristics were well matched. The first session was attended by 286 out of 376 (76%) intervention participants; 259 (69%) reached the minimum adherence (day 1, and the one-to-one session) and 216 (58%) achieved full adherence to the programme.

There was no between-group difference in HIT-6 scores at 12 months [adjusted mean difference −0.3 points, 95% confidence interval (CI) −1.23 to 0.67 points; p = 0.56]. The limits of this 95% CI excluded our target (worthwhile) effect size of 2.0 points and the smaller minimally clinically important difference of 1.5 points suggested by others for studies of episodic migraine. At 4 months there was a difference favouring the CHESS self-management programme (adjusted mean difference −1.0 points; 95% CI −1.91 to −0.006 points; p = 0.049). There were few differences in secondary outcomes. The self-management group had 1.5 (95% CI 0.48 to 2.56; p = 0.004) more headache days over the preceding 28 days at 4 months. They also had improved pain self-efficacy scores at 4 and 12 months. Use of acute drugs, including both prescribed and over-the-counter drugs, and prophylactic drugs was unchanged over time with no between-group differences. Using electronic/paper diary data the difference over 12 months in number of headache days was 0.2 days (95% CI −0.11 to 0.46 days; p = 0.234), difference in duration of each headache was 0.4 hours (95% CI −0.47 to 1.28 hours; p = 0.361) and difference in average headache severity on a 0–10 scale was 0.2 (95% CI −0.08 to 0.46; p = 0.163). We found no subgroup effects. Our complier-average causal effect and sensitivity analyses were not materially different.

There were seven adverse events: two in the standard-care arm and five in the self-management arm.

The CHESS intervention generated 0.031 (95% CI −0.005 to 0.063) additional quality-adjusted life-years (QALYs) and increased NHS and Personal Social Services costs by £268 (95% CI £176 to £377), generating an incremental cost-effectiveness ratio of £8617 with an 83% chance of being cost-effective at a willingness to pay of £20,000 per QALY gained.

Our process evaluation, including all 736 participants, showed that we recruited a nationally representative population including people from practices based in all 10 deciles of the Index of Multiple Deprivation; 18% of participants were from minority ethnic groups. Intervention fidelity was good, with adherence being slightly better than competence [adherence 83% (interquartile range 67–100%); competence 70% (interquartile range 50–90%)].

We carried out semistructured interviews with a purposive sample of 26 study participants. Most participants described gaining some new knowledge or insight about their headaches from the intervention they received, and a few changed medication. Some felt more confident to manage their headaches, but many did not.

CHESS was well received by participants, facilitators and general practitioners. Participants enjoyed interacting with others and valued the opportunity to talk, share and discuss their chronic headache experiences with others in a similar situation in a safe knowledgeable space.

Patient and public involvement

There has been substantial patient and public involvement in the design, conduct and interpretation of the CHESS programme. Throughout the programme we worked closely with three UK migraine charities and a lay advisory group to help direct the research and ensure that the patient voice was embedded in our work.

Conclusions

Over the duration of the CHESS programme, we have advanced our understanding of the challenges of living with chronic headaches and made some progress in developing the methodology for running randomised controlled trials of complex interventions for people living with chronic headaches.

Our data effectively excluded the possibility that this short intervention is effective for the treatment of chronic migraine or chronic tension-type headache and episodic migraine. Although there was no effect on our chosen headache-specific outcomes, we have not excluded the possibility that it produces a worthwhile QALY gain, as measured by the EuroQol-5 Dimensions, five-level version.

The health burden of chronic headache disorders, principally chronic migraine, is debilitating. Those living with the condition warrant support to optimise their care planning according to their needs and the latest knowledge about treatment and management. Further advances in this field must be driven by new theoretically and/or biologically informed intervention models.

Research recommendations

- New work to better understand the health impact of chronic headache disorders and to identify modifiable risk factors for a poor outcome.
- Development and testing of new non-pharmacological interventions for a tightly phenotyped group with chronic migraine.
- Research is needed to support improved classification of headache disorders in primary care to allow better targeting of the available drug treatments of proven effectiveness, and reduce medication overuse.

Trial registration

This trial is registered as ISRCTN79708100.

Funding

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SYNOPSIS

Background

Headaches are second only to low back pain as a global cause of years lived with disability, accounting for 6.4% of the total years lived with disability.[1] Only dental caries are more common than migraine and tension-type headaches.[1] Headaches are the most common neurological disorder treated in primary care, accounting for around 3% of general practitioner (GP) consultations; however, 70% of these patients do not get a formal diagnosis.[2,3] Two-thirds (64%) of people seen in a specialist headache clinic have not had a headache diagnosis from their GP. Of those with migraine, fewer than half have been offered specific migraine treatment.[4]

For many people with headache disorders their symptoms are intermittent and they can be managed with symptomatic treatment as required. However, for a substantial group of people, headaches become a chronic disabling disorder. This group contributes disproportionally to the health burden, and economic cost, of headache disorders.

Treatment guidelines for headache disorders are typically formulated in a biomedical framework, with the main focus being on drug treatments for those with a diagnosed headache disorder. For example, the only non-pharmacological intervention recommended for people with chronic tension-type headache or chronic migraine in the 2012 National Institute for Health and Care Excellence (NICE) guidelines[5] published was acupuncture. There is a need for more non-pharmacological treatments to help those living with headache disorders.

In 2015, when we started this programme of work, very little was known about how best to support those who have developed a chronic problem consequential to a primary headache disorder. We anticipated that any supportive self-management programme would need to include helping more people to get a headache diagnosis, avoiding medication overuse headaches, providing medication appropriate for the headache type and supportive self-management for a chronic painful disorder.

Headache researchers usually expect those individuals studied to have an established headache diagnosis prior to study entry.[6,7] This work, however, started from the premise that most people with frequent headaches do not have an established diagnosis, and was developed from the perspective of headaches as a chronic disorder. There is not, however, a recognised clinical entity of chronic headaches. In epidemiological studies researchers use a definition of chronic headaches based on the definition of chronic migraine or chronic tension-type headache, specifically headaches on ≥15 days per month for the previous 3 months.[8–11] This matches neither the conventional definition for chronicity of pain used by International Association for the Study of Pain (IASP), of pain persisting for greater than 3 months,[12] nor the definitions of chronicity used for other headache disorders, for example chronic cluster headache.[9] In addition, the chronicity of headaches defined in this manner is labile.[9,12] In a community study of migraine,[13] three-quarters [386/526 (73%)] of people with chronic migraine had one or more 3-month period in the following year when their headache frequency was consistent with episodic (<15 headache days per month) rather than chronic migraine.[13] Nevertheless, this epidemiological definition is a useful shorthand to describe our population of interest: people living with headaches affecting them on most days. Our overarching aim was to develop and test a supportive education and self-management group intervention implementable in primary care for people with chronic headaches. This is an area with little previous methodological work and an absence of substantial previous UK experience of recruiting people from primary care for studies of headache

interventions. A broad programme of research was needed to set the scene for our randomised controlled trial (RCT).

Key areas of uncertainty were as follows:

- Was it possible to recruit people from primary care who met our definition of chronic headache?
- How easy would it be to identify people who might have other headache types not suitable for our intervention package?
- What is the patient experience of living with chronic headaches (including chronic migraine)?
- What should be the content of the self-management support intervention?
- What format should be used for the delivery of the self-management support intervention?
- How acceptable would our intervention package be to people living with chronic headaches?
- How should we measure outcomes?

These were all addressed in the phase 1 feasibility study. In phase 2 we ran a full RCT, with a cost-effectiveness analysis and an embedded process evaluation.

Phase 1: trial feasibility

The trial feasibility phase was made up of four core areas of work, each of which mapped onto our work packages (WPs):

- WP1 – developing a strategy to identify people with chronic headaches from primary care.
- WP2 – developing and evaluating a telephone headache classification interview.
- WP3 – developing and evaluating an education and self-management support intervention for people living with chronic headaches.
- WP4 – selecting the most appropriate patient-reported outcome measure (PROM).

The trial feasibility phase aimed to answer the questions of what can be done, what should be done, and how best it can be done for a future RCT. Here we describe these packages of work and how these informed the trial feasibility (see *Figure 1*).

Recruiting feasibility sample (work package 1)

Objective: to develop and test strategies for recruiting people living with chronic headaches from primary care.

To determine recruitment feasibility, we needed to:

- Develop a strategy to identify people with chronic headaches from primary care. Our scoping work identified that the standard clinical terminology system (Read codes) for coding chronic headache disorders in general practice was rarely used. We developed a search strategy incorporating age, consultation for headaches and prescription of headache-specific medication to identify our target population.
- For any future trial, we needed to be sure we could recruit practices. To test this, during the feasibility phase we aimed to recruit practices in the West Midlands. With the help of our local Clinical Research Network (CRN) we recruited 14 practices, giving us a total practice population of 128,634. A detailed account of the recruitment process is given in our published paper (see *Appendix 1*).[14]

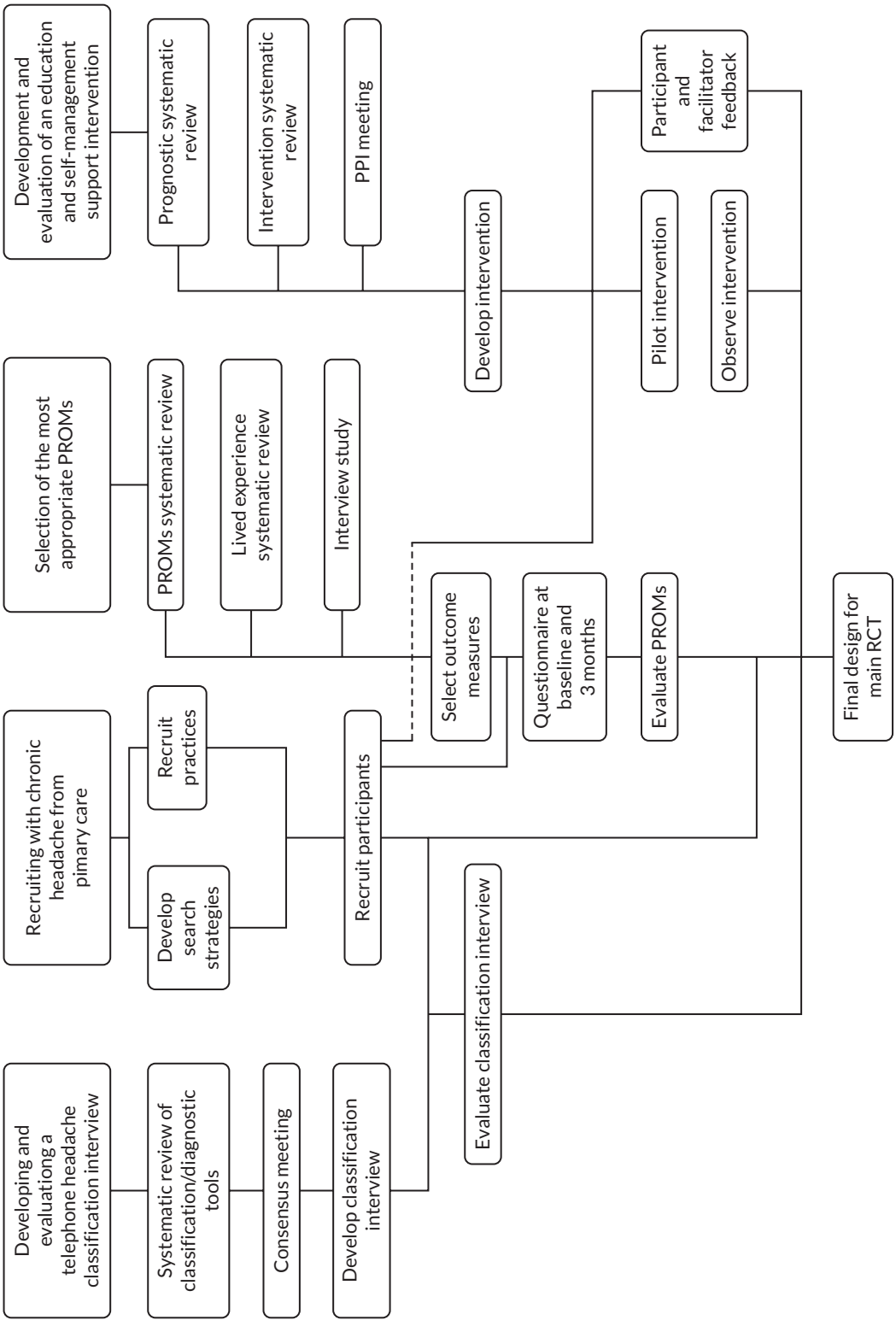

FIGURE 1 Components of the trial feasibility phase. PPI, patient and public involvement. Reproduced with permission from White *et al.*[14] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The figure includes minor additions and formatting changes to the original.

From the practice population of 128,634 we obtained informed consent from 131 participants (see *Figure 2*).[14] Participants' mean age was 49 years [interquartile range (IQR) 38.5–58 years, standard deviation (SD) 13.3 years], 108 (82%) were female and 125 (95%) were white. These participants consented to:

- completing an electronic (smartphone/web-based) headache diary (a paper version was also available) for 3 months
- filling out a baseline, 2-week and 3-month questionnaire
- taking part in two telephone interviews
- the research team sharing the headache assessments with the participants' GPs.

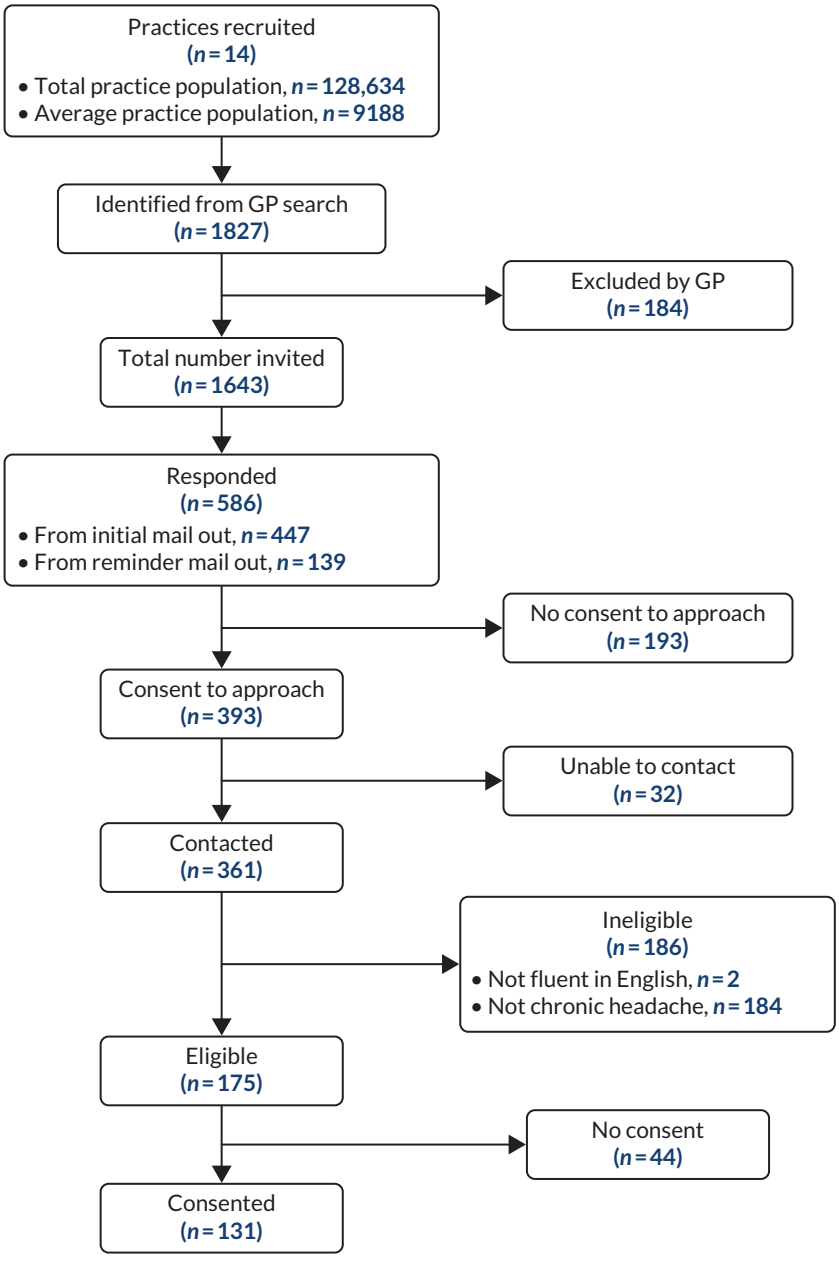

FIGURE 2 Practice and participant recruitment for the feasibility study. Reproduced with permission from White *et al.*[14] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The figure includes minor additions and formatting changes to the original.

They also agreed to potentially being invited to two further studies:

1. an interview study to explore the experience of living with frequent headaches, how we might refine our proposed support programme, and what outcomes are important to people living with frequent headaches
2. a pilot study in which we invite people to take part in our chronic headache education and self-management support programme.

The sample size for the feasibility study was driven by the need for sufficient data to measure the level of agreement of the classification interviews in WP2. The original sample size was 170; this was revised to 153 paired interviews owing to a change in planned analyses approved by the Programme Steering Committee (PSC) and the funder in March 2016. Later, the PSC agreed that recruitment could stop at 131 participants after reviewing the agreement analysis for the first 100 paired classification interviews. This cohort of 131 participants provided us with a sampling frame for the feasibility work; full details are in our published paper (see *Appendix 1*).[14]

Developing and evaluating a structured telephone interview for diagnosing common chronic headache disorders (work package 2)

Objective: to develop and evaluate a brief diagnostic interview to support diagnosis for people with chronic headaches, focusing on the diagnosis of the three common chronic headache disorders – migraine, chronic tension-type headache and medication overuse headache.

Within this WP it was important not only to be able to identify the population of interest for the main trial, but also to feel confident that those who have other headache types not suitable for our trial were appropriately identified, and referred for relevant support. We first reviewed the literature on diagnostic tools.

Systematic review of diagnostic tools for chronic headache

We searched for studies aiming to validate tools for diagnosis and/or classification of headaches. We searched the published literature between January 1988 and June 2016 using MEDLINE® (National Library of Medicine, Bethesda, MD, USA), Applied Social Sciences Index and Abstracts (ASSIA), Embase® (Elsevier, Amsterdam, the Netherlands), Web of Knowledge™ (Clarivate™, Philadelphia, PA, USA) and PsycInfo® (American Psychological Association, Washington, DC, USA). Methodological quality was assessed using items from the Quality of Diagnostic Accuracy Studies (QUADAS-2) tool. We identified 4348 titles and removed 2459 duplicates; after screening the remaining titles we obtained full-text results for 195 papers. Thirty-eight papers met our inclusion criteria validating 30 tools designed to diagnose, classify or screen for headache disorders. Of these, 21 tools were for classification of one headache type and nine were for multiple headache types. Full details are given in our published paper (see *Appendix 2*).[15]

We did not find any tools that we could use for our proposed trial and felt that it was important to develop our classification tool based on the evidence as well as a collaboration with clinicians and patients. We therefore organised a consensus conference. Full details are in our published paper (see *Appendix 3*).[16]

Consensus conference

The aim of the day was to reflect on the evidence from the review and draw on the expertise of the delegates to help inform the content of the Chronic Headache Education and Self-management Study (CHESS) nurse telephone classification interview.

The purpose of the meeting was to develop a classification interview that would:

- confirm study eligibility – participants aged ≥18 years with chronic headache, defined as a headache on ≥15 days per month for at least 3 months
- classify the participant's headache type as part of the active intervention to inform treatment and advice (this was done during the face-to-face part of the intervention).

Twenty-six delegates attended (10 neurologists with specialist interest in headaches, three general neurologists, five headache specialist nurses, one GP with a special interest in headaches and seven people living with chronic headaches) attended our 'Classification Consensus Conference' at the University of Warwick in August 2015.

They were split into four multidisciplinary groups. Using facilitated discussions each group was asked to address the following four questions:

1. What do we need to know from a person to exclude secondary headaches?
2. What do we need to know from a person to exclude primary headaches other than chronic migraine and tension-type headache?
3. What do we need to know from a person to distinguish between chronic tension-type headache and chronic migraine?
4. What do we need to know from a person to identify medication overuse headache?

The facilitators aimed to get consensus on discussed items; when there was uncertainty, items were taken to a plenary session in which they were further discussed followed by voting to gain consensus. Further work by the research team developed and refined the final classification logic model underpinning the classification interview (see *Figure 3*).

The classification logic model is presented as a linear process. However, it was developed to be completed non-sequentially as information was obtained during the interview and it is not a diagnostic algorithm.

Having developed the classification tool, the next phase was to validate the tool by training nurses to use the tool.

Training and validation

On 22 February 2016 six research nurses who would complete the telephone classification interviews attended a training day. Nurses were provided with a detailed manual and further one-to-one support to ensure that they felt confident in conducting the interviews (see *Report Supplementary Material 1*).

To validate the telephone classification tool, we did paired interviews whereby participants received an interview with the nurse and soon after a second interview with a headache specialist doctor from the National Migraine Centre (NMC).[17] These doctors used their standard approach to telephone assessment and did not use the CHESS logic model.[16]

Level of agreement was measured using proportion of concordance, the kappa statistic and prevalence-adjusted bias-adjusted kappa.[18] The sample size calculation was based on the kappa statistic of the level of agreement between the nurse interview and the specialist doctor. Nurses carried out 111 classification interviews and the doctors carried out 108 interviews. We obtained paired data on 107 participants.

There was generally good agreement between nurse and doctor interviews (proportion of concordance > 0.75).[16] We reviewed cases in which both parties disagreed on the classification and those in which both classified the headaches as 'other' (non-chronic migraine or chronic tension-type headache).[16] Typically, the disagreements were around whether the headaches were episodic or were chronic migraine. Four people had an excluded headache type: two people had cluster headaches, one had a hemicrania continua and one had a primary stabbing (ice pick) headache. This confirmed that, although ineligible primary headache types are uncommon, they were sufficiently common to justify identifying them prior to randomisation.

A striking, and unexpected, observation from this work was that only a very small proportion of those we assessed had chronic tension-type headaches: only 6 out of 107 (6%). This had consequences for our approach to the primary analysis for the RCT described in phase 2.

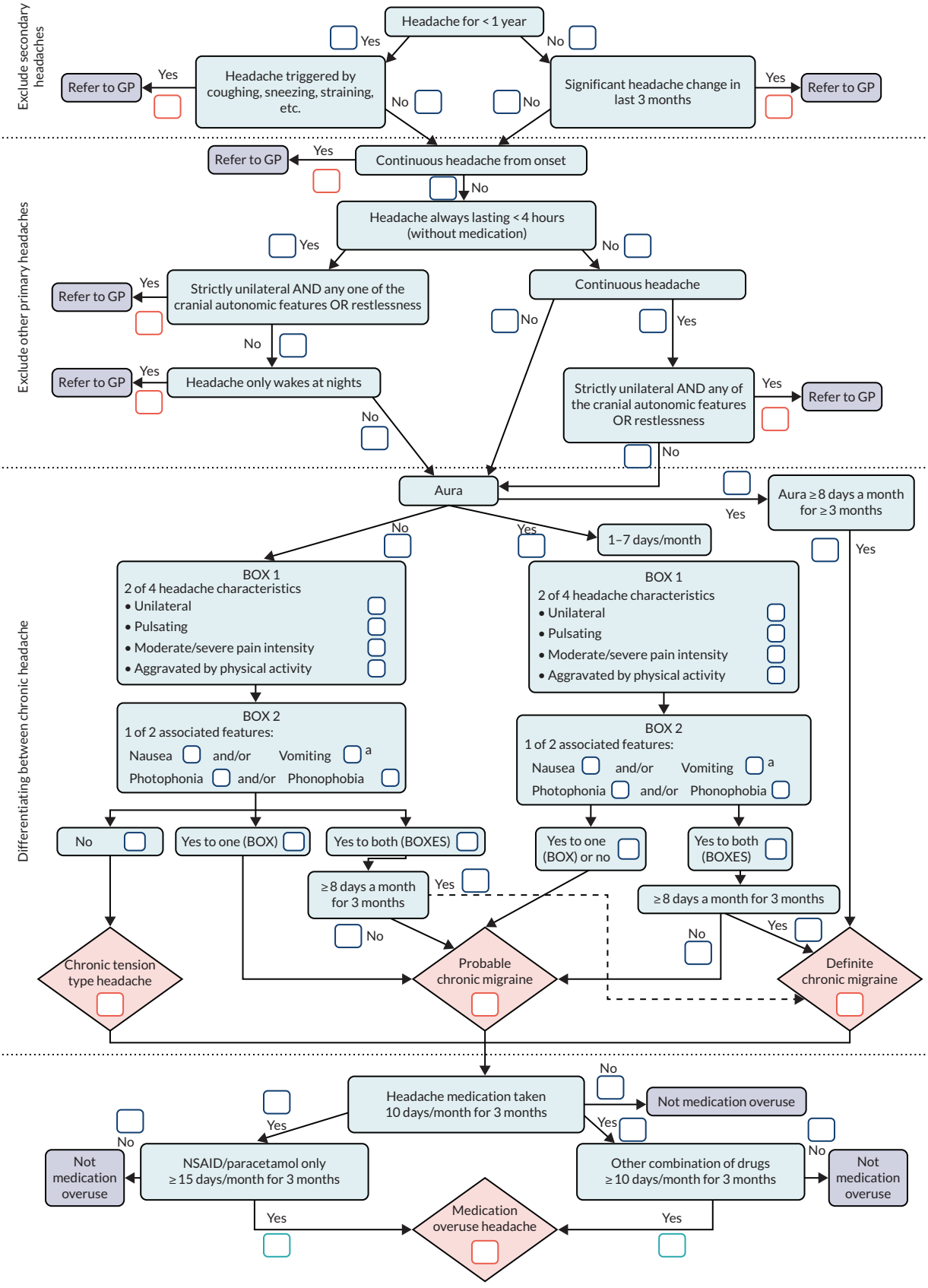

FIGURE 3 Classification logic model. a, Tension-type headache, has mild nausea. NSAID, non-steroidal anti-inflammatory drug. Reproduced with permission from Potter *et al.*[16] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The figure includes minor additions and formatting changes to the original.

Developing and evaluating the intervention (work package 3)

Objective: to develop and pilot an education and self-management support intervention for the management of common chronic headache disorders (the CHESS intervention) that is both theoretically informed and based on best evidence.

Details of our intervention development are in our published paper (see *Appendix 4*).[19]

We first reviewed the existing literature to understand the experience of chronic headaches from the patient perspective, what content and approaches might be effective for this population and what modifiable prognostic factors exist to be targeted in future interventions.

Systematic reviews

Details of each review are in our published papers (see *Appendices 5–7*).[20–22]

Lived experience of chronic headache (see *Appendix 5*)[20]

We systematically reviewed and appraised the qualitative literature on the lived experiences of those living with chronic headaches. We included qualitative studies of adults (aged ≥18 years) with chronic headaches. We searched MEDLINE, Embase, ASSIA, PsycInfo, Scopus® (Elsevier, Amsterdam, the Netherlands) and Web of Science™ (Clarivate) between January 1988 and July 2016. We included studies that used qualitative methodology, or mixed methodology if the qualitative findings were reported separately. We excluded studies that did not have a patient's perspective, theses, dissertations and conference papers. We appraised the included studies for risk of bias. We used a thematic analysis across the studies followed by a meta-ethnographic approach.

Four studies met our inclusion criteria. Analysis identified three overarching themes:

1. 'headache as a driver of behaviour' – forcing patients to stop activities or take increasing medication to function
2. 'the spectre of headache' – the worries, fear and guilt that patients carry
3. 'strained relationships' – the effect their headaches and behaviour have on those around them.

Although chronic tension-type headaches were represented in the data, they may have been overshadowed by chronic migraine features.

Prognostic factors in chronic headache (see *Appendix 6*)[21]

We included prospective cohort studies and RCTs of chronic headaches, published in English. We included adults with chronic migraine, or chronic tension-type headache, with or without medication overuse headache disorders. We excluded studies with participants < 18 years old, dissertations and conference proceedings. We searched Cochrane, MEDLINE/PubMed® (National Library of Medicine), Embase, PsycInfo, Web of Science and ASSIA, from January 1980 to June 2016. Two reviewers independently extracted data and assessed the methodological quality. RCTs were included only if a subgroup analysis was reported or enough data to perform subgroup analysis were presented. We assessed the adequacy of any moderator analyses.

Twenty-seven studies met our inclusion criteria: 17 prospective cohort studies and 10 RCTs with subgroup analyses. There was moderate evidence for depression and anxiety, poor sleep, stress, medication overuse and poor self-efficacy predicting a poor outcome. There was inconclusive evidence for treatment expectations, age and age at onset, body mass index, employment and headache features predicting a poor outcome.

Broadly speaking, the factors identified were consistent with prognostic factors seen in people with chronic painful musculoskeletal disorders, supporting the notion that adapting approaches used to help people live better with other chronic disorders can be applied to people living with chronic headaches.[23,24]

Style and content of intervention programmes (see *Appendix 7*)[22]

Our aim in this review was to identify the components and method of delivery used in non-pharmacological educational and self-management interventions for headache disorders. We included RCTs comparing a relevant educational and/or self-management intervention for headache disorders with usual care. We excluded studies with participants aged < 18 years old, invasive treatments such as acupuncture, interventions purely focusing on physical exercise, dissertations and conference proceedings. We searched the Cochrane Library, MEDLINE, Embase, Web of Science and PsycInfo from January 1980 to June 2016.

We included 16 studies in the review. We found positive overall effects of self-management interventions over usual care for pain intensity, headache-related disability and quality of life. A moderate effect was seen on mood. A greater effect on mood was observed in interventions that included a cognitive–behavioural therapy (CBT) component than those without, and for group interventions when compared with one-to one delivery.

Interview study

We conducted the interview study to build on our understanding from the systematic reviews to aid the development of the intervention. More details are included in our published paper (see *Appendix 4*).[19]

We had planned to conduct interviews on the sampling frame developed in WP1. At the time we needed to do these interviews to inform intervention development, this sampling frame was not established. Therefore, our sample was obtained through Migraine Action, one of our charity partners (Migraine Action merged with The Migraine Trust in 2018) and approved by the PSC and funder in October 2015. We sent 100 invitations leading to 21 responses. Of these, seven met our inclusion criterion of headaches on ≥15 days per month for at least 3 months. A topic guide was informed by the literature review. The guide allowed the exploration of perceptions of helpful and unhelpful treatment strategies. All interviews were audio-recorded for transcription.

The results suggested that participants had tried a range of therapies and interventions, some of which were helpful while others were not. Access to education and peer support was deemed positive, as was learning new skills such as relaxation, mindfulness and stress management.

Developing the intervention package

The reviews and the interview study were summarised and presented at a multidisciplinary intervention development day held in November 2015 at the Royal College of General Practitioners in London. The aim of the day was to start to scope out what the CHESS intervention should look like. Eighteen people attended, bringing together clinical, academic and lay expertise. The facilitated discussions were factored around four core areas (see *Box 1*).

There was overall agreement that the intervention should be a group education and self-management intervention with an integrated one-to-one consultation. The group intervention would be for 8–10 participants and be modular, but participants should attend all the sessions. Suggestions were to run the programme during school hours in community settings when possible. It was agreed that the intervention should be delivered by a nurse and a layperson living with chronic headaches and delivered in a non-didactic manner. The content should include educational material, self-management material, medication advice, plus a digital versatile disc (DVD) suitable to share with friends and family. Providing a DVD for family and friends was a suggestion from patient partners that the academic team had not previously considered. Ongoing support was agreed as up to 8 weeks of telephone support by the nurse, individually negotiated with participants.

BOX 1 Intervention day discussion core areas

1. Tailored headache education
    i. How can the classification interview be used for the intervention for supporting optimisation of drug treatment?
    ii. What written information is needed (for GP and patient)?
    iii. What should be the structure of this consultation?
    iv. What should it be the content of this consultation?
    v. How long should it last?
    vi. Where should it be conducted and by whom?
2. Generic chronic headache self-management
    i. What format should the self-management intervention take?
    ii. What should the content be?
    iii. How should it be delivered (format, length)?
    iv. Who should it be delivered by?
    v. Where should it be delivered?
    vi. What material do we need to develop for the intervention arm?
    vii. Do we need any material for the GP?
3. Control group
    i. What would be deemed an acceptable control arm?
    ii. What material do we need to develop for the control arm?
    iii. Do we need any material for the GP?
4. Ongoing support
    i. How should any ongoing post intervention support be provided?
    ii. How should this be standardised?
    iii. How should this be recorded?

The group felt strongly that there should be a comparator control group arm and not just usual care. As the literature[22] suggested beneficial use of relaxation, this was deemed a good control intervention. It was agreed that a relaxation compact disc (CD), adapted from a previous study,[25] would be developed for CHESS. Control participants were also to be provided with customised information on their headache type after a classification interview.

In the feasibility phase the intervention was designed to be delivered, by a nurse and a layperson, over 2.5 days with a one-to-one nurse consultation and individualised follow-up.

Testing and refining the intervention package

Having developed the intervention package and a facilitator manual to accompany this (see *Report Supplementary Materials 2* and *3*), we delivered three groups using the 2.5-day intervention format described. Groups were run between July and September 2016. We approached 79 participants from our sampling frame (see *Appendix 1*).[14] Thirteen participants attended: six attended the first group, three the second group and four the third group. Difficulty with attendance was as a result of commitment of time over 2 consecutive days.

As part of the formative evaluation the process evaluation team observed group two and concluded that the intervention had been delivered as per protocol. They interviewed 12 out of the 13 participants who attended these feasibility groups. Some participants had also completed a feedback form at the end of each day.

Overall, everyone had appreciated connecting with others with the same condition, and this was a driver to return. The course content and pace were well received. Group discussions were appreciated, as was the lay facilitation. The nurse one-to-one sessions were highly valued by most, with the majority wanting telephone follow-ups. The majority said that they would recommend the course to others. Only two had some reservations: one felt that it would be useful for people newly diagnosed and one wanted more individual tailoring of advice.

We interviewed three nurses and two lay facilitators to ask about their experiences of running the groups. This feedback resulted in the removal of the half-day follow-up because participants found it difficult to get the time off to attend. The final and the third feasibility group piloted the 2-day revised format intervention, which was subsequently adopted for the main RCT (see *Figure 4*). For the main study we also provided additional facilitator training on medication use.

During the feasibility phase it became clear that recruiting laypeople with chronic headaches as facilitators would be challenging because of the unpredictable nature of the condition. This was discussed at a trial management meeting in June 2016, at which there was agreement to recruit allied health professionals to co-facilitate with the nurse.

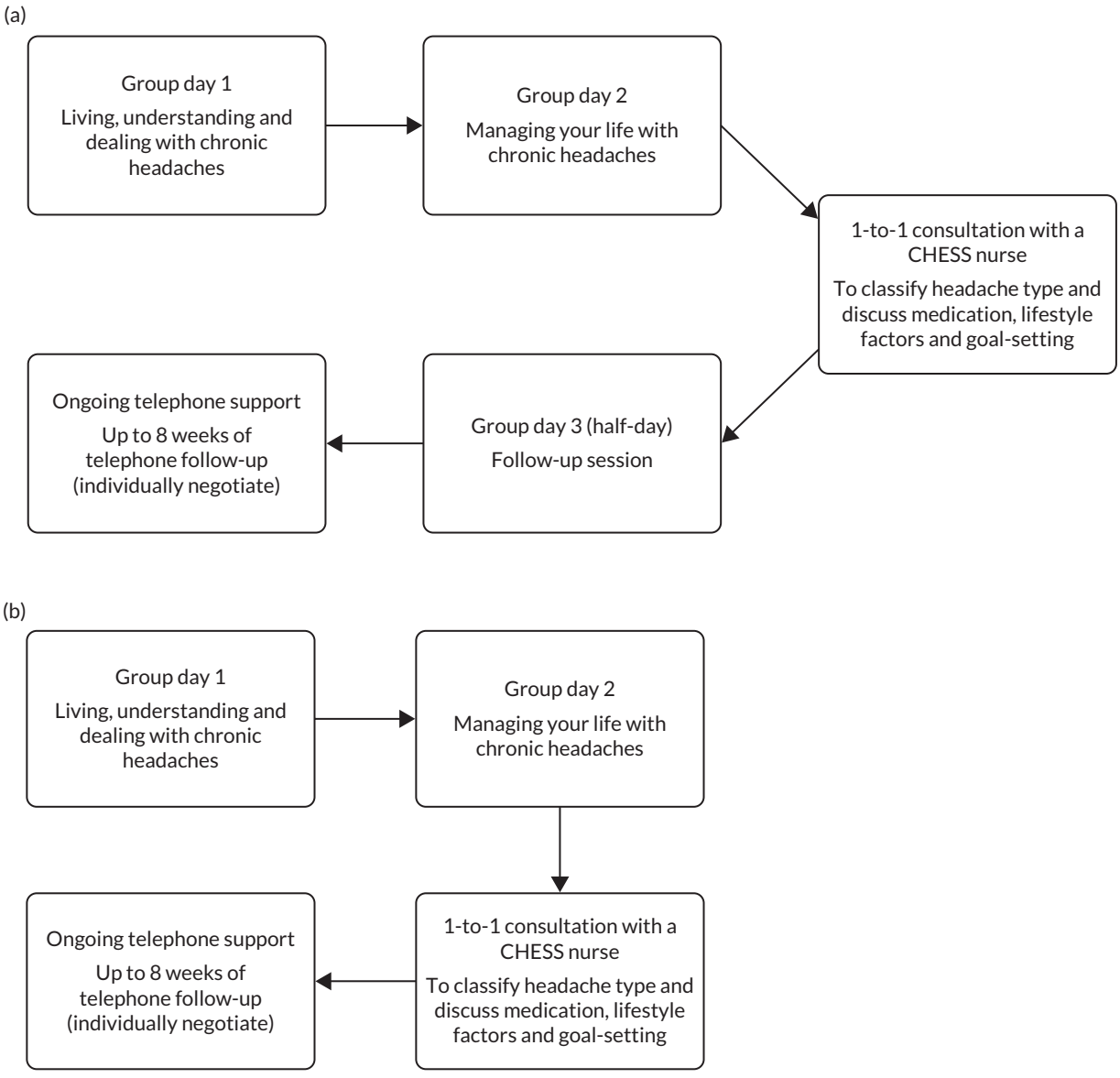

FIGURE 4 Intervention structure. (a) Feasibility phase and (b) main study.

The theoretical underpinnings and behaviour change rational and techniques for the CHESS intervention, and course content, are described elsewhere (see *Appendix 4*).[19] The CHESS intervention materials are available from http://wrap.warwick.ac.uk/171671.

Choice of clinical effectiveness and cost-effectiveness outcome measures (work package 4)

Objective: to select most appropriate outcome measures for the RCT of the CHESS intervention package.

This work is described in our published papers and appendices (see *Appendices 8–10*).[26,27]

Systematic review of patient-reported outcome measures (see Appendix 8)[26]

We wanted to assess the quality and acceptability of outcome measures for chronic and episodic headache. We searched for multi-item PROMs evaluated following completion by adults aged ≥ 18 with episodic or chronic headache. We searched published literature between January 1980 and December 2016 using MEDLINE and Embase. We assessed study methodological quality using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist, and PROM measurement quality and acceptability by reference to accepted international standards.[28–32]

We included 46 papers providing evidence for 23 PROMs. Six measures looked at the impact of headaches overall and five were specific to the impact of migraines. Six assessed responses to, and/or satisfaction with, migraine-specific drug treatments. A further six generic measures had been assessed in headache populations. Assessment of reliability was generally limited with acceptable evidence for the six-item Headache Impact Test-6 (HIT-6).[33] Assessment of responsiveness was rare and patient involvement was limited and poorly reported. Overall, the HIT-6, the Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1[34] and the Patient Perception of Migraine Questionnaire – Revised (PPMQ-R)[35] had acceptable evidence of reliability and validity, although that was still limited. For a generic 'headache' population only the HIT-6 had acceptable evidence of validity and reliability.

Based on the review, and cognitive interviews, detailed below, the HIT-6 was selected as the primary outcome measure for the RCT. Many of the assessed measures had a migraine focus, making them challenging to apply to a generic chronic headache population. However, among the team, patient and public involvement (PPI) research partners and the lay advisory group, there was a sense that a lot of the questions in the 14-item MSQ v2.1 had relevance to our population.

Outcomes for the trial (see Appendix 9)[27]

With the permission of GSK plc (formerly GlaxoSmithKline plc; Brentford, UK), the developers of the MSQ v2.1, we modified this measure, changing the focus of each item from 'migraine' to 'headache'. The adapted measurement was renamed as the Chronic Headache Quality of Life Questionnaire (CHQLQ).

We did a mixed-methods comparative evaluation of the CHQLQ and HIT-6. Feasibility study participants completed the postal questionnaires at three time points: baseline and at 2 and 12 weeks. This provided the raw data necessary to inform the psychometric evaluation. A range of analyses informed the determination of data quality, reliability, validity, responsiveness to important change in health and score interpretation. The questionnaire included headache-specific, generic and several domain-specific measures. In addition, we carried out semistructured cognitive interviews with 14 participants within 24 hours of them completing the 2-week questionnaire to explore the relevance, acceptability, clarity and comprehensiveness of the headache-specific (and generic) measures.[36–39] We wanted to explore what participants felt was missing and how individuals determined any improvement in their headache. Interviews were audio-recorded and transcribed.

Both the CHQLQ and HIT-6 were well completed, had good psychometric properties and were relevant to the experience of headaches. The CHQLQ captured the wide-ranging impact of chronic headache, in particular the emotional impact, to a greater extent than HIT-6.

Our original intention was to make a final decision on the primary outcome for the trial informed by our quantitative study. It was not possible to complete this work before starting the main trial. For this reason, we set HIT-6 as the primary outcome for the trial and the CHQLQ as a secondary outcome.

Electronic data capture (see Appendix 10)

We wanted to explore electronic means of capturing data on the frequency, severity and duration of headaches. The application (app) was developed by Clinvivo Ltd, a University of Warwick spin–out. We developed three questions to capture headache frequency, duration and severity. The developers drafted a version that was initially tested by the research team and members of the lay advisory group.

We agreed a secure data management process to enable data captured from the app to be tracked against each participant's trial number. A system of flagging participants who had not responded for more than 3 weeks was also implemented. Eight feasibility participants were asked to complete the app over an 11-week period. The overall feedback was positive and completion rates reasonable: the team agreed to include the smartphone app as part of the main trial.

Professor Martin Underwood, the chief investigator, is a director and shareholder of Clinvivo Ltd. The use of this company was suggested in the original application for funding. Professor Underwood subsequently recused himself from all contracting decisions, which followed University of Warwick standard financial procedures. He had no involvement in this aspect of the work from either a University of Warwick or a Clinvivo Ltd perspective during the lifetime of the study. He is not an author on the draft paper describing this work. He has edited this report with respect to the use of the smartphone app.

Mapping study of health outcomes in people living with chronic headaches (see Appendix 11)[40]

A piece of work mapping between health-specific outcomes and health utility measures was included in the original proposal embedded in our existing data collection. During the lifetime of the programme we concluded that it would be better to collect data for this outside the main trial. Recruiting an external cohort of chronic headache patients (separate from the main trial participants) meant that externally generated mapping coefficients could be obtained to inform the economic evaluation of the CHESS intervention. We set up a separate substudy to collect data for headache clinics. This additional work was approved by the funder in September 2019 but was considerably delayed because of the COVID-19 pandemic. In the mapping substudy, mapping or crosswalk algorithms were developed to estimate EuroQol-5 Dimensions, three-level version (EQ-5D-3L), and Short Form questionnaire-6 Dimensions (SF-6D) health utilities from responses to the HIT-6 and the CHQLQ. Data from cross-sectional cohort of 349 people living with chronic headaches in England were used to develop the mapping functions while baseline data from CHESS participants served as a validation sample. *Appendix 11* presents further details of the methods, analyses, and results. Overall, censored least absolute deviations models generated the best performance in terms of accuracy of predictions. EQ-5D-3L and SF-6D utilities were best predicted from the HIT-6 without the need for additional patient-level information, whereas predictions for the CHQLQ required age and gender in addition to the summary score.

Other related work

We describe here other activities done as part of the CHESS programme that are outside the main narrative.

Core Outcome Set in Migraine (see *Appendix 12*)[39]

In WP2 we identified inconsistencies in outcome reporting alongside often poorly defined outcomes. We recognised the need and opportunity to develop a core outcome set for migraine trials. We decided that this would have wider relevance than focusing on the needs of just our trial. We made the decision to focus on a core outcome set for migraine trials, rather than for headache trials, informed by the overwhelming proportion of those we recruited in WP1 having migraines.

In a two-step process, we defined the core domain set (what to measure), followed by the core measurement set (how to measure specified domains). We identified >50 domains from our systematic reviews and our qualitative work. These data were presented in two questionnaires, one for episodic migraine, the other for chronic migraine. We did a modified, three-round electronic-Delphi study with patients and professionals.

Professor Underwood, the chief investigator for this study, is a director and shareholder of Clinvivo Ltd, who provided the Delphi platform. He recused himself from any discussions related to the choice of Delphi platform for this study.

The results of this Delphi study (see *Report Supplementary Material 4*). were discussed at a consensus day, at which the aim was to ratify the core domains, agree on the core measurement set and recommend the core outcome set. Through group facilitation and discussion, a two-domain core outcome set was agreed for chronic and episodic migraine:

1. migraine-specific pain – to be assessed with an 11-point numerical pain rating scale, and frequency as the number of headache/migraine days over a specified period
2. migraine-specific quality of life to be assessed with the Migraine Functional Impact Questionnaire.[41]

Although the Migraine Functional Impact Questionnaire is a new PROM, it has strong evidence of face and content validity and essential measurement properties (when compared with existing measures of headache-specific quality of life). Participants in the consensus meeting felt that it better represented the important elements of headache-specific quality of life that were identified during the Delphi process. The Migraine Functional Impact Questionnaire had not been published when we started the CHESS RCT and so we were not able to use this as an outcome.

Relationship between chronic headaches and chronic low back pain (see *Appendix 13*)[42]

Our approach to seeking to help people with chronic headaches draws on approaches used to treat people with chronic musculoskeletal pain. As an additional piece of work, we did a systematic review of studies looking at the association between chronic headache and chronic back pain, full details published elsewhere.[42] We identified 14 studies reporting on our primary outcome: the association between chronic headache disorders and persistent low back pain (LBP). Different papers found odds ratios ranging between 1.55 [95% confidence interval (CI) 1.13 to 2.11] and 8.00 (95% CI 5.3 to 12.1). The strength of these findings was constrained by the variable approaches used by the original authors to define both chronic headaches and back pain. This supports our decision to use a biopsychosocial approach, grounded in previous work on chronic musculoskeletal pain, to inform our headache intervention.

Multicentre trial (work package 5)

Objective: to run a multicentre RCT, including an economic evaluation, of the CHESS intervention package.

Details of the trial have been published elsewhere (see *Appendices 14* and *15*).[43,44] Further information is available in our original application, final protocol, data management plan, statistics analysis plan and health economics analysis plan (see *Report Supplementary Material 5–8*). Here we address the research question:

- Is the CHESS intervention package clinically effective and cost-effective when compared with a usual-care control?

Clinical methods

Practices identified people who had consulted with headaches or who had been prescribed a migraine-specific drug (triptans/pizotifen) in the previous 2 years.[14] The list of people was screened by a GP in the practice to identify people it would not be appropriate to approach, for example people with a severe uncontrolled mental health problem or a terminal illness. *Table 1* provides a list of the full inclusion/exclusion criteria. The practice then sent out packs inviting people to express an interest in the trial. Those who were interested returned an expression of interest form to the research team. The research team telephoned the potential participant to confirm their eligibility and obtain verbal consent to start the smartphone app, or paper headache symptom diary. A study pack with the participant information leaflet, consent form and baseline questionnaire was sent to the potential participant. Once the consent form and baseline questionnaire were received, a classification interview call was arranged (see *Figure 5*).

Nurses used the classification tool (see *Figure 3*) to confirm study eligibility and flagged any people with suspected non-eligible headaches for a second telephone interview with a doctor from the NMC. Participants classified as having an eligible headache type were then eligible for randomisation. If there was not a group an individual could attend, they were not randomised.

Our population of interest was people meeting an epidemiological definition of chronic headaches, that is, people with headaches for ≥ 15 days per month for at least 3 months.[8,10,11] At our classification day, it was decided to focus the trial just on people with migraine or tension-type headaches. People suspected of having other chronic headache types were directed to their GPs. For reporting we present three primary headache phenotypes:

1. definite chronic migraine – people meeting *International Classification of Headache Disorder*, third edition (ICHD-3) criteria for chronic migraine, that is at least 8 days per month with a migraine attack with or without aura[9]
2. chronic tension type headache and episodic migraine – people meeting ICHD-3 chronic tension-type headache and ICHD-3 criteria for episodic migraine
3. chronic tension-type headache.

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Able and willing to comply with the study procedures and provide written informed consent	Unable to attend the group sessions
Aged ≥18 years (no upper limit)	No access to a telephone (for classification interview)
Living with chronic headache: defined as headache on ≥ 15 or more days per month for at least the preceding 3 months	Has an underlying serious psychological disorder with ongoing symptoms that preclude or significantly interfere with participation in the group intervention
The nurse telephone classification interview confirms headache type to be chronic migraine, or chronic tension-type headache, with or without medication overuse headache	Previous entry or randomisation in the present trial
Fluent in written and spoken English	Currently participating in another clinical trial of headache treatments or unregistered medicinal product, or < 90 days have passed since completing participation in such a trial

Notes
During the lifetime of the study we added living at the same address as someone already randomised to the trial as an exclusion.
Reproduced with permission from Patel *et al.*[43] This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original table.

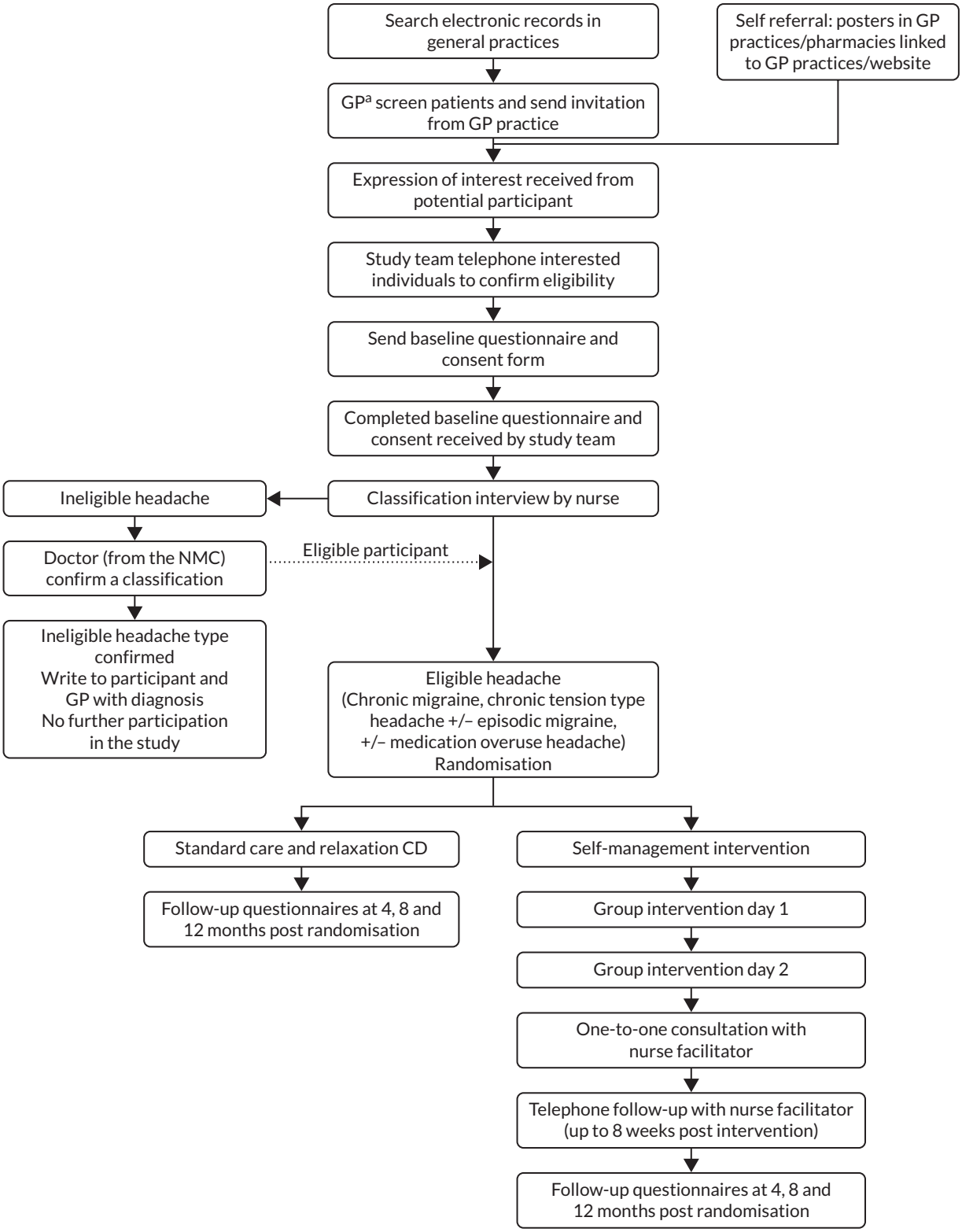

FIGURE 5 Study flow chart. NMC, National Migraine Centre. Adapted with permission from Patel *et al.*[43] This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Each group included those with and without medication overuse headache. Because not all migraine attacks meet the strict criteria for a migraine attack either because of early treatment or because they are mild,[9] we report chronic migraine and chronic tension-type headache with episodic migraine together for our primary analysis. People meeting our definition of probable chronic migraine are typically managed in the same manner as people with definite chronic migraine and received the same advice within the trial.

In the feasibility study, 97 out of 103 (94%) of those assessed as having an eligible headache type had 'chronic migraine'.[16] With the agreement of the Trial Steering Committee, the Data Monitoring Committee and the funder, we specified that, if at least 85% of our participants had 'migraine', that our primary analysis would just be on the population with 'migraine', with sample size inflated, if necessary, to ensure adequate statistical power for this analysis.

Between April 2016 and March 2018, we trained 30 facilitators. Quality assurance for the intervention was monitored in several ways, including observations of sessions, audio-recordings of sessions, participant feedback and facilitators' personal reflections (see *Report Supplementary Material 9*).

The control intervention quality was assessed by keeping record of when packs had been sent to participants, any contact with control participants, attrition rates, when letters had been sent to the GP and date of classification interview.

Randomisation and masking

The unit of randomisation for this parallel-group study was the individual participant. The randomisation allocation ratio was 1 : 1.07 in favour of the intervention group to account for clustering in one arm. Randomisation was done using minimisation, stratifying by geographical locality (Midlands and Greater London) and headache type (chronic migraine, chronic migraine with episodic migraine or chronic tension-type headache only, with or without medication overuse headache). To maintain allocation concealment all baseline data were collected prior to randomisation. Randomisation was done using Warwick Clinical Trials Unit's randomisation programme by a person independent of the research team. It was not possible to mask the study team, facilitators or participants from the treatment allocation.

Groups of four or five geographically proximate practices were clustered with the aim of starting recruitment around the same time in several practices. Participants were randomised in batches, with a target size of around 20 to ensure sufficient participants to populate a group and reduce any delay between randomisation and starting the intervention group. Participants unable to attend the group that they were originally allocated to were offered attendance at another group if available.

Participants were informed of their allocation by the study team via a telephone call. Written confirmation of the randomisation and headache classification was also sent to the participant and to their GP.

Post-randomisation withdrawals and exclusions

All participants were followed up when possible, and data were collected in accordance with the trial protocol until the end of the trial. No further data were collected for participants who explicitly withdrew their consent, and only the data collected up the point of withdrawal were used in the final analysis.

Outcome measures

Primary outcome measure

Our primary outcome was the HIT-6 score at 1 year.[33] It consists of six questions with five responses (never to always: score 6, 8, 10, 11 and 13 points). The score ranges from 36 to 78 points, with higher scores indicating greater headache severity (see *Report Supplementary Material 10*).

Secondary outcome measures

We used the CHQLQ as a secondary headache disability outcome. Our other secondary outcome measures were headache days in the preceding 28 days; typical headache duration and severity in previous 28 days; EuroQoL-5 Dimensions, five-level version (EQ-5D-5L);[45] SF-12 version 2,[46] reported as physical and mental component scores; Hospital Anxiety and Depression Scale (HADS);[47] Pain Self-Efficacy Questionnaire (PSEQ);[48] and Social activity: Social Integration Subscale (SIS) of the Health Education Impact Questionnaire (heiQ).[49]

Baseline data collected included basic demographic data and data on the troublesomeness of other bodily pains.[50]

We collected data on total headache days, average duration of headache and headache severity from participants weekly for 6 months and then monthly, starting from the initial eligibility call. These outcomes were collected according to patient preference using a smartphone app or paper diary records (not both).

We sent postal questionnaires at 4, 8 and 12 months. HIT-6 scores, headache days and EQ-5D-5L scores were, if needed, collected by telephone. To maximise follow-up rates, we used several strategies, including sending high street vouchers with each initial questionnaire and study pens with reminder questionnaires and a shorter questionnaire being sent as a second reminder (see *Report Supplementary Material 11*).

Sample size

We estimated the sample size using Moerbeek and Wong's[51] method, which accounts for clustering in one arm. Based on similar trials[52] we used an intracluster correlation coefficient of 0.01.

The sample size (n = 689: relaxation arm, n = 333; self-management arm, n = 356) was estimated to assess the clinical effectiveness in the migraine population, providing 90% power to detect a target (worthwhile) between-group difference of 2 points (SD 6.87, from the feasibility study) in the HIT-6 outcome at 12 months using a two-sided test and a 5% significance level with 20% loss to follow-up.[14] Some support for this being a plausible effect size came from a pilot study[53] of a similar intervention for migraine. Some overrun on sample size was expected to allow all groups to be adequately populated.

Primary and secondary analyses

The primary analysis approach was intention to treat. Data were summarised and reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines for RCTs.[54] Our statistical analysis plan is available in *Report Supplementary Material 7*.

Participant characteristics and outcomes were summarised as mean and SD for continuous data or frequency and percentage for categorical data, summarised by treatment arm. The median and IQR were presented if data deviated substantially from a normal distribution.

The primary end point was 12 months. For the primary and secondary analyses, treatment effects were estimated using linear mixed-effects models with partial clustering to account for the trial design with clustering in the self-management arm [command 'mixed' from Stata® (StataCorp LP, College Station, TX, USA)]. Analyses were adjusted for age, gender, the baseline value of the dependent variable and baseline stratification factors (type of headache and geographical locality). The adjusted treatment effect estimates and associated 95% CIs were presented for all analyses. All statistical tests were two-sided at

the 5% significance level. Analyses were conducted using the statistical software package Stata 15 and R (The R Foundation for Statistical Computing, Vienna, Austria) version 4.0.3.

Complier-average causal effect analyses

We carried out complier-average causal effect (CACE) analyses for both levels of adherence for the primary outcome only. Minimal adherence was defined as attending day 1 of the intervention plus the one-to-one session. Full adherence was defined as the participant attending both days, plus individualised contact with the nurse.

Subgroup analyses

We carried out prespecified subgroup analyses using formal statistical tests for interaction to examine whether baseline anxiety (HADS anxiety score, ≤ 10 and > 10 points), depression (HADS depression score, ≤10 and >10 points) and severity (HIT-6 score, ≤ 64 and > 64 points) moderated treatment effect.[55]

Symptom diary (total headache days, average duration of headache and headache severity)

These data were analysed using longitudinal analyses adjusting for the same variables as those used in the primary analyses (fixed effects) and participant as random effects.

Additional analyses

We assessed treatment effects in terms of the primary outcome for the whole population, including those with tension-type headache only, for chronic migraine and chronic tension-type headache with episodic migraine separately, and for those with or without medication overuse headache. These results will contribute to future meta-analyses and inform future guidelines.

Sensitivity analyses

We performed two sensitivity analyses: one excluding those interviewed for the process evaluation and another excluding those who reported <15 headache days on their baseline questionnaire.

Adverse events and serious adverse events

The frequency and percentage of adverse events (AEs) and serious adverse events (SAEs) in the trial are reported.

Clinical results

The results are in *Appendix 15*.[44] A detailed statistical report is available as *Report Supplementary Material 12*. A separate statistical report is also available for all 736 randomised participants, including those without migraine, as *Report Supplementary Material 13*.

Screening and recruitment

Between April 2017 and March 2019 we recruited from 164 general practices with a combined patient population of 1,529,684. Of the 32,998 potential participants identified from screening we approached 31,020 (94%). We received 2179 expressions of interest (including 41 self-referrals). We contacted 1871 (86%); of these, 1159 (62%) were eligible. Of these, 92 (8%) did not proceed because there were no suitable groups for them to attend and 785 of the remaining 1067 (74%) returned consent forms. We did classification calls with 751 (96%) of these. Nine people (1%) withdrew at this time. Six (<1%) were excluded because of a non-eligible headache (two cluster headache, two new daily persistent headache, one cervicogenic headache and one hemicrania continua; *Figure 6*). The final number of recruited participants was therefore 736 (including 27 self-referrals).

Of these, 727 (99%) had chronic migraine or chronic tension type headache and episodic migraine. Henceforth, unless otherwise specified, all the results refer to this group. Two participants were withdrawn from the trial by the study team soon after randomisation; one because they were living with someone already randomised to the trial, the other because the person made known that they had recently started in a trial of a calcitonin gene-related peptide (CGRP) monoclonal antibody for their headaches.

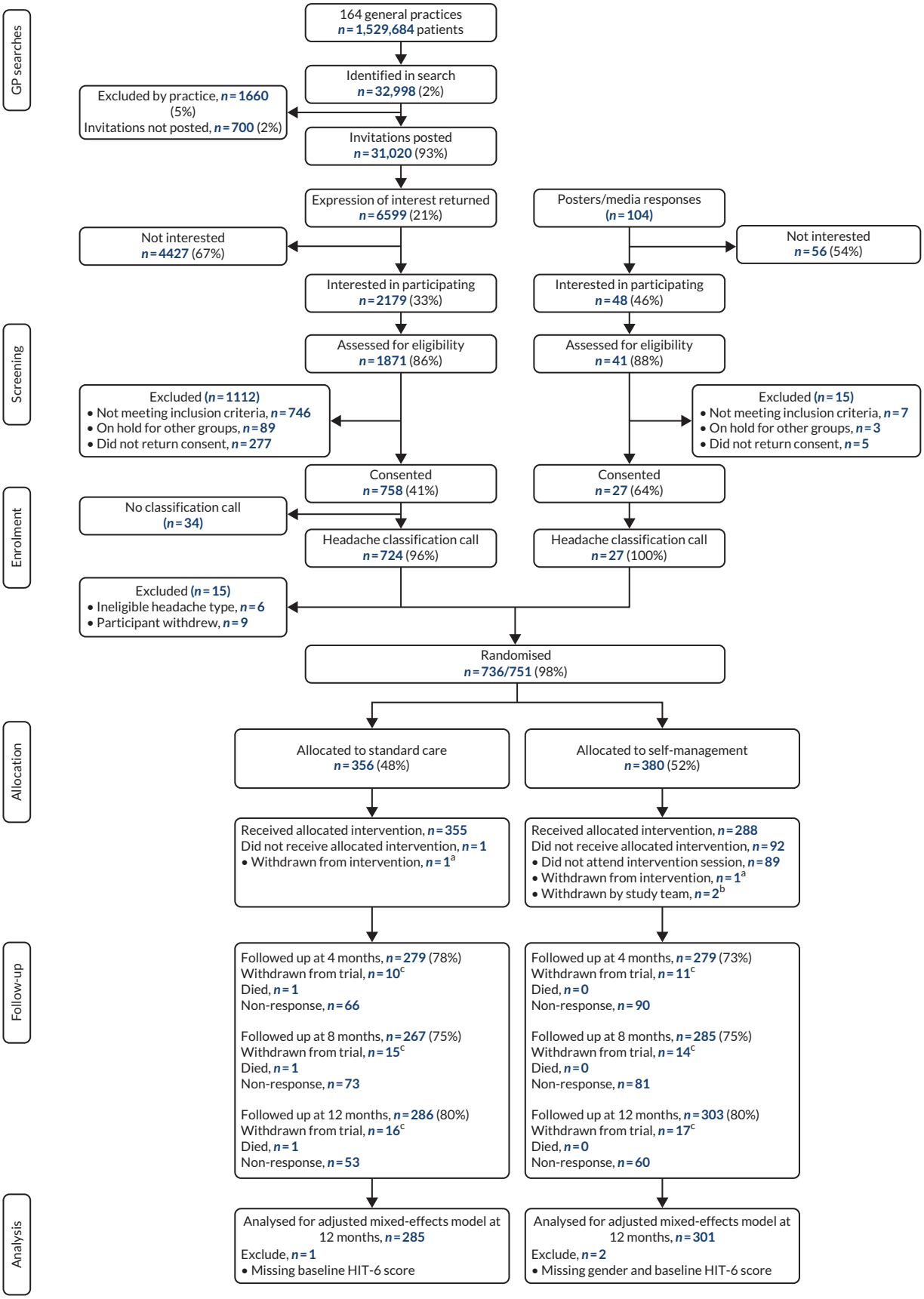

FIGURE 6 Consolidated Standards of Reporting Trials flow chart. a, Participants withdrew from intervention only and continued to be on follow-up; b, Complete withdrawal. One withdrawn on the day of randomisation, and one 2 days after randomisation; c, cumulative number of complete withdrawals. Adapted with permission from Underwood *et al.*[44] This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Participant baseline characteristics

Baseline characteristics were well matched between treatment arms. Most participants were white (586/727; 81%) and the majority were female (604/727; 83%) and the mean age was 48 years (SD 15 years). Just over half (396/727; 55%) had definite chronic migraine, 46% (331/727) had chronic migraine or chronic tension type headache with episodic migraine and 407 out of 727 (56%) had medication overuse headache. The median number of headache/migraine days over the last 4 weeks reported at baseline was 16 (IQR 11–20) days. Thirty-eight per cent (274/721) reported <15 headache days in the preceding 4 weeks.

We reached a diverse population that was representative of national averages in terms of ethnic mix and levels of deprivation, with a good mix of rural and urban areas.

Medication use was similar across both groups. At baseline, 662 out of 727 (91%) had used acute treatments, and 235 out of 727 (32%) had used prophylactic medications.

The overall mean HIT-6 score (primary outcome) at baseline was 64.5 points (scale range 36–78 points; SD 5.5 points), suggesting that most participants had severe symptoms. People with chronic migraine had greater headache severity, lower quality of life, less self-efficacy and less social interaction than those with chronic tension type headache and episodic migraine. Many participants had chronic pain other than their headaches: 375 out of 727 (52%) had at least moderately troublesome neck and 277 out of 727 (38%) had at least moderately troublesome back pain (see *Report Supplementary Material 12*).

Participant follow-up

Follow-up rates for the primary outcome were 76% (551/727) at 4 months, 75% (546/727) at 8 months and 80% (582/727) at 12 months. Three participants had missing baseline data. The primary analysis included data from 579 out of 727 (80%) participants. Thirty-two (4%) participants withdrew completely from the study including follow-up.

Adverse events

There were two SAEs, both deaths unrelated to the trial. There were seven AEs: five in the self-management arm that occurred during the intervention sessions and were related to developing a migraine or becoming upset during a session. Two were in the usual-care arm: one related to the content of the relaxation CD, and one participant became upset during a process evaluation interview.

Intervention data

We had 42 intervention groups, run by 20 facilitators, at 35 venues in the Midlands and London. Median group size at randomisation was nine (IQR 7–12) and median attendance on day 1 was 6.5 (IQR 5–9). The first session was attended by 286 out of 376 (76%) of those randomised, 259 out of 376 (69%) achieved partial adherence and 216 out of 376 (57%) full adherence (see *Report Supplementary Material 12*).

Effect of COVID-19

One-year follow-up was due to be completed soon after the UK national lockdown on 23 March 2020. Inability to access the office during this time meant that we were unable to manage reminder questionnaires. For this reason, more 12-month core outcomes were collected by telephone. The COVID-19 pandemic also made it impossible for the study team to visit general practices to collect data for the health economics analyses. We developed new processes to allow practice teams to extract these data remotely on our behalf.

Primary outcome: six-item Headache Impact Test

We found no evidence of a positive effect at 12 months, the primary end point (mean difference −0.3 points, 95% CI −1.23 to 0.67 points), or at 8 months (mean difference 0.07 points, 95% CI −0.95 to 1.09 points) (see *Table 2*). At 4 months participants in the self-management support group had statistically significantly lower HIT-6 scores (better headache-related quality of life: mean difference of −1.0 point; 95% CI −1.91 to −0.006 points) than participants in the standard-care group. The intracluster correlation coefficients were

TABLE 2 The HIT-6 adjusted treatment differences at different time points[a]

Model	Time point (months)		
	4	8	12
ITT			
Mean difference (95% CI)	−1.0 (−1.91 to -0.006)	0.07 (−0.95 to 1.09)	−0.3 (−1.23 to 0.67)
p-value	0.049	0.888	0.560
CACE (minimum adherence)			
Mean difference (95% CI)	−1.3 (−2.57 to -0.02)	0.04 (−1.22 to 1.31)	−0.4 (−1.67 to 0.87)
p-value	0.046	0.945	0.540
CACE (full adherence)			
Mean difference (95% CI)	−1.6 (−3.10 to -0.01)	0.05 (−1.46 to 1.56)	−0.5 (−2.00 to 1.05)
p-value	0.048	0.945	0.540

ITT, intention to treat.
a Adjusted for age, sex, headache type, geographical locality. and baseline measure of the outcome. Positive difference favours control.

Note
HIT-6 (range 36–78 points; higher = worse).
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very small (< 0.0001) in all our analyses. The findings from our CACE analyses, sensitivity analyses and additional analyses were not materially different. There was no evidence of treatment effect modification in our prespecified subgroup analyses.

Secondary outcomes

There was no evidence of a difference in headache days between the groups at the 8-month and 12-month follow-ups. However, at 4 months participants in the self-management support group reported 1.5 (95% CI 0.48 to 2.56) more headache days in the previous 28 days than participants in the standard-care group. The mean difference of EQ-5D visual analogue scale score at 12 months was 3.9 points (95% CI 0.90 to 6.88 points), favouring the self-management support group, but there were no statistically significant differences at 4 or 8 months. At 4 and 12 months, but not at 8 months, those in the self-management group had stronger self-efficacy beliefs as measured by the PSEQ. The mean differences were 2.3 points (95% CI, 0.51 to 4.00 points) and 2.1 points (95% CI 0.17 to 3.96 points) at 4 and 12 months, respectively. We did not find any differences in the role restrictions, limitations or emotional impact domains of the CHQLQ, EQ-5D-5L, the SF-12 mental and physical component scores, the HADS, or the SIS of the heiQ at any time point (see *Figure 7*).

At 8 months the mean headache duration in the self-management group was 9.2 hours (SD 7.3 hours), whereas the mean duration in the standard-care group was 8.0 hours (SD 6.9 hours) (difference, 2.0 hours; 95% CI 0.55 to 3.42 hours). There were no statistically significant differences at 4 or at 12 months (see *Report Supplementary Material 12*).

Estimates and 95% CI rescaled to range from 0 to 100 for graphical representation purposes only (see *Figure 7*). To obtain the estimated difference and its 95% CI in its original scale, the value from graph is multiplied by (maximum value/100). For example, the estimated difference for the HADS anxiety score at the 4-month follow-up was (−0.801 × 21/100) −0.16821. Full details of results are available from *Appendix 15* and *Report Supplementary Material 12*).

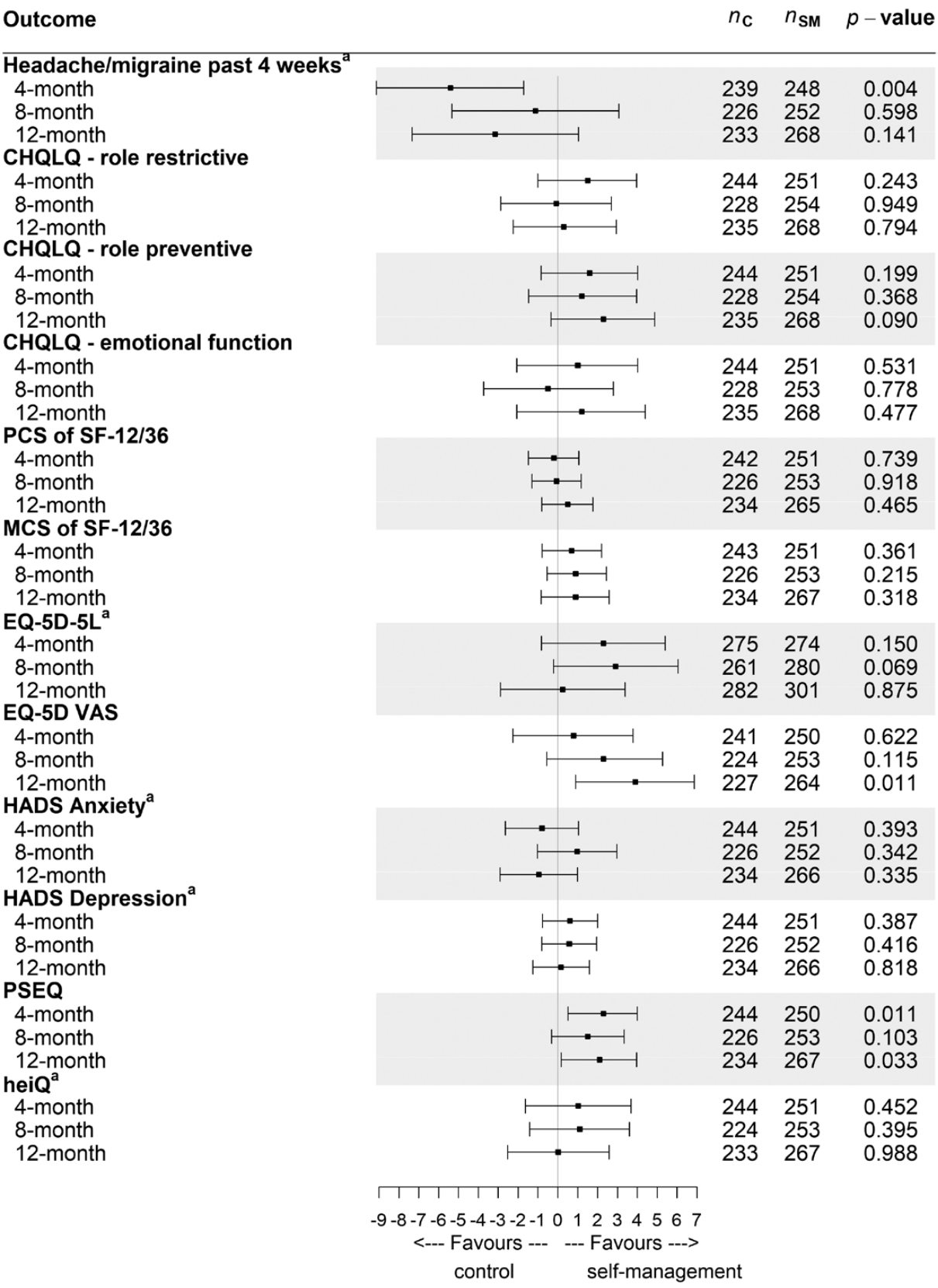

FIGURE 7 Treatment differences and 95% CIs for secondary outcomes adjusted for age, gender, baseline value of the dependent variable, headache type and geographical locality at the 4-, 8- and 12-month follow-ups. MCS, mental component score; PCS, physical component score; SF-12/36, Short Form questionnaire-12/36 items. Adapted with permission from Underwood *et al.*[44] This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Medication use

At baseline, 91% of participants were using acute treatments (painkillers/triptans) and 32% were using preventative medications. There was no change over time or any between-group differences in proportions using acute prescribed and over-the-counter acute medications or prophylactic medications. Neither were there any statistically significant between-group differences in the defined daily doses used by those using acute and prophylactic drug treatments.

There were two statistically significant differences in drug use in those reporting use of that group of drugs; more defined daily doses of beta-blockers (p = 0.005) at 4 months and fewer defined daily doses of opioids (p = 0.02) were used at 8 months in the self-management support group (see *Appendix 15* and *Report Supplementary Material 12*).

There were no differences in proportions using acute medications for ≥10 or ≥15 days in the last 28 days at any time point. Overall, at 12 months, 43%, and 21% participants, respectively, used painkillers/triptan for headaches on ≥10 or ≥15 days out of the last 28 days. This compares with 63% and 38%, respectively, at baseline (see *Report Supplementary Material 12*).

Second-line prophylactic drugs [Botox® (AbbVie Inc., North Chicago, IL, USA) and CGRP monoclonal antibodies] were used by five participants. Four received Botox injection (self-management support group, n = 2; standard-care group, n =2) and two people from the self-management support group were prescribed erenumab. One participant received both Botox and erenumab.

Headache symptom diary

No statistically significant differences were observed between the two groups from the longitudinal analyses for any of these outcomes. The estimated between-group difference for the number of headache days over 1 year was 0.2 (95% CI −0.11 to 0.46) days, for the duration of headache the estimated difference was 0.4 (95% CI −0.47 to 1.28) hours and for headache severity the estimated difference was 0.2 (95% CI −0.08 to 0.46) points on a 0–11 scale.

Health economics methods

Health economic analyses

Our health economic analyses are reported in more detail in *Appendix 16*. For a full report of our economic analyses, see *Report Supplementary Material 14*.

We did a prospective within-trial economic evaluation to estimate the cost-effectiveness of the CHESS intervention. For costs we used 2019 Great British pounds and for outcomes we used quality-adjusted life-years (QALYs). Our base-case analysis was conducted from the perspective of the NHS and Personal Social Services (PSS).[56]

We estimated resource use using the intervention costs, calculated in a micro-costing exercise, and NHS health and social care costs estimated from participant questionnaires and general practice records. We derived the unit costs of community health and social services from the *Unit Costs of Health and Social Care 2019*,[57] published by the PSS Research Unit. Drug costs were estimated from the *Prescription Cost Analysis*[58] and the *British National Formulary*.[59]

For our analyses we converted the EQ-5D-5L into health utilities based on the UK tariff for the EQ-5D-3L using the van Hout *et al.*[60] and Hernandaez-Alarva and Pudney[61] crosswalk algorithms.[60,62,63] We used the van Hout *et al.*[60] crosswalk method for our base-case analysis. For our sensitivity analyses, we used the Hernandaz-Alava and Pudney[61] method to estimate QALYs from the ED-5D-5L and Brazier and Roberts'[64] algorithm to generate these from the Short Form questionnaire-12 items (SF-12).

To account for missing data we used multiple imputation by chain equations implemented through the R package MICEmic[65] assuming that data were missing at random. We imputed missing costs and health

utility values at the level of resource category and health-related quality of life assessment, stratified by intervention arm.[66] We pooled parameter estimates across 50 imputed data sets using Rubin's rules.[67]

Base-case cost-effectiveness

Our base-case cost-effectiveness analysis estimated the cost–utility of the CHESS intervention compared with usual care from the perspective of the NHS and PSS. We calculated economic costs and QALYs for each patient over a 12-month post-randomisation time horizon. We calculated total costs by summing costs associated with the delivery of the intervention and utilisation of broader hospital- and community-based health and social care services.

We fitted bivariate generalised linear mixed-effects regressions assuming a gamma distributed error structure and logarithmic link function to imputed data in R using methods for cost-effectiveness analyses of cluster-randomised and multinational trial data. The models account for the within- and between-cluster correlation between costs and effects measured from the same individuals.

We calculated the incremental cost-effectiveness ratio (ICER) for the CHESS intervention compared with standard care by dividing the between-group difference in adjusted mean total costs by the between-group difference in adjusted mean QALYs. We calculated the incremental net (monetary) benefit of the intervention compared with usual care for cost-effectiveness thresholds ranging from £15,000 to £200,000 per QALY gained.

We estimated the uncertainty of our cost-effectiveness estimates using the Monte Carlo method using 2000 bootstrapped replications.[68] We did the following sensitivity analyses:

- QALYs generated from EQ-5D-5L utilities using the Hernandez-Alava and Pudney[61,62] crosswalk function
- utilities generated from via the SF-12/SF-6D tariff for the UK[64]
- costs calculated from a societal perspective
- unadjusted analysis of the multiple imputation data
- adjusted complete-case analysis.

We did the following subgroup analyses:

- medication overuse (yes vs. no)
- geographical locality (London vs. Midlands)
- gender (female vs. male)
- age (<40 vs. ≥40 years).

TABLE 3 Within-trial cost-effectiveness estimates

Analysis	Incremental estimates (95% CI)		ICER (£)
	Costs (£)	QALYs	
Base case[a]	268 (176 to 377)	0.031 (–0.005 to 0.063)	8617
EQ-5D-5L,[a] Hernandez-Alava and Pudney[61]	269 (170 to 388)	0.028 (–0.001 to 0.055)	9535
SF-12 (SF-6D) utility[a]	269 (162 to 399)	0.008 (–0.02 to 0.035)	32,083
Societal costs[a]	25 (–702 to 1231)	0.033 (–0.001 to 0.063)	765
Unadjusted analysis	229 (82 to 432)	0.033 (–0.112 to 0.127)	6895
Adjusted complete-case analysis[a]	321 (202 to 465)	0.017 (–0.01 to 0.042)	18,968

a Adjusted for age, gender, headache type, baseline costs and baseline utilities.

Health economics results

The acquisition cost of the CHESS intervention was £266.95 per participant. In our base-case analysis the ICER was £8617. There was an 83% probability that the CHESS analysis was cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. This finding was robust to either of the EQ-5D-5L algorithms. However, using data from the SF-12 the ICER was £32,083. From a societal perspective the ICER was just £765 (see *Table 3*).

In our subgroup analyses we found lower ICERs for those aged ≥40 years, females, those with medication overuse headache, and those living in the Midlands (see *Appendix 16*, table 3).

Process evaluation

This process evaluation protocol and results are available in *Appendices 17* and *18*,[69,70] and as an archived full report available in *Report Supplementary Material 15*, prepared ahead of the main results being available. For the process evaluation we have included all 736 randomised participants.

The aims of the process evaluation of the main trial were to:

- assist in the interpretation of the results of the main effectiveness trial
- develop a set of transferable principles regarding the intervention to inform its implementation on a wider scale, if the intervention proves to be effective.

Methods

We used a mixed-methods approach. Quantitatively, we described reach/context, recruitment, dose delivered, dose received and fidelity. Qualitatively, we explored the experiences of participants, intervention facilitators and GPs about their involvement in the trial (see *Table 4*).

TABLE 4 Process evaluation components, sources and type of data

Key process evaluation components	Source of data	Type of data
Reach and context	NHS GP practice data and trial data	Practice numbers and location. Census and national statistics
Recruitment	Trial recruitment data	Routine trial data
		Sample of expression of interest forms from those who declined to participate
Dose delivered	Trial intervention delivery records	Groups delivered/not delivered and why
		Location of groups
Dose received	Trial intervention attendance sheets	Attendance data
	Trial data	Reasons given for not attending
Fidelity	Intervention group audio-recordings	Audio-recording data 10% form completion check for adherence
	Participants one-to-one consultation forms	
	GP feedback forms	
Impact of intervention	Participant interviews	Interview transcripts
Experience of participating in the trial	Staff interview/focus groupsParticipant interviews	Intervention staff focus group notes and recordings
	Participant feedback forms	Patient interview recordings/tran-scriptsParticipant feedbackGP feedback
	GP feedback forms	

Results

Reach/context

The intervention team delivered 42 (2-day) group sessions. Of the 380 (migraine plus tension-type headache) participants allocated to the 2-day group sessions, 288 (76%) attended at least part of the 2-day course, and 92 (24%) were not exposed to the CHESS intervention at all. Of the 288 who did attend the group sessions, 227 (79%) attended both days, whereas 61 (21%) only attended day 1. Of the 288 who took part in at least one session, 261 (91%) had a one–to-one interaction with the nurse. Overall, 261 out of 380 (69%) participants achieved the predefined minimum dose (attended at least some of the course and the one-to-one discussion with the nurse). Only 217 (57%) fully adhered to the intervention. Intervention fidelity was good, with adherence being slightly better than competence [adherence, 83% (IQR 67–100%); competence, 70% (IQR 50–90%)].

Assessment of a 10% (n = 27) random sample of the case report forms completed during the one-to-one sessions found that the sessions were fully completed as required by the protocol.

Written feedback on the 2-day group session and the one-to-one session with the nurse was provided by 117 participants. There were high levels of satisfaction with the course overall and with the facilitators, although there were lower satisfaction scores for the venues, the relaxation and taster sessions, and the mindfulness session. Similar views were expressed during interviews.

During focus groups, intervention facilitators reported that they found some sessions more challenging to deliver than others, notably sessions on acceptance, impact of thoughts mood and emotions on headaches, mindfulness and relaxation for headaches, medication management and managing setbacks.

Twenty-eight participants took part in the interview study exploring their experience of the trial (self-management support group, n = 17; standard-care group, n = 9; randomised to intervention but did not attend any sessions, n = 2) soon after receiving the intervention and 12 months after randomisation. In the first interview, all participants were generally positive about the intervention they experienced. Group participants liked the group format and valued meeting with others to share information. Those with advanced headache knowledge found the group confirmatory, but they were positive about the opportunity to discuss experiences with others. Some interviewees felt that people earlier in their headache trajectory might have more to gain from the intervention. There were people, all with high levels of knowledge about headache, who would have liked a session on where to find information about cutting-edge treatments. The most popular sessions were on lifestyle, stress and anxiety, and sleep, as interviewees felt that they had gained understanding of how these may affect headaches. Many participants did not like the sessions on mindfulness and relaxation for headaches and on managing setbacks. Participants also valued being able to review their headaches and management at the one-to-one sessions with the nurse.

Interview data at 12 months indicated that, although some participants had made changes to how they managed their headaches, such as changing medications and recognising triggers, most had changed very little. Among those who had made little change, there were some for whom life had become more problematic with family issues, work and other health issues.

Conclusion of process evaluation

The process evaluation suggests that CHESS reached a diverse population across different geographical settings. Attendance reached our predefined dose, but many participants were not exposed to the intervention. The interventions were delivered with fidelity and, although generally well received, with some sessions liked more than others, both intervention facilitators and participants had reservations

about several components of the course. There is evidence that participants valued the group and one-to-one aspects of the intervention giving them the opportunity to explore and review their headaches and its management. The process evaluation provides no clear explanation as to why the CHESS intervention appears ineffective.

Patient and public involvement

There has been substantial PPI contributing to the design, conduct, and interpretation of the CHESS programme. This is reported in detail in our published paper (see *Appendix 19*).[71]

Throughout the programme we worked closely with three UK migraine charities and a lay advisory group to help direct the research and ensure that the patient voice had been embedded in our work. We used guidance from the National Institute for Health and Care Research (NIHR) standards for public involvement to help support us in establishing and implementing PPI.[72] We started from the premise that PPI representatives were full members of the team and we sought, as far as possible, to reduce power differential.[73] We sought to work in an environment of mutual respect and with each team member valuing others' contributions.

Our lay patient partners were paid for their time and travel; we reimbursed our charity partners for their travel. We summarise the PPI contribution throughout the trial.

Development of research idea

The original research question, 'Will an education and self-management programme help people living with chronic headache?', is based on a research recommendation in the 2012 NICE guidelines on the management of headaches.[5] Members of the lay guideline development group helped identify the research question.

Grant application

Our co-applicants included representatives of the three leading UK migraine charities. The involvement at this stage was from our charity partners. It did not include direct patient involvement.

Establishing a lay advisory group

We established a lay advisory group, from our larger lay reference group, at the start of the programme. We sought to establish a group of 8–10 people living with chronic headaches. Members needed access to e-mail but not specific skills. Our charity partners approached a diverse group of people with chronic headaches. We also approached people through a University of Warwick PPI initiative. We contacted responders to identify their headache type and basic demographic details. Ten people joined the CHESS lay advisory group. This group then developed their own rules of engagement (see *Appendix 19*, box 2).[71]

Trial oversight

We invited representatives of each of the three charities to our monthly trial management groups. The charities found it difficult to commit their staff to meeting times. Our independent PSC had two lay members who contributed to eight meetings over the duration of the programme. One lay representative contributed to our Data Monitoring Committee.

Feasibility study research ethics application

When we sought research ethics approval for the feasibility study our lay advisory group was not established. Our charity partners helped us to find five people who critically reviewed our patient-facing documents.

Headache classification day

Our lay reference group contributed to the classification day, ensuring that the key questions generated were relevant to people with chronic headache and health professionals. Seven lay people attended on the day.

Electronic data collection

The CHESS lay advisory group helped to refine the questions used in the electronic diary and provided feedback on the acceptability, the user experience and the app. A suggestion from our lay advisory group included the addition of a calendar indicating the period of recall.

We provided participants with a summary of their diary data once data collection was complete. The group commented on, and made recommendations to improve, the individual data summary sent to main trial participants at the end of their data collection period.

Intervention design and development

Seven members of Migraine Action took part in an individual, face-to-face interview about their headaches and the treatments they had tried, to inform the intervention development.

Our intervention development day was chaired by one of our professional charity partners and attended by three lay representatives, suggested by our charity partners.

Patient-reported outcome measures

During the feasibility study three members of the lay advisory group helped analyse data from interviews exploring participants' views on the relevance, clarity, comprehensiveness and acceptability of four PROMs.

Core outcome set for migraine

Three PPI members actively collaborated in all stages of the core outcome set for migraine (COSMIG) project, allowing co-development of a three-stage international Delphi survey, subsequent data interpretation, co-facilitation of the consensus meeting and co-authorship of the subsequent publication.[39]

Public and media engagement

Following a university press release we were invited onto *The Victoria Derbyshire Show* (BBC News, London, UK). We were represented by one of our lay members and the chief investigator. Our lay member was able to speak about their experience of chronic headaches and the impact this had on their life. This generated public interest in CHESS.

Post-results patient and public (lay) discussion group

Once the trial outcome was known we sought an additional patient and public perspective on the findings. We ran a 2-hour virtual discussion group with 10 people drawn from the CHESS reference group. The process evaluation team presented an overview of the process evaluation results followed by the trial outcomes. The group were disappointed with the outcome but not completely surprised. Although the CHESS intervention provided useful knowledge and tools, the group thought that developing new skills and behaviours takes time. Participants thought a longer intervention may be needed to reinforce learning and to support behaviour change.

Patient and public involvement learning points

Our thinking on patient involvement has developed substantially since we submitted the first application for funding in June 2012. At that time, we had planned a formal evaluation of PPI in the programme. We were asked to remove this by the funding board at the outline stage. This does mean we have missed the opportunity to do a more in-depth prospective evaluation. Nevertheless, we have identified some key learning points:

- More training in the research process for both our lay and professional PPI partners.
- Lay input, in addition to charity input, into the development of the grant may have provided a different perspective.
- A designated team member to be the PPI contact could have improved engagement.
- Regular correspondence to update the lay advisory group throughout the duration of the programme.

Discussion

The CHESS programme has been a substantial amount of work over several years. We have advanced our understanding of the challenges of living with chronic headaches and made some progress in developing the methodology for running RCTs of complex interventions for people living with chronic headaches. Specifically, we have:

- reviewed and added to the qualitative literature on the experience of living with chronic headaches
- demonstrated that we can recruit people from the community for trials of headache treatments
- developed an approach to classifying headache disorders using a nurse telephone interview
- reviewed the existing literature on quality-of-life assessment for people with chronic headache
- developed a core outcome set for people living with migraine
- developed a mapping algorithm to improve health economics analyses in headache studies
- reviewed the literature on prognostic factors for people living with chronic headaches
- validated a patient-centred outcome measure for studies of people living with chronic headaches, as opposed to people living with migraine.

Nevertheless, our intervention had no meaningful impact on headache-related quality of life or headache days. This is intensely disappointing for the research team and, more importantly, we do not have anything new to offer people living with what can be a profoundly debilitating, and poorly understood, disorder.

In phase 1 we did all our preparatory work for the planned RCT. This can be broadly divided into new fieldwork and systematic reviews. The fieldwork demonstrated that is possible to recruit people with headache disorders from general practice, providing participants to evaluate our classification interviews, our package of outcome measures and pilot our intervention ahead of the main RCT.

We found in our systematic reviews ample evidence that the disability caused by chronic headaches fits within the same broad theoretical framework used to approach other chronic painful disorders. Although the available literature was sparse, our review of qualitative studies had resonance with that found in other chronic pain disorders such as LBP. It is perhaps surprising that we identified only four qualitative studies of the experience of living with chronic headaches. This contrasts with 187 such studies, largely of chronic musculoskeletal pain, found in a review of reviews of the experience of living with chronic pain.[74]

There is a need for further work to explore the experience of living with, and receiving care for, chronic headaches. In our review of prognostic factors, we identified potentially modifiable prognostic factors that are common to the wider pain literature: anxiety, depression, poor sleep, stress and poor self-efficacy.[21,23] Further evidence supporting the relationship between chronic headaches and chronic musculoskeletal pain comes from our review demonstrating the association between primary headache disorders and persistent LBP.[42] Looking more widely at the headache literature, including episodic and chronic migraine and tension-type headache, we found evidence that self-management interventions could have positive effects on headache-related disability, mood and pain intensity, but not on headache frequency.[22] A subsequent Cochrane systematic review[75] of psychological therapies for episodic or chronic migraine, however, concluded that high-quality research to determine if psychological therapies were effective was absent. The evidence for the use of self-management support programmes for chronic musculoskeletal pain is mixed.[25,76] Nevertheless, we had sufficient evidence to consider that a self-management support intervention based on psychological principles might be effective for our population of interest. We were also anticipating that the provision of a diagnostic classification, advice on specific drug treatments for migraine and addressing medication overuse would enhance the overall effect.

Our review of patient-reported outcomes identified a limited evidence base for patient-reported outcomes for use in headache studies.[26] Only the HIT-6 had sufficient evidence to support its use in a mixed headache population. We therefore adapted the MSQ v2.1 as a new measure, the CHQLQ, that is about headaches in general. We demonstrated that it had good measurement properties. This may be a better measure than the HIT-6 for trials for studies of people with chronic headaches.

Our work on COSMIG identified that headaches days and headache-related quality of life should be given equal standing.[39] For these reasons, it was important to look again at how to measure patient-centred outcomes for our trial. When this work was done, an additional migraine-specific measure became available: the Migraine Functional Impact Questionnaire. This has superior measurement properties to the MSQ v2.1 and was also seen to have greater face validity by our patient partners.[77] For these reasons we are recommending this as part of the core outcome set for migraine studies.

As is usual in NIHR trials we included the EuroQoL-5 Dimensions (EQ-5D) to allow the calculation of health utilities for our health economics analysis.[44] We had concerns about the use of this in our population because of the unpredictable and rapidly changing pattern of headache disorders. The EQ-5D measures health state 'today' and does not take into account the, sometimes large, differences in health states within, or between, days. In our systematic review of PROMs we found only limited evidence to support the use of EQ-5D in headache disorders.[26] We did find acceptable evidence of construct validity for the Short Form questionnaire-36 items[78] and some limited evidence for the SF-12.[46] The longer measurement period of the short-form suite of measures may make them a more appropriate outcome measure. In the light of our concerns about the EQ-5D we included the SF-12 in our final package of outcome measures to also allow us to calculate health utility from the SF-6D. In our mapping study we were to show that health utility values for economic evaluations could be predicted from the HIT-6 or the CHQLQ.

Overall, our work on outcome measures for headache studies has informed the approaches we should use to measure outcomes in headache trials. Importantly we have shown that patient-centred outcomes that assess quality of life need to be given equal weighting with headaches days in future trials of interventions for headaches/migraine. We have identified, and for chronic headaches validated, appropriate outcomes that can be used in future studies. By involving patients in all stages of this work we have been able to ensure its relevance to our population of interest.

The core of phase 2 was our RCT. Because we exceeded our planned sample size, and the effects of clustering in the intervention arm were negligible, we had ample statistical power to identify any clinically important between-group differences. There was no evidence of any positive effect on clinically relevant outcomes at 12 months, when we measured our primary outcome, or at 8 months, with the limits of the 95% CI excluding our target (worthwhile) effect size. Others, in a study of episodic migraine, have suggested that the minimal clinically important between-group difference for the HIT-6 should be 1.5 points.[79] Even against these stricter criteria, not directly applicable to our population, we have excluded a worthwhile benefit at 12 months. Neither did any of our sensitivity, or pre-planned subgroup, analyses at 12 months show a possible benefit. However, there was a small beneficial effect on HIT-6 at 4 months (shortly after the individualised one-to-one nurse consultation and follow-up of self-management programme), around half of our target (worthwhile) difference of 2 points. However, the 95% CI limits effectively excluded any possibility of achieving the target difference: −1.0 points (95% CI, −1.91 to −0.006 points). At the same time point there was also an increase in headache days (mean 1.5 days, 95% CI 0.48 to 2.56 days) in the past 28 days. Findings from the overall analysis of 736 randomised participants were not materially different.

It is possible that the HIT-6 was not the best primary outcome measure to use for this trial. We would now prefer the CHQLQ to better capture the overall impact of chronic headaches. However, no difference was seen on any of its three domains at any time point.

Among our secondary outcomes for pain self-efficacy, there was a treatment benefit at 4 and 12 months but not at 8 months. It is possible this indicates that our intervention affected one of our main intermediate outcomes without feeding through as patient benefit, although these may also be chance observations because of the large number of comparisons made.

It was disappointing that only three-quarters of those randomised to the self-management support intervention attended any sessions. All participants had confirmed availability for sessions prior to randomisation. Poor attendance is common in trials of group interventions for chronic pain. In two similar previous studies we observed non-attendance rates of 11%[80] and 17%.[25] However, the minimal adherence rate observed in CHESS (69%) compares favourably with that observed on our two previous studies (70%[25] and 63%).[80] The effect sizes observed in our CACE analysis did not differ materially from the primary analysis, suggesting that poor attendance was not the explanation for our disappointing findings.

Surprisingly, although there was only a modest delay (median 8 days) between being assessed for study entry, when the presence of chronic headache was established, and completion of the baseline questionnaire, just 62% of those randomised reported headaches on at least 15 of the previous 28 days. This might reflect some response shift in questionnaire completions, or short-term variability in headache days.[13,81] In practical terms, it is the population we recruited that would be offered this intervention if it had been successful. So this is not of great concern.

Another important aspect of the preparatory work we did for our trial was to develop an approach to classification that allowed us to phenotype our trial entrants. Although many headache classification tools are available, we did not find any fit for our purpose.[15] We needed a tool that would both screen out people with headache disorders other than migraine and tension-type headache, and positively phenotype those with migraine. We therefore needed to develop our own tool. These classification interviews were not a substitute for a full diagnostic consultation informed by a prospectively completed headache diary. Nevertheless, at the point in the care pathway where there was a need to identify those who might need further consideration of headache disorders other than migraine or tension-type headache, and to identify those likely to have migraine, they represented the unstructured approach typically used in primary care. Our approach has the potential for implementation in primary care. Beyond this current grant we have secured additional Programme Grants for Applied Research (PGfAR) Programme Development Grant (PDG) funding from NIHR (PGfAR PDG NIHR202614) to adapt this for online use by people with headaches to allow self-classification of migraine.

Developing our intervention programme was another success for the feasibility stage. Finding that we could not use lay co-facilitators was disappointing, but finding this out in the feasibility phase allowed adaption for the main study.

After performing analyses of multiple outcomes at multiple time points and including multiple sensitivity and subgroup analyses, we could not find any evidence of any clinically relevant positive effects from the CHESS intervention. We have conclusively demonstrated that our intervention is ineffective. This is a surprising finding, as the CHESS intervention had a good theoretical underpinning, targeted modifiable psychological variables and was well regarded by the participants (see *Appendix 18*). Furthermore, the educational and classification components of the intervention should have led to increased use of prophylactic medications and a reduction in medication overuse.

The control intervention was more than just usual care: we gave the results of the classification interview to participants and their GPs. If people in the control group used medication more appropriately as a consequence of this information, then this might have reduced the apparent effect size. That there was no difference in the use of prophylactic medications in either group over time makes this unlikely.

Our base-case cost-effectiveness analysis shows a high probability that the CHESS intervention is cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. This finding is robust

in a sensitivity analysis using the Hernandez-Alava EQ-5D-5L conversion algorithm,[61] but not when utilities were calculated from SF-12 data. This may reflect tentative evidence in the external literature that suggests that the EQ-5D generates larger utility gains associated with improvements in headache-related outcomes.[82,83] Before starting this work we had concerns that the EQ-5D might not be the best measure of health utility to use in a headache population because its 1-day measurement window would not adequately capture substantial day-to-day, or within-day, fluctuations in health state affecting people with migraine. Data derived from the SF-12 might be more stable. Whatever the explanation for this difference, it does raise the possibility that our base-case analysis may be overestimating the cost-effectiveness of the CHESS intervention. Conversely, the much reduced ICER found when we used a societal perspective suggests that the CHESS intervention might represent better value for money than our base-case analysis if a different perspective is used.

It is not clear why the CHESS intervention appears to generate additional QALYs when it has no meaningful effect on our headache-specific outcomes. It is possible that the EQ-5D-5L, but not the SF-12, is measuring non-specific effects from attending the CHESS intervention not measured using headache-specific outcomes. Or it might be that there is an early benefit, evidenced by the 4-month HIT-6 findings, that is having proportionally larger impact in the area under the curve analysis. Although these health economic findings are important, it is not clear how they can be used to inform treatment choices in the absence of clear clinical benefit.

Not all trials of complex interventions have a process evaluation run independent from the main trial. This work has given us good insights into the experiences of people living with chronic headaches and of their experiences within the trial. Although this process evaluation was thorough, it did not provide us with any insights as to why the intervention was ineffective.

The dose delivered by the intervention was good, in that sessions were delivered as planned. Intervention fidelity was good, and consistent with that observed for other, similar, interventions.[14]

The premise of our intervention was that those living with migraine had the potential to improve their experience of headache through what they chose to do or not do. Our results add to the evidence that this is not the case. This may come as a relief to those living with migraine, as it reduces the burden on them to control a problem that our process evaluation indicates can feel uncontrollable. It allows migraine to be recognised as an intermittently and unpredictable disabling condition that requires a flexible response from society.

It is unclear why a multifaceted, theory-driven (best-practice), evidence-based intervention, specifically designed for those with chronic headache conditions, that was well delivered and well received failed to make a difference.

Patient and public involvement has helped shape the overall design and development of this programme of work. It has provided important input into the style and content of our intervention, and how we should measure and assess patient outcomes in chronic headache disorders. We have been able to reflect on our experiences of PPI in the research programme. Our thinking has, of course, developed over the lifetime of the CHESS research programme. For the future we think that we can make our processes more efficient and ensure that PPI is rewarding and supportive for all those involved.

Reflections on what was and what was not successful in the programme

Overall, the programme was delivered well, and we achieved our overarching aim of developing and testing a self-management support programme for people living with chronic headaches. We successfully undertook a series of systematic reviews to set the scene for the rest of the work. Our feasibility study was complicated as we were seeking to achieve multiple objectives within the same

framework. This did make it difficult to explain to participating general practices and study participants. Recruitment rates for the main trial from general practice were smaller than originally thought. In our original application we thought we would need to work with 30–40 general practices. In the end we needed to work with 164 practices.

Limitations relating to the method or execution of the research

This was an ambitious programme of work that in phase 1 needed integration of interlinked work packages. The original timelines were, in some areas, too ambitious, needing some changes as to how we collected data, notably recruiting for some interviews through our charity partners rather than from feasibility study participants. In addition, work on validating the CHQLQ was not completed prior to starting the main trial, meaning that we set the HIT-6 as our primary outcome, although our view now is that this is not the most suitable outcome for studies of this nature. This has not, however, affected our final conclusion as the results from the two measures are consistent. The COVID-19 pandemic had a limited impact on the trial. Follow-up finished early in the first wave of the pandemic, meaning that we had some reduction in the data available for our secondary outcomes and we needed to make changes to how we collected data from GP surgeries.

Conclusions from the whole programme

Our data effectively exclude the possibility that this short intervention is effective for the treatment of people with chronic migraines, or chronic tension-type headache and episodic migraine. Nevertheless, the health burden of chronic headache disorders, principally chronic migraine, is debilitating. Further advances in this field must be driven by new theoretically and/or biologically informed intervention models.

Recommendations for future research

- New work to better understand the health impact of chronic headache disorders and to identify modifiable risk factors for a poor outcome.
- Development and testing of new non-pharmacological interventions for a tightly phenotyped group with chronic migraine.
- Work is needed to improve classification of headache disorders in primary care to allow better targeting of the available drug treatments of proven effectiveness, and reduce medication overuse.

Implications for practice and any lessons learnt

There is no need, at this time, to implement formal supportive self-management support programmes, of the type tested here, for people living with chronic migraine.

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General practices

London

Akerman Medical Practice, Albion Street Group Practice, Argyle Health Practice, Artesian Health Centre, Aylesbury Medical Centre, Balham Park Surgery, Belsize Priory Medical Practice, Binfield Road Surgery, Blackfen Medical Centre, Blithehale Medical Centre, Brayford Square Surgery, Bridge Lane Group Practice, Brockley Road Surgery, Brondesbury Medical Centre, Chrisp Street Health Centre, City Wellbeing Practice, Clapham Park Group Practice, Commercial Way Surgery, Crosslands Surgery, Crown Dale Medical Centre, Decima Street Surgery, Dr Driver & Partners, Dun Cow Surgery, Essex Lodge Surgery, Forest Hill Group Practice, Fortune Green Practice, Gill Medical Practice, Greengate Medical Centre, Grove Park Terrace Surgery, Hampstead Group Practice, Harford Health Centre, Herne Hill Road Medical Practice, Heston Living Care, Hounslow Family Practice, James Wigg Group Practice, Jubilee Street Practice, Keats Group Practice, Knoll Medical Practice, Lambeth Walk Group Practice, Manor Place Surgery, Minet Green Health Practice, Mocketts Wood Surgery, Morden Hill Surgery, Mount Medical Centre, New Eltham Medical Centre, Northgate Medical Practice, Nexus Health Group, Old Dairy Health Centre, Open Door Surgery, Park Group Practice, Parliament Hill Surgery, Prince of Wales Medical Centre,

Princess Street Group Practice, Queens Crescent Practice, Sir John Kirk Close Surgery, Southfields Group Practice, St Paul's Way Medical Centre, Stratford Health Centre, Stanford Medical Centre, Streatham Common Practice, Surrey Docks Health Centre, Talbot Medical Centre, The 301 East Street Surgery, The Beeches Surgery, The Bromley Common Practice, The Exchange Surgery, The Spitalfields Practice, The Woodlands Practice, Twickenham Park Medical Centre, Upton Lane Medical Centre, West Hampstead Medical Practice, Whitechapel Health Centre and Woodgrange Medical Practice.

Midlands

Abingdon Surgery, Alcester Health Centre, All Saints Medical Centre, All Saints Surgery, Alrewas Surgery, Apollo Surgery, Aspley Medical Practice, Avonside Health Centre, Balance Street Practice, Barton Family Practice, Bennfield Surgery, Berinsfield Health Centre, Boathouse Surgery, Broad Street Surgery, Broadshires Health Centre, Budbrooke Medical Centre, Bulkington Surgery, Burbury Medical Centre, Bushloe Surgery, Castle Medical Centre, Chase Meadow Health Centre, Church Street Practice, Churchfields Surgery, Clifton Hampden Surgery, Cobbs Garden Surgery, College Road Surgery, Copsewood Medical Centre, Corbett Medical Centre, Coventry Road Medical Practice, Cradley Surgery, Cripps Health Centre, Dordon & Polesworth Group Practice, Downsfield Medical Centre, Dr Rasib and Partners, Dr Reily and Partners, Dr Singh & Partners, Dr Sood and Partners, Dr Walji & Partners, Dudley Park Medical Centre, East Leicester Medical Practice, Eaton Wood Medical Centre, Eden Court Medical Practice, Elmswood Surgery, Erdington Medical Centre, Eynsham Medical Group, Farrier House Surgery, Forrest Medical Centre, Gate Medical Centre, Great Witley Surgery, Greet Medical Practice, Holbrooks Health Team, Hall Green Health, Hazelwood Group Practice, Henley Green Medical Centre, High Street Surgery, Hockley Farm Medical Practice, Jockey Road Medical Centre, Kingsfield Medical Centre, Kingsmount Medical Centre, Lapworth Surgery, Leen View Surgery, Limbrick Wood Surgery, Long Furlong Medical Centre, Manor Court Surgery, Lisle Court Medical Centre, Marcham Road Family Health Centre, Maypole Health Surgery, Mere Green Surgery, Mill View Surgery, Mortimer Medical Practice, Moseley Avenue Surgery, New Road Surgery, Northgate Surgery, Norton Canes Health Centre, Omnia Practice Yardley, Green Medical Centre, Park Leys Medical Practice, Peel Croft Surgery, Phoenix Family Care, Priory Gate Practice, Queslett Medical Centre, Red House Surgery, River Brook Medical, Rivergreen Medical Centre, Riversley Road Surgery, Rother House Medical Centre, Salters Medical Practice, Sherbourne Medical Centre, Shipston Medical Centre, Spring Gardens Health Centre, St Johns House Medical Centre, St Wulfstan Surgery, Sunrise Medical Practice, The Atherstone Surgery, The Chiltern Surgery, The Fairfields Practice, The Forum Health Centre, The Grange Medical Centre, The Malthouse Surgery, The Marches Surgery, The New Dispensary, The Old Priory Medical Centre, The Surgery at Aylestone, The Westgate Practice, Thornloe Lodge Surgery, Trinity Court Surgery, Wallingford Medical Practice, Walsgrave Health Centre, Westfield Surgery, Westside Medical Centre, Wetmore Road Surgery, Whaddon Medical Centre, White Horse Medical Practice, Willenhall Primary Care Centre 1, Windrush Medical Practice, Woodlands Medical Centre and Yardley Wood Health Centre.

Clinical Commissioning Groups

- Coventry and Rugby.
- South Warwickshire.
- North Warwickshire.
- Birmingham Cross City.
- East Staffordshire.
- South East Staffordshire and Seisdon Peninsula.
- Birmingham South Central.
- Nottingham City.
- Nottingham North & East.
- Nottingham West.
- Leicester City.

- East Leicester & Rutland.
- Camden.
- Hounslow.

CHESS digital versatile disc

Slate & Mortar Ltd (Birmingham, UK).

CHESS mindfulness compact disc and handout

Mindlab Goodworks Ltd (Teddington, UK) and Gill Davies.

Relaxation compact disc production

Warwick Audio Visual Department.

National Migraine Centre

Paul Booton, David Bloomfield, Jessica Briscoe, Charlotte Burr, Nazeli Manukyan, Katy Munro, Judith Pearson, Swati Raina, Lauren Shirazi and Heather Sims.

Migraine Trust

Angus Baldwin, Susan Haydon, Wendy Thomas and Arlene Wilkie.

Migraine Action

Simon Evans.

Clinical Research Networks

- Leicester.
- North London.
- Nottingham.
- South London.
- Thames Valley South Midlands.
- West Midlands.

Contributions of authors

Martin Underwood (https://orcid.org/0000-0002-0309-1708) was the chief investigator for the programme. **Martin Underwood and Manjit Matharu (https://orcid.org/0000-0002-4960-2294)** devised the original concept and Manjit Matharu was clinical lead. **Dawn Carnes (https://orcid.org/0000-0002-3152-3133)**, **Sandra Eldridge (https://orcid.org/0000-0001-5638-2317)**, **David R Ellard (https://orcid.org/0000-0002-2992-048X)**, **Frances Griffiths (https://orcid.org/0000-0002-4173-1438)**,

Kirstie Haywood (https://orcid.org/0000-0002-5405-187X), **Siew Wan Hee (https://orcid.org/0000-0002-0415-263X)**, **Harbinder Sandhu (https://orcid.org/0000-0003-1522-8078)**, **Stavros Petrou (https://orcid.org/0000-0003-3121-6050)**, **Tamar Pincus (https://orcid.org/0000-0002-3172-5624)**, **Stephanie JC Taylor (https://orcid.org/0000-0001-7454-6354)** and Manjit Matharu were the original co-applicants for the programme grant.

Sian Newton (https://orcid.org/0000-0001-8035-0411), **Choe Norman (https://orcid.org/0000-0002-3275-3141)** and **Kimberley Stewart (https://orcid.org/0000-0002-9814-8331)** were trial managers and **Helen Higgins (https://orcid.org/0000-0002-7095-4542)** and **Emma Padfield (https://orcid.org/0000-0003-4832-9609)** were senior project managers. **Sandra Eldridge, Siew Wan Hee and Dipesh Mistry (https://orcid.org/0000-0002-0875-9260)** led the statistical analysis and interpretation. **Felix Achana (https://orcid.org/0000-0002-8727-9125)**, **Hema Mistry (https://orcid.org/0000-0002-5023-1160)** and Stavros Petrou led the health economic analysis and interpretation. Dawn Carnes, **Shilpa Patel (https://orcid.org/0000-0003-0726-4888)**, Harbinder Sandhu, Tamar Pincus and Stephanie JC Taylor and led the development of the self-management intervention, and **Rachel Potter (https://orcid.org/0000-0001-6655-8996)** and Manjit Matharu led the headache classification and one-to-one consultations. Kirstie Haywood led the outcome measurement work. David R Ellard, Frances Griffiths, **Vivien Nichols (https://orcid.org/0000-0002-3372-1395)** and Stephanie JC Taylor led the process evaluation.

All authors made substantial contributions to the design of the work or the acquisition, analysis or interpretation of the data, and provided a critical review and final approval of the report.

Publications

2016

Fifth European Headache and Migraine Trust International Congress, Glasgow

Haywood K, Mars TS, Potter R, Patel S, Underwood M. *Assessing the Impact of Chronic and Episodic Headache and Treatment Outcomes: A Systematic Review of Patient-Reported Outcome Measures (PROMS)*. 5th European Headache and Migraine Trust International Congress, Glasgow, UK, 15–18 September 2016.

Patel S, Carnes D, Matharu M, Pincus T, Sandhu H, Underwood M, Probyn K. *Development of an Educational and Self-management Intervention for Chronic Headache – Chronic Headache Education and Self-Management Study (CHESS)*. 5th European Headache and Migraine Trust International Congress, Glasgow, UK, 15–18 September 2016.

Probyn K, Caldwell F, Bowers H, Matharu M, Patel S, Sandhu H, Underwood M, Pincus T. *Style and Content of Educational and Self-management Interventions for Chronic Headache – A Systematic Review*. 5th European Headache and Migraine Trust International Congress, Glasgow, UK, 15–18 September 2016.

Probyn K, Caldwell F, Bowers H, Matharu M, Sandhu H, Underwood M, Pincus T. *Predictors of Chronic Headache – A Systematic Review*. 5th European Headache and Migraine Trust International Congress, Glasgow, UK, 15–18 September 2016.

Potter R, Dodd K, Matharu M, Probyn K, Pincus T, Underwood M. *Development of a Chronic Headache Classification Interview – Chronic Headache Education and Self-management Study (CHESS)*. 5th European Headache and Migraine Trust International Congress, Glasgow, UK, 15–18 September 2016.

2017

The British Pain Society's 50th Anniversary Annual Scientific Meeting, Birmingham

Nichols V, Ellard D, Griffiths F, Atiya K, Underwood M, Taylor S. *The Lived Experience of Chronic Headache and Its Treatment: A Qualitative Review and Synthesis of Qualitative Studies*. The British Pain Society's 50th Anniversary Annual Scientific Meeting, Birmingham, UK, 3–5 May 2017.

Patel S, Sandhu H, Carnes D, Matharu M, Pincus T, Potter R, Probyn K, Taylor S, Underwood M. *Development of an Educational and Self-management Intervention for Chronic Headache – The Chronic Headache Education and Self-management Study (CHESS)*. The British Pain Society's 50th Anniversary Annual Scientific Meeting, Birmingham, UK, 3–5 May 2017.

Probyn K, Mistry D, Bowers H, Caldwell F, Patel S, Sandhu H, Underwood M, Matharu M, Pincus T. *Non-Pharmacological Self-management For People Living With Migraine or Tension-Type Headache: A Systematic Review Including Analysis of Intervention Components*. The British Pain Society's 50th Anniversary Annual Scientific Meeting, Birmingham, UK, 3–5 May 2017.

Probyn K, Bowers H, Mistry D, Caldwell F, Patel D, Sandhu H, Underwood M, Matharu M. *Prognostic Factors for Chronic Headache: A Systematic Review*. The British Pain Society 50th Anniversary Annual Scientific Meeting, Birmingham, UK, 3–5 May 2017.

South East Regional Society for Academic Primary Care Conference, Cambridge

Vivien Nichols, Stephanie Taylor, David Ellard, Frances Griffiths. *"Maybe the next one will work?" How People with Chronic Headache Manage. A Qualitative Study*. South East Regional Society for Academic Primary Care Conference, Cambridge, UK, 26–27 January 2017.

Society for Academic Primary Care Conference, Warwick

Patel S, Sandhu H, Carnes D, Taylor S, Matharu M, Pincus T, Probyn K, Potter R, Underwood M. *Development of an Educational and Self-management Intervention for Chronic Headache – Chronic Headache Education and Self-Management Study (CHESS)*. Society for Academic Primary Care Conference, Warwick, UK, 12–14 July 2017.

Potter R, Matharu M, Dodd K, Wan Hee S, Underwood M. *Development and Validation of a Chronic Headache Classification Interview – Chronic Headache Education and Self-management Study (CHESS)*. Society for Academic Primary Care Conference, Warwick, UK, 12–14 July 2017.

Nichols V, Ellard D, Griffiths F, Underwood M, Taylor S. *What Is It Like for Patients Living with Chronic Headache? A Systematic Review and Synthesis of Qualitative Studies*. Society for Academic Primary Care Conference, Warwick, UK, 12–14 July 2017.

Probyn K, Bowers H, Mistry S, Caldwell F, Underwood M, Matharu M, Pincus T. *Can We Identify Factors Predicting Prognosis and Influencing Response to Preventative Interventions for Chronic Headache?* Society for Academic Primary Care Conference, Warwick, UK, 12–14 July 2017.

Probyn K, Bowers H, Mistry D, Caldwell F, Underwood M, Patel S, Sandhu H, Matharu M, Pincus T. *Non-pharmacological Self-management with CBT, Patient Education, Mindfulness and Relaxation for Migraine and Tension-type Headache: A Systematic Review*. Society for Academic Primary Care Conference, Warwick, UK, 12–14 July 2017.

10th Congress the of European Pain Federation, Copenhagen

Probyn K, Bowers H, Mistry D, Caldwell F, Underwood M, Patel S, Sandhu H, Matharu M, Pincus T. *Non-pharmacological Self-management for People Living with Migraine or Tension-type Headache: A Systematic Review Including Analysis of Intervention Components*. European Pain Federation 10th Congress of European Pain Federation, Copenhagen, Denmark, 6–9 September 2017.

Potter R, Matharu M, Wan Hee S, Underwood M. *Development and Validation of a Chronic Headache Classification Interview – Chronic Headache Education and Self-management Study (CHESS)*. European Pain Federation 10th Congress of European Pain Federation, Copenhagen, Denmark, 6–9 September 2017.

Nichols V, Ellard D, Griffiths F, Underwood M, Taylor S. *The Lived Experience of Chronic Headache: A Systematic Review and Synthesis of Qualitative Studies*. European Pain Federation 10th Congress of European Pain Federation, Copenhagen, Denmark, 6–9 September 2017.

Probyn K, Bowers H, Mistry D, Caldwell F, Underwood M, Matharu M, Pincus T. *Can We Identify Factors Predicting Prognosis and Influencing Response to Preventative Interventions for Chronic Headache?* European Pain Federation 10th Congress of European Pain Federation, Copenhagen, Denmark, 6–9 September 2017.

2018

Society for Academic Primary Care 2018 Conference, London

Potter R, White K, Matharu M, Taylor S, Sandhu H, Underwood M. *Chronic Headache Education and Self-management Study (CHESS) – A Feasibility Study*. Society for Academic Primary Care Conference, London, UK, 10–12 July 2018.

Potter R, White K, Matharu M, Taylor S, Sandhu H, Ellard D, Underwood M. *Chronic Headache Education and Self-management Study (CHESS)*. Society for Academic Primary Care Conference, London, UK, 10–12 July 2018.

17th International Association for the Study of Pain World Congress on Pain, Boston, MA

Potter R, Matharu M, Dodd K, Wan Hee S, Hoverd E, Underwood M. *Development and Validation of a Telephone Classification Interview for Chronic Headache*. 17th International Association for the Study of Pain World Congress on Pain, Boston, MA, USA, 12–16 September 2018.

Patel S, Sandhu H, Carnes D, Taylor S, Matharu M, Pincus T, Probyn K, Potter R, Underwood M. *Development of an Educational and Self-management Intervention for Chronic Headache*. 17th International Association for the Study of Pain World Congress on Pain, Boston, MA, USA, 12–16 September 2018.

Potter R, White K, Matharu M, Taylor S, Sandhu H, Ellard D, Underwood M. *Design and Chronic Headache Education and Self-management Study (CHESS): Trial Design*. 17th International Association for the Study of Pain World Congress on Pain, Boston, MA, USA, 12–16 September 2018.

2019

UK Trial Managers' Network Annual Conference, Birmingham

White K, Potter R, Underwood M on behalf of the CHESS team. *Chronic Headache Education and Self-management Study (CHESS) – Challenges and Facilitators to Study Recruitment and Delivery*. UK Trial Managers' Network Annual Conference, Birmingham, UK, 2019.

Norman C, Patel S on behalf of the CHESS Team. *Chronic Headache Education and Self-management Study (CHESS) – Smartphone Application*. UK Trial Managers' Network Annual Conference, Birmingham, UK, 2019.

2022

Ellard D, Nichols V, Griffiths F, Underwood M, Taylor S on behalf of the CHESS team. *A process evaluation of the chronic headache education and self-management study (CHESS)* Association for the Study of Pain 19th IASP World Congress on Pain 2022 Toronto, Canada, 2022.

Underwood M, on behalf of the CHESS team. The CHESS trial. *A supportive self-management programme for people livings with chronic headaches: a randomised trial and economic evaluation.* Association for the Study of Pain 19th IASP World Congress on Pain 2022 Toronto, Canada, 2022.

Data-sharing statement

All requests for data should be sent to the Warwick Clinical Trials Unit data access team (wctudataaccess@warwick.ac.uk). Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Chronic Headache Education and Self-management Study (CHESS): a mixed-methods feasibility study to inform the design of a randomised controlled trial

Background

Self-management support programmes are effective in a range of chronic conditions; however, there is limited evidence for their use in the treatment of chronic headaches. The aim of this study was to test the feasibility of four key aspects of a planned, future evaluative trial of a new education and self-management intervention for people with chronic headache: (1) recruiting people with chronic headache from primary care, (2) a telephone interview for the classification of chronic headaches, (3) the education and self-management intervention itself, and (4) the most appropriate patient-reported outcomes (PROMS).

Methods

Participants were identified and recruited from general practices in the West Midlands region of the UK. We developed a nurse-led chronic headache classification interview and assessed agreement with an interview with headache specialists. We developed and tested a group-based education and self-management intervention to assess training and delivery receipt using observation, facilitator, and participant feedback. We explored the acceptability and relevance of PROMs using postal questionnaires, interviews and a smartphone app.

Results

Fourteen practices took part in the study and participant recruitment equated to 1.0/1000 registered patients. Challenges to recruitment were identified. We did 107 paired headache classification interviews. The level of agreement between nurse and doctor interviews was very good. We piloted the intervention in four groups with 18 participants. Qualitative feedback from participants and facilitators helped refine the intervention including shortening the overall intervention and increasing the facilitator training time. Participants completed 131 baseline questionnaires, measurement data quality, reliability and validity for headache-specific and generic measures were acceptable.

Conclusion

This study indicated that recruiting people with chronic headache from primary care is feasible but challenging, our headache classification interview is fit for purpose, our study intervention is viable, and our choice of outcome measures is acceptable to participants in a future randomised controlled trial (RCT).

Appendix 2 Diagnostic and classification tools for chronic headache disorders: a systematic review

Background or aim

Despite guidelines and the International Classification of Headache Disorders (ICHD-III beta) criteria, the diagnosis of common chronic headache disorders can be challenging for non-expert clinicians. The aim of the review was to identify headache classification tools that could be used by a non-expert clinician to classify common chronic disorders in primary care.

Methods

We conducted a systematic literature review of studies validating diagnostic and classification headache tools published between January 1988 and June 2016 from key databases: MEDLINE, ASSIA, Embase, Web of Knowledge and PsycINFO. Quality assessment was assessed using items of the Quality of Diagnostic Accuracy Studies (QUADAS-2).

Results

The search identified 38 papers reporting the validation of 30 tools designed to diagnose, classify or screen for headache disorders: nine for multiple headache types, and 21 for one headache type only. We did not identify a tool validated in primary care that can be used by a non-expert clinician to classify common chronic headache disorders and screen for primary headaches other than migraine and tension-type headache in primary care.

Conclusions

Despite the availability of many headache classification tools we propose the need for a tool that could support primary care clinicians in diagnosing and managing chronic headache disorders within primary care, and allow more targeted referral to headache specialists.

Appendix 3 Development and validation of a telephone classification interview for common chronic headache disorders

Background

For a trial of supportive self-management for people with chronic headache we needed to develop and validate a telephone classification interview that can be used by a non-headache specialist to classify common chronic headache types in primary care. We aimed to specifically exclude secondary headaches other than medication overuse, exclude primary headache disorders other than migraine and tension-type headache (TTH), distinguish between chronic migraine and chronic TTH, and identify medication overuse headache.

Methods

We held a headache classification consensus conference to draw on evidence and expertise to inform the content of a logic model underpinning the classification interview. Nurses trained to use the logic model did telephone classification interviews with participants recruited from primary care. Doctors specialising in headache did a second validation interview.

Results

Twenty-six delegates attended the headache classification conference including headache specialist doctors, nurses and lay representatives (with chronic headache). We trained six nurses to do the classification interviews and completed 107 paired interviews; median days between interviews was 32 days (interquartile range 21–48 days). We measured level of agreement between the nurse and doctor interviews using proportion of concordance, simple kappa and prevalence-adjusted bias-adjusted kappa (PABAK). Proportion of concordance of agreement between nurse and doctor interviews was 0.76, simple kappa coefficient $\kappa = 0.31$ (95% CI 0.09 to 0.52), and PABAK 0.51 (95% CI 0.35 to 0.68), a moderate agreement. In a sensitivity test following review of headache characteristics recorded, concordance was 0.91, $\kappa = 0.53$ (95% CI 0.28 to 0.79), and PABAK 0.81 (95% CI 0.70 to 0.92), a very good agreement.

Conclusion

We developed and validated a new evidence-based telephone classification interview that can be used by a non-headache specialist to classify common chronic headache types in primary care.

Appendix 4 Development of an education and self-management intervention for chronic headache – CHESS trial (Chronic Headache Education and Self-management Study)

Background

Self-management interventions are well recognised and widely used in chronic conditions. Their application to chronic headaches has been limited and generally of low quality. We describe here our process for developing an evidence-based, and theory driven, education and self-management intervention for those living with chronic headache.

Methods

Our intervention was designed using several core information sources: the results of three systematic reviews; qualitative material from those living with chronic headaches; our knowledge from existing self-management interventions; and finally collaborative input from a multidisciplinary team of clinicians, academics, patients and charity partners. We manualised the intervention and associated training as a package for use in a feasibility study. We made adaptations for its use in a randomised controlled trial.

Results

We piloted the intervention in four groups with a total of 18 participants. Qualitative feedback from 12 participants and five facilitators allowed the intervention to be refined for the main randomised controlled trial. Some of the key changes included shortening of the overall intervention, changes to the originally planned facilitators and spreading the facilitator training over 3 days rather than 2.

We are now testing the final revised intervention in a randomised controlled trial of its clinical effectiveness and cost effectiveness. The group component of the intervention is delivered over 2 days with the first day focused on living, understanding and dealing with chronic headaches and the second day exploring how to adapt and take control of one's life with chronic headaches.

Conclusion

Our pilot work indicates that our intervention is feasible to deliver, and with the relevant changes would be acceptable for use with this population. Our randomised control trial is ongoing. We anticipate publishing final results in 2021. The CHESS intervention materials are available from http://wrap.warwick.ac.uk/171671/1/Chronic-Headache-Education-and-Self-management-Support-study-CHESS-additional-information.zip.

Appendix 5 The lived experience of chronic headache: a systematic review and synthesis of the qualitative literature

Objective

To systematically review the qualitative literature of the lived experience of people with a chronic headache disorder.

Background

Chronic headaches affect 3–4% of the population. The most common chronic headache disorders are chronic migraine, chronic tension-type headache and medication overuse headache. We present a systematic review and meta-ethnographic synthesis of the lived experience of people with chronic headache.

Methods

We searched seven electronic databases, hand-searched nine journals and used a modified Critical Appraisal Skills Programme checklist to appraise study quality. Following thematic analysis we synthesised the data using a meta-ethnographic approach.

Results

We identified 3586 unique citations; full texts were examined for 86 studies and four were included in the review. Included studies differed in their foci: exploring, patient-centred outcomes, chronic headache as a socially invisible disease, psychological processes mediating impaired quality of life and the process of medication overuse. Initial thematic analysis and subsequent synthesis gave three overarching themes: 'headache as a driver of behaviour' (directly and indirectly), 'the spectre of headache' and 'strained relationships'.

Conclusion

This meta-synthesis of published qualitative evidence demonstrates that chronic headaches have a profound effect on people's lives, showing similarities with other pain conditions. There were insufficient data to explore the similarities and differences between different chronic headache disorders.

Appendix 6 Prognostic factors for chronic headache: a systematic review

Objective

To identify predictors of prognosis and trial outcomes in prospective studies of people with chronic headache.

Methods

This was a systematic review of published literature in peer-reviewed journals. We included (1) randomized controlled trials (RCTs) of interventions for chronic headache that reported subgroup analyses and (2) prospective cohort studies, published in English, since 1980. Participants included adults with chronic headache (including chronic headache, chronic migraine, and chronic tension-type headache with or without medication overuse headache). We searched key databases using free text and MeSH terms. Two reviewers independently extracted data and assessed the methodologic quality of studies and overall quality of evidence identified using appropriate published checklists.

Results

We identified 16,556 titles, removed 663 duplicates, and reviewed 199 articles, of which 27 were included in the review—17 prospective cohorts and 10 RCTs with subgroup analyses reported. There was moderate-quality evidence indicating that depression, anxiety, poor sleep and stress, medication overuse, and poor self-efficacy for managing headaches are potential prognostic factors for poor prognosis and unfavorable outcomes from preventive treatment in chronic headache. There was inconclusive evidence about treatment expectations, age, age at onset, body mass index, employment, and several headache features.

Conclusion

This review identified several potential predictors of poor prognosis and worse outcome postinterventions in people with chronic headache. The majority of these are modifiable. The findings also highlight the need for more longitudinal high-quality research of prognostic factors in chronic headache.

Appendix 7 Non-pharmacological self-management for people living with migraine or tension-type headache: a systematic review including analysis of intervention components

Objectives

To assess the effect of non-pharmacological self-management interventions against usual care, and to explore different components and delivery methods within those interventions.

Participants

People living with migraine and/or tension-type headache.

Interventions

Non-pharmacological educational or psychological self-management interventions, excluding biofeedback and physical therapy. We assessed the overall effectiveness against usual care on headache frequency, pain intensity, mood, headache-related disability, quality of life and medication consumption in meta-analysis. We also provide preliminary evidence on the effectiveness of intervention components and delivery methods.

Results

We found a small overall effect for the superiority of self-management interventions over usual care, with a standardised mean difference (SMD) of −0.36 (−0.45 to −0.26) for pain intensity, −0.32 (−0.42 to −0.22) for headache-related disability, 0.32 (0.20 to 0.45) for quality of life and a moderate effect on mood [SMD 0.53 (−0.66 to −0.40)]. We did not find an effect on headache frequency [SMD −0.07 (−0.22 to 0.08)].

Assessment of components and characteristics suggests a larger effect on pain intensity in interventions that included explicit educational components [−0.51 (−0.68 to −0.34) vs. −0.28 (−0.40 to −0.16)], mindfulness components [−0.50 (−0.82 to −0.18) vs. 0.34 (−0.44 to −0.24)] and in interventions delivered in groups versus one-to-one delivery [0.56 (−0.72 to −0.40) vs. −0.39 (−0.52 to −0.27)] and larger effects on mood in interventions including a cognitive–behavioural therapy (CBT) component with an SMD of −0.72 (−0.93 to −0.51) compared with those without CBT −0.41 (−0.58 to −0.24).

Conclusion

Overall we found that self-management interventions for migraine and tension-type headache are more effective than usual care in reducing pain intensity, mood and headache-related disability, but have no effect on headache frequency. Preliminary findings also suggest that including CBT, mindfulness and educational components in interventions, and delivery in groups, may increase effectiveness.

Appendix 8 Assessing the impact of headaches and the outcomes of treatment: a systematic review of patient-reported outcome measures (PROMs)

Aims

To critically appraise, compare and synthesise the quality and acceptability of multi-item patient-reported outcome measures for adults with chronic or episodic headache.

Methods

Systematic literature searches of major databases (1980–2016) to identify published evidence of PROM measurement and practical properties. Data on study quality (COSMIN), measurement and practical properties per measure were extracted and assessed against accepted standards to inform an evidence synthesis.

Results

From 10,903 reviewed abstracts, 103 articles were assessed in full: 46 provided evidence for 23 PROMs, eleven specific to the health-related impact of migraine (n = 5) or headache (n = 6), six assessed migraine-specific treatment response/satisfaction and six were generic measures. Evidence for measurement validity and score interpretation was strongest for two measures of impact, Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) and Headache Impact Test 6-item (HIT-6), and one of treatment response, the Patient Perception of Migraine Questionnaire (PPMQ-R). Evidence of reliability was limited, but acceptable for the HIT-6. Responsiveness was rarely evaluated. Evidence for the remaining measures was limited. Patient involvement was limited and poorly reported.

Conclusion

While evidence is limited, three measures have acceptable evidence of reliability and validity: HIT-6, MSQ v2.1 and PPMQ-R. Only the HIT-6 has acceptable evidence supporting its completion by all 'headache' populations.

Appendix 9 Measuring health-related quality of life in chronic headache: a comparative evaluation of the Chronic Headache Quality of Life Questionnaire and Headache Impact Test

Objective

To compare the quality and acceptability of a new headache-specific patient-reported measure, the Chronic Headache Quality of Life Questionnaire (CHQLQ) with the six-item Headache Impact Test (HIT-6), in people meeting an epidemiological definition of chronic headaches.

Methods

Participants in the feasibility stage of the Chronic Headache Education and Self-management Study (CHESS) (n = 130) completed measures three times during a 12-week prospective cohort study. Data quality, measurement acceptability, reliability, validity, responsiveness to change and score interpretation were determined. Semistructured cognitive interviews explored measurement relevance, acceptability, clarity and comprehensiveness.

Results

Both measures were well completed with few missing items. The CHQLQ's inclusion of emotional well-being items increased its relevance to participant's experience of chronic headache. End effects were present at item level only for both measures. Structural assessment supported the three and one-factor solutions of the CHQLQ and HIT-6, respectively. Both the CHQLQ (range 0.87 to 0.94) and HIT-6 (0.90) were internally consistent, with acceptable temporal stability over 2 weeks (CHQLQ range 0.74 to 0.80; HIT-6 0.86). Both measures responded to change in headache-specific health at 12 weeks [CHQLQ smallest detectable change (improvement) range 3 to 5; HIT-6 2.1].

Conclusions

While both measures are structurally valid, internally consistent, temporally stable and responsive to change, the CHQLQ has greater relevance to the patient experience of chronic headache.

Appendix 10 Headache smartphone app – development and application in the Chronic Headache and Self-management Study (CHESS)

Headache smartphone app – Development and application in the Chronic Headache Education and Self-management Study (CHESS)

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Paper in preparation

Background

As part of the CHESS programme grant we developed an app to allow frequent collection of headache related outcome data on headache frequency, duration and severity. In this section we summarise the work and outcomes.

Methods

Development of the app

The app was developed by Clinvivo Ltd, a University of Warwick spin–out company specialising in electronic data collection. The research team and our patient and public lay advisory group worked with Clinvivo Ltd to design and pilot the app ahead of testing in a large randomised controlled trial.

The research team drew on the existing literature as well as the clinical expertise of the team to draft three questions which aimed to capture the frequency, severity, and duration of headaches. We involved our lay advisory group to ensure the data we proposed to collect and the method of collection were acceptable. Our advisory group members played a key role in helping us refine the questions and provided feedback on the usability and acceptability of the app before its application in the trial. The inclusion of a calendar to show recall period was a suggestion that came from our PPI work.

As part of the app development we considered what processes should be for those participants who may change their device or instal the app on a new device over the duration of the trial. We also thought carefully about the need for reminders and implemented a process for those who failed to download the app and those who had not responded for more than 3 weeks.

Table 1: Final questions for the CHESS app

Questions	Data collected
On how many of the last 7 days (as indicated in green on the calendar) have you had a headache?	**Insert number of headaches**
On those days you had a headache, on average how long did they last?	**Scale**: **0 - 24 hours**
On those days you had a headache on average how severe were they?	**0 (No pain) to 10 (Extremely severe pain)**

Completion of the app

All participants who were eligible to take part in the trial were asked to complete the smartphone app. It was completed weekly for six months from eligibility and then monthly for the remaining six months, providing a total of 12 months data. Instructions on how to download and use the app were sent out with baseline consent packs, which provided a step-by-step guide together with screen shots and a specific enrolment code for people to use with the app. If participants did not have access to a smartphone or did not wish to use the app, a paper version was provided as an alternative.

Data management

The data were collated by Clinvivo Ltd and emailed to the CHESS team daily. Data including date and time outcomes were completed and these data were tracked against each participant's trial number.

Summary results

Initially the app was tested by the research team and by members of the CHESS lay advisory group.[14] The app was subsequently tested with eight participants over an 11 week period. Completion rates varied, but there were no reports of any issues with either downloading or

Randomised controlled trial

Of the 736 participants randomised to the trial, 679 (92%) opted to respond using the smartphone app and 57 (8%) chose to respond using the paper questionnaire. The proportions opting for app and paper reporting was similar across the two trial arms.

There is evidence of a statistically significant association between the mode of reporting (i.e. app/paper) and whether participants respond or not, with a higher proportion of participants responding using the app compared to paper reporting (Table 2). Here non-responders are defined as participants who did not provide any responses at all.

Table 2: Response rates comparing the App and paper diary

	App (N=679)	**Paper (N=57)**	**P-value**
Non-responders	176 (25.9%)	36 (63.2%)	<0.001
Responders	503 (74.1%)	21 (36.8%)	

Each participant was expected to provide 32 responses in total. The distribution of the completion rates for those responding using the smartphone app varied with 0% completion by 176 participants, 1-12% by 98, 26-50% by 94, 51-75% by 137 and 76-100% by 174. The completion rate of the participants using the smartphone app was low with a median completion rate of 44%.

In total, 33 (4.5%) participants withdrew during the trial and one (0.1%) participant died.

When comparing the characteristics of the participants by mode of reporting, the participants who opted to respond using the smartphone app were on average younger, more educated and employed. Moreover, on average they had greater headache severity (HIT-6), lower emotional function and better quality of life (EQ-5D VAS).

When comparing the non-responders and responders of the app, the responders were on average younger, white, employed with on average lower severity on the days they had a headache/migraine and lower pain not related to headache. Responders reported on average better role preventative quality of life score, better quality of life (EQ-5D VAS) and stronger self-efficacy beliefs (PSEQ).

Feedback

All participants had the opportunity to receive a personalised summary of their data at the end of the 12-month app data collection. They could opt in or out of this when they completed the final study 12-month questionnaire.

Qualitative interviews

Participants who had completed the four-month follow-up questionnaire were invited to take part in a semi-structured interview in which the smartphone app was discussed. A total of 26 participants spoke about the App. Three participants were not aware of the App and the reason for this was unclear. Of the remaining 23, seven found it easy to use and four especially valued the reminder prompts. Two participants specifically spoke about their thought processes around how they decided on their response and how this was challenging at times because it was difficult to recall. Referring to personal diaries made responding easier for some. Technical issues were one of the main barriers to completion. Two participants could not access the App after changing their phone (although another had managed to do this). One had initial problems setting the App up but went on to use it successfully. Four people did not have SMART phones, two used an iPad, one completed the paper version satisfactorily and one had not realised there was a paper version so no data was collected. The two participants using iPads found it unsatisfactory as they were more likely to miss the window for completion due to inconvenient timing or not always being on their devices. Six participants spoke about missing weeks when they had not remembered to complete the app, missed the reminder or were locked out of the system. One person said after missing a few weeks they just gave up.

Discussion & Conclusion

Our app was developed specifically for data collection in the CHESS trial. It was developed to be quick and easy to use with input from our lay members. The overall results suggest frequent data collection using the smartphone app was possible in this population although completion rates were low. The app seemed to appeal more to those that were younger, educated and employed. No differences were observed in the proportions opting for either app or paper in the two arms of the trial. Response rates were greater amongst participants responding using the app compared to paper reporting. Those using the app had greater headache severity (HIT-6), lower emotional function and better quality of life (EQ-5D VAS).

Responders, regardless of method were generally younger, white, and employed. They had lower pain severity when reporting headaches and less unrelated pain. Clinically responders had better quality of life (EQ-5D VAS) and stronger self-efficacy beliefs (PSEQ).

Our feasibility work had highlighted that completion rates were low. As a result, how to use the app was discussed with potential participants early in the recruitment process and the instructions for the app were sent out following the eligibility call with the consent form and baseline questionnaire. This allowed participants time to get used to completing the app prior to randomisation.

Completeness of data and consistency varied. It is unclear if those that were more affected by their chronic headaches may have been less inclined to complete the dairy. It is also unclear if those that were already using some form of headache app may have been less likely to complete this additional app. The results of the qualitative works suggest that tech issues played a big factor in completion rates. It is also likely that the burden of completion may have been too much for some participants, leading to a lack of interest.

We have been reliant on self-report for completion of the app, which can present challenges. In particular, participants were asked to recall on average their headache frequency, severity, and duration over a period of seven days over the first six months, followed by monthly for the remaining six months. Participants in the interviews mentioned needing to refer to paper notes to support them completing the app. We therefore need to be cautious interpreting the results due to recall and accuracy difficulties.

As part of the CHESS programme we developed an app to collect headache frequency, duration, and severity. The app was developed with input from our lay advisory group and tested with participants from our feasibility study before use in the main RCT. Overall completion rates were disappointingly low at 44%. Burden of completion and tech issues are likely to have contributed.

Competing interests

MU and RF are directors and shareholders of Clinvivo Ltd. MU recused himself from any discussions related to the choice of Delphi platform for this study.

Appendix 11 Mapping between headache specific and generic preference-based health-related quality of life measures

Background

The Headache Impact Test (HIT-6) and the Chronic Headache Questionnaire (CH-QLQ) measure headache-related quality of life but are not preference-based and therefore cannot be used to generate health utilities for cost-effectiveness analyses. There are currently no established algorithms for mapping between the HIT-6 or CH-QLQ and preference-based health-related quality-of-life measures for the chronic headache population.

Methods

We developed algorithms for generating EQ-5D-5L and SF-6D utilities from the HIT-6 and the CHQLQ using both direct and response mapping approaches. A multi-stage model selection process was used to assess the predictive accuracy of the models. The estimated mapping algorithms were derived to generate UK tariffs and was validated using the Chronic Headache Education and Self-management Study (CHESS) trial dataset.

Results

Several models were developed that reasonably accurately predict health utilities in this context. The best performing model for predicting EQ-5D-5L utility scores from the HIT-6 scores was a Censored Least Absolute Deviations (CLAD) (1) model that only included the HIT-6 score as the covariate (mean squared error (MSE) 0.0550). The selected model for CH-QLQ to EQ-5D-5L was the CLAD (3) model that included CH-QLQ summary scores, age, and gender, squared terms and interaction terms as covariates (MSE 0.0583). The best performing model for predicting SF-6D utility scores from the HIT-6 scores was the CLAD (2) model that included the HIT-6 score and age and gender as covariates (MSE 0.0102). The selected model for CH-QLQ to SF-6D was the OLS (2) model that included CH-QLQ summary scores, age, and gender as covariates (MSE 0.0086).

Conclusion

The developed algorithms enable the estimation of EQ-5D-5L and SF-6D utilities from two headache-specific questionnaires where preference-based health-related quality of life data are missing. However, further work is needed to help define the best approach to measuring health utilities in headache studies.

Appendix 12 A core outcome set for preventative intervention trials in chronic and episodic migraine (COSMIG): an international, consensus-derived and multi-stakeholder initiative

Objective

Typically, migraine prevention trials focus on reducing migraine days. This narrow focus may not capture all that is important to people with migraine. Inconsistency in outcome selection across trials limits the potential for data pooling and evidence synthesis. In response, we describe the development of core outcome set for migraine (COSMIG).

Design

A two-stage approach sought to achieve international, multistakeholder consensus on both the core domain set and core measurement set. Following construction of a comprehensive list of outcomes, expert panellists (patients, health-care professionals and researchers) completed a three-round electronic-Delphi study to support a reduction and prioritisation of core domains and outcomes. Participants in a consensus meeting finalised the core domains and methods of assessment. All stages were overseen by an international core team, including patient research partners.

Results

There was a good representation of patients [episodic migraine (n = 34) and chronic migraine (n = 42)] and health-care professionals (n = 33) with high response and retention rates. The initial list of domains and outcomes was reduced from >50 to 7 core domains for consideration in the consensus meeting, during which a two-domain core outcome set was agreed.

Conclusion

International and multistakeholder consensus emerged to describe a two-domain core outcome set for reporting research on preventive interventions for chronic and episodic migraine: migraine-specific pain and migraine-specific quality of life. Intensity of migraine pain assessed with an 11-point Numerical Rating Scale and the frequency as the number of headache/migraine days over a specified time period. Migraine-specific quality of life assessed using the Migraine Functional Impact Questionnaire.

Appendix 13 The association between headache and low back pain: a systematic review

Background

To systematically review studies quantifying the association between primary chronic headaches and persistent low back pain (LBP).

Main text

We searched five electronic databases. We included case-control, cross-sectional and cohort studies that included a headache and back pain free group, reporting on any association between persistent LBP and primary headache disorders. Methodological quality was assessed using the Newcastle–Ottawa Scale. Our primary outcome was the association between primary headache disorders and persistent LBP. Our secondary outcomes were any associations between severity of LBP and severity of headache, and the relationship between specific headache sub-types classified as per International Classification of Headache Disorders (ICHD) criteria and persistent LBP.

We included 14 studies. The sizes of the studies ranged from 88 participants to a large international study with 404,206 participants. Odds ratios for the association were between 1.55 [95% confidence interval (CI) 1.13 to 2.11] and 8.00 (95% CI 5.3 to 12.1). Study heterogeneity meant statistical pooling was not possible. Only two studies presented data investigating persistent LBP and chronic headache disorders in accordance with ICDH criteria.

Conclusions

We identified a positive association between persistent LBP and primary headache disorders. The quality of the review findings is limited by diversity of populations, study designs and uncertainty about headache and LBP definitions.

Appendix 14 Usual care and a self-management support programme versus usual care and a relaxation programme for people living with chronic headache disorders: a randomised controlled trial protocol (CHESS)

Introduction

Chronic headaches are poorly diagnosed and managed and can be exacerbated by medication overuse. There is insufficient evidence on the non-pharmacological approaches to helping people living with chronic headaches.

Methods and analysis

Chronic Headache Education and Self-management Study is a pragmatic randomised controlled trial to test the effectiveness and cost-effectiveness of a self-management education support programme on top of usual care for patients with chronic headaches against a control of usual care and relaxation. The intervention is a 2-day group course based on education, personal reflection and a cognitive–behavioural approach, plus a nurse-led one-to-one consultation and follow-up over 8 weeks. We aim to recruit 689 participants (356 to the intervention arm and 333 to the control arm) from primary care and self-referral in London and the Midlands. The trial is powered to show a difference of 2.0 points on the Headache Impact Test, a patient-reported outcome measure at 12 months post randomisation. Secondary outcomes include health-related quality of life, self-efficacy, social activation and engagement, anxiety and depression, and health-care utilisation. Outcomes are being measured at 4, 8 and 12 months. Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life-year gained.

Ethics and dissemination

This trial will provide data on effectiveness and cost-effectiveness of a self-management support programme for chronic headaches. The results will inform commissioning of services and clinical practice. North West – Greater Manchester East Research Ethics Committee have approved the trial. The current protocol version is 3.6 date 7 March 2019.

Appendix 15 Supportive Self-Management Program for People With Chronic Headaches and Migraine: A Randomized Controlled Trial and Economic Evaluation

Background and objectives

Chronic headache disorders are a major cause of pain and disability. Education and supportive self-management approaches could reduce the burden of headache disability. We tested the effectiveness of a group educational and supportive self-management program for people living with chronic headaches.

Methods

This was a pragmatic randomised controlled trial. Participants were aged 18 years or older with chronic migraine or chronic tension-type headache, with or without medication overuse headache. We primarily recruited from general practices. Participants were assigned to either a 2-day group education and self-management program, a one-to-one nurse interview, and telephone support or to usual care plus relaxation material. The primary outcome was headache related-quality of life using the Headache Impact Test (HIT)-6 at 12 months. The primary analysis used intention-to-treat principles for participants with migraine and both baseline and 12-month HIT-6 data.

Results

Between April 2017 and March 2019, we randomised 736 participants. Because only 9 participants just had tension-type headache, our main analyses were on the 727 participants with migraine. Of them, 376 were allocated to the self-management intervention and 351 to usual care. Data from 586 (81%) participants were analyzed for primary outcome. There was no between-group difference in HIT-6 (adjusted mean difference = −0.3, 95% CI −1.23 to 0.67) or headache days (0.9, 95% CI −0.29 to 2.05) at 12 months. The Chronic Headache Education and Self-management Study intervention generated incremental adjusted costs of £268 (95% CI, £176–377) [USD383 (95% CI USD252 to USD539)] and incremental adjusted quality-adjusted life years (QALYs) of 0.031 (95% CI −0.005 to 0.063). The incremental cost-effectiveness ratio was £8,617 (USD12,322) per QALY gained.

Discussion

These findings conclusively show a lack of benefit for quality of life or monthly headache days from a brief group education and supportive self-management program for people living with chronic migraine or chronic tension-type headache with episodic migraine.

Appendix 16 CHESS health economic evaluation summary

CHESS health economic evaluation summary

Achana F, Khan K, Petrou S, Underwood M, Mistry H.

A detailed report of health economic evaluation is available as additional project documents.

OVERVIEW

We did a prospective within-trial economic evaluation to estimate the cost-effectiveness of the CHESS intervention compared with usual care alone for people living with chronic headaches. Findings are reported in accordance with Consolidate health Economic Evaluation Reporting Standards (CHEERS) guidelines.[1]

METHODS

Measurement and valuation of resource use

We calculated economic costs using estimates of resource inputs associated with the intervention and estimates of broader utilisation of hospital and community-based health and social care services.

Intervention costing

We did a micro-costing exercise to estimate the resource use associated with delivery of the CHESS intervention. We obtained hourly costs of staff time for delivery of the intervention from the Unit Costs of Health and Social Care for 2019[2] see Table 1. We estimated cost of venue hire based on charges incurred. We allowed for staff travel costs based on a car rate of 45pence/mile.[3] The cost of CDs and DVDs was based on cost for the discs, i.e., we did not include cost of developing the content. We allowed for depreciation on equipment (phones, laptops, projectors) over 5-10 years. Other equipment costs were included as the total cost.

Hospital and community-based health and social care service use

We collected hospital and community-based health and social care services over 12 months from:

- Data extracted from primary care electronic record systems held at GP surgeries.
- Economic questionnaires completed by trial participants at baseline, four, eight, and twelve-months

Data extracted from the GP records were the primary data source. Participant questionnaires were a secondary source of information used for participants for whom data from the electronic GP records were unavailable. Non-NHS/PSS costs were only available from the participant reported data.

The unit costs of community health and social services were derived from latest Unit Costs of Health and Social Care 2019 report published by the Personal Social Services Research Unit (PSSRU)[2], and the national reference costs 2019 tables; medication costs were from the prescription cost analysis 2019 tables[4], and the online version of the British National Formulary (BNF) 2019 version.[5]

Outcomes

The primary health outcome for the within-trial economic evaluation was the quality-adjusted life year (QALY) as recommended in the NICE reference case.[6] We used both the EQ-5D-5L[7] and SF-12[8] converted into multi-attribute utility scores using established algorithms.[9-10] EQ-5D-5L responses were converted into health utilities based on values mapped onto the EQ-5D-3L descriptive system[11] using the van Hout[12] and Hernandaez-Alarva crosswalk algorithms.[13] We generated SF-6D QALYs from the SF-12 using Brazier's algorithm.[10] Our base-case used the van Hout algorithm.[12]

Statistical Methods

Summary of resource use and costs

We generated participant level costs for each resource variable by multiplying the quantity reported with the respective unit cost, weighted by length of stay or duration of contact where appropriate. We generated summary statistics (means, standard errors and completion rates) stratified by intervention arm and assessment point. Between treatment-group differences for mean resource use and mean costs at each assessment point were compared using the two-sample t-test. Statistical significance was assessed at the 5% significance level. We implemented non-parametric bootstrapping, generating 2,000 replications of the data. Estimates of standard errors surrounding mean resource use (or cost) estimates and 95% confidence intervals surrounding between-group differences for mean resource use (or costs) were obtained from the bootstrap samples.

Summary of health-related quality of life data

We generated summary statistics (means, standard errors and completeness rates) for health utilities, and these were stratified by intervention arm, assessment point and health-related quality of life instrument. Estimates of between-group difference in mean health utility values and 95% bootstrap confidence intervals surrounding mean group differences were generated based on 2,000 bootstrap resamples of the data.

Missing data

We used multiple imputation by chain equations implemented through the R package MICE[14] to predict values for any missing items, assuming data were missing at random. We imputed missing costs and health utility values at the level of resource category and health-related quality of life assessment, stratified by intervention arm in accordance with good practice recommendations outlined in Faria et al.[15] We generated fifty imputed datasets to inform the base-case and subsequent sensitivity and subgroup analyses using Rubin's rules.[16]

Base-case cost-effectiveness

Economic costs and QALYs were calculated for each patient over a 12-month post-randomisation time horizon. We controlled for treatment allocation, age, gender, headache type, baseline costs (in the cost equation) and baseline utilities (in the QALY equation).

We characterised uncertainty around the mean cost-effectiveness estimates through a Monte Carlo method.[17] We plotted cost-effectiveness acceptability curves to give graphical display of the probability that the intervention is cost-effective across a wide range of cost-effectiveness thresholds.

We did the following sensitivity analyses:

- QALYs generated from EQ-5D-5L utilities using the Hernandez-Alava and Pudney crosswalk function[13]
- utilities generated via the SF-6D UK based on SF-12 responses [10]
- costs calculated from a societal perspective
- unadjusted analysis of the multiple imputation data
- adjusted complete case analysis.

We did the following sub-group analyses:

- medication overuse (yes/no),
- geographical location (London versus Midlands)
- gender (male versus female)
- age (<40 years versus ≥40 years.)

RESULTS

The mean total cost of the CHESS intervention was £266.95. We allowed £0.40 for the cost of control CD. There were no substantial differences in other health and social care costs making the mean difference in NHS/PSS costs £263.03 (95% CI £204.01 to £321.51). Mean total societal costs were also higher for the intervention group £344.64 (95% C: -£344.27 to £1,356.53) (Table 1)

Table 1: Total NHS/PSS and total societal costs

Category	Number with complete cases		Mean (standard error costs, £		Mean cost difference, £ (95% CI)	P-value
	Intervention	Usual care	Intervention	Usual care		
Intervention	376	351	266.95 (4.79)	0.4 (0)	266.55 (257.46, 276.62)	<0.001
Primary care	356	312	268.25 (14.34)	285.48 (16.45)	-17.22 (-62.14, 24.55)	0.4105
Secondary care	358	318	71.82 (11.81)	52.83 (10.24)	18.99 (-11.25, 48.7)	0.216
Medications	376	351	7.21 (1.34)	12.06 (3.18)	-4.85 (-14.66, 0.2)	0.1495
Total NHS/PSS costs	356	312	614.88 (20.77)	351.85 (20.42)	263.03 (204.01, 321.51)	<0.001
Private medical expenses	356	312	16.6 (7.52)	14.34 (6.07)	2.26 (-15.3, 22.93)	0.81
Additional costs	280	250	91.96 (27.21)	47.89 (13.98)	44.07 (-6.59, 118.66)	0.149
Productivity costs	262	241	1164.14 (312.75)	1268.63 (316.25)	-104.49 (-927.51, 813.71)	0.821
Total Non-NHS/PSS costs	242	212	1226.42 (343.6)	1126.32 (256.39)	100.1 (-570.47, 1198.51)	0.815
Total societal costs	242	212	1779.9 (340.65)	1435.25 (260.52)	344.64 (-344.27, 1356.53)	0.405

Cost-effectiveness results

Base-case analysis

The CHESS intervention generated incremental adjusted costs of £268 (95% CI £176 to £377) and incremental adjusted QALYs of 0.031 (95% CI -0.005 to 0.063). The incremental cost-effectiveness ratio (ICER) was £8,617 per QALY. The incremental net monetary benefit was £354 (95% CI -£375 to £1,084) with probability that the intervention is cost-effective approaching 0.83 if the cost-effectiveness threshold is £20,000 per QALY gained (Figure 1).

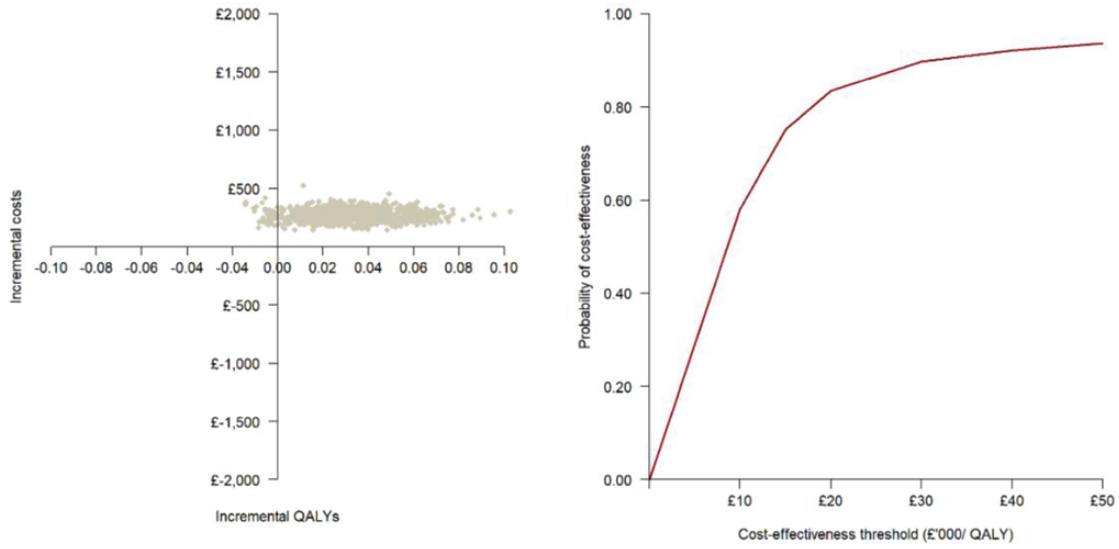

Figure 1: Cost-effectiveness plane and cost-effectiveness acceptability curve.

Sensitivity analyses

The ICERs in our sensitivity analyses ranged from £765 per QALY gained based on societal costs to £32,083 per QALY gained using QALYs derived from SF-12 (SF-6D) utilities. In the sensitivity analysis using societal costs, the incremental net monetary benefit and probability of cost-effectiveness were £626 (95% CI -£602 to £1,854) and 0.84 at £20,000 per QALY gained respectively. For the analysis based on SF-6D utilities, the net monetary benefit was negative at £20,000 per QALY, suggesting that the intervention would, on average, generate a loss of £101 (95% CI -£463 to £666) for the NHS and PSS at this cost-effectiveness threshold (Table 2).

Subgroup analyses

The results of our sub-group analyses suggest that at the £20,000 per QALY cost-effectiveness threshold, the intervention is most likely to be cost-effective among over 40-year olds with probability 0.89, among females with probability 0.85, among medication overuse headaches with probability 0.84 and among participants from the West Midlands with probability 0.81 (Table 3).

Long-term economic modelling

Our study protocol had allowed for long-term economic modelling if the within-trial analysis suggested the intervention was clinically effective and cost-effective treatment for chronic headaches. This was not done given that intervention was not clinically effective and is unlikely to be adopted in routine practice despite the positive cost-effectiveness outcomes suggested by the within-trial economic evaluation.

Table 2: Within-trial cost-effectiveness estimates

	Incremental estimates (95% CI)			Incremental net monetary benefit (95% CI)			Probability of cost-effectiveness £/QALY		
Analysis	Costs (£)	QALYs	ICER	£15K/QALY	£20K/QALY	£30K/QALY	£15K	£20K	£30K
Base-case (van Hout EQ5D-5L)	268 (176, 377)	0.031 (-0.005, 0.063)	8617	199 (-352, 750)	354 (-375, 1084)	666 (-423, 1755)	0.752	0.834	0.897
EQ5D-5L, Hernandez-Alava	269 (170, 388)	0.028 (-0.001, 0.055)	9535	154 (-297, 606)	296 (-297, 889)	578 (-299, 1456)	0.752	0.835	0.902
SF6D utility	269 (162, 399)	0.008 (-0.02, 0.035)	32083	-143 (-570, 283)	-101 (-666, 463)	-17 (-861, 826)	0.247	0.361	0.475
Societal costs	25 (-702, 1231)	0.033 (-0.001, 0.063)	765	463 (-681, 1608)	626 (-602, 1854)	952 (-490, 2393)	0.784	0.843	0.894
Intervention (16 participants)	157 (81, 245)	0.032 (-0.002, 0.062)	4965	317 (-181, 814)	474 (-185, 1133)	790 (-192, 1772)	0.887	0.916	0.939
Intervention (3 participants)	834 (689, 1000)	0.032 (-0.005, 0.065)	26167	-356 (-956, 244)	-197 (-976, 583)	122 (-1022, 1266)	0.118	0.303	0.586
Unadjusted analysis	229 (82, 432)	0.033 (-0.112, 0.127)	6895	270 (-1789, 2329)	436 (-2281, 3153)	768 (-3264, 4801)	0.621	0.658	0.688
Adjusted complete case analysis	321 (202, 465)	0.017 (-0.01, 0.042)	18968	-67 (-508, 374)	17 (-556, 591)	187 (-656, 1029)	0.392	0.519	0.665

Table 3: Subgroup analyses results

	Incremental estimates (95% CI)		Incremental net monetary benefit (95% CI)				Probability of cost-effectiveness £/QALY		
Subgroup	Costs (£)	QALYs	ICER	£15K/QALY	£20K/QALY	£30K/QALY	£15K	£20K	£30K
Age group									
Under 40-year olds	371 (192, 615)	0.017 (-0.047, 0.07)	22173	-120 (-1056, 816)	-36 (-1272, 1199)	131 (-1708, 1970)	0.399	0.477	0.548
40 or more-years	226 (106, 375)	0.047 (-0.011, 0.097)	4790	481 (-436, 1398)	717 (-503, 1936)	1188 (-639, 3014)	0.868	0.891	0.92
Sex									
Male	484 (211, 909)	0.017 (-0.074, 0.088)	28261	-227 (-1543, 1089)	-142 (-1871, 1588)	30 (-2535, 2595)	0.369	0.416	0.492
Female	230 (118, 368)	0.046 (-0.018, 0.102)	4969	465 (-582, 1512)	697 (-695, 2088)	1160 (-922, 3242)	0.816	0.851	0.882
Medication over use									
No	303 (166, 479)	0.028 (-0.025, 0.072)	10991	111 (-700, 921)	248 (-823, 1320)	524 (-1072, 2120)	0.579	0.654	0.725
Yes	238 (103, 413)	0.042 (-0.021, 0.095)	5692	390 (-634, 1414)	599 (-759, 1957)	1018 (-1010, 3047)	0.802	0.843	0.879
Region									
London	270 (140, 438)	0.024 (-0.021, 0.064)	11089	95 (-609, 799)	217 (-713, 1147)	461 (-923, 1845)	0.605	0.685	0.756
West midlands	253 (0, 652)	0.059 (-0.05, 0.143)	4310	628 (-1254, 2509)	921 (-1568, 3411)	1509 (-2201, 5219)	0.78	0.814	0.836

Discussion

Our base-case cost-effectiveness analysis shows a high probability (0.83) that the CHESS intervention is cost-effective at the cost-effectiveness threshold of £20,000 per QALY gained. This finding is robust in a sensitivity analysis using the Hernandez-Alava EQ-5D-5L conversion algorithm, but not when calculating utilities from SF-12 data. This may reflect tentative evidence in the external literature that suggests that the EQ-5D generates larger utility gains associated with improvements in headache-related outcomes.[18-19] This difference does raise the possibility our base-case may be over-estimating the cost-effectiveness of the CHESS intervention. Conversely, the much reduced ICER found when we used a societal perspective suggests that the CHESS intervention might represent better value for money if a broader perspective is used.

It is not clear why the CHESS intervention appears to generate additional QALYs when it has no meaningful effect on our headache specific outcomes. It is possible the EQ-5D-5L, but not the SF-12, is measuring non-specific effects from attending the CHESS intervention not measured using headache specific outcomes. Or it might be that there is an early benefit, evidenced by the four months HIT-6 findings that is having proportionally larger impact in the area under the curve analysis.

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Appendix 17 The CHESS trial: protocol for the process evaluation of a randomised trial of an education and self-management intervention for people with chronic headache

Background

Process evaluation is increasingly common alongside complex randomised controlled trials (RCTs). This evaluation helps in understanding the mechanisms of impact and how the study processes were executed, and it includes any contextual factors which may have implications for the trial results and any future implementation. This process evaluation is for the Chronic Headache Education and Self-management Study (CHESS) RCT, which is evaluating an education and self-management group behavioural intervention for people with chronic headache. Chronic headache is defined as headaches which are present for ≥15 days per month. The most common types are chronic migraine and chronic tension-type and medication overuse headaches.

Methods

We will use a mixed-methods approach. Quantitative data will be taken from routine trial data which will help us to assess the reach of the study (i.e. did we reach those whom we expected and from where?). Intervention attendance (dose received) and attrition and qualitative data will augment our understanding about reasons why people may not wish to take part in or failed to attend sessions. Interviews with intervention facilitators and trial participants will gain different perspectives on taking part in the trial.

Fidelity will be assessed through listening to audio-recordings for adherence to course content and competence of the facilitation of a sample of sessions.

Discussion

Our process evaluation will allow us to gain insight into how the trial was delivered, the obstacles and enablers encountered and the possible reasons why the interventions may or may not be effective.

Appendix 18 Chronic Headache Education and Self-Management Study (CHESS): a process evaluation

Background

The Chronic Headache Education and Self-Management Study (CHESS) multicentre randomised trial evaluated the impact a group education and self-management support intervention with a best usual care plus relaxation control for people living with chronic headache disorders (tension type headaches or chronic migraine, with or without medication overuse headache). Here we report the process evaluation exploring potential explanations for the lack of positive effects from the CHESS intervention.

Methods

The CHESS trial included 736 (380 intervention: 356 control) people across the Midlands and London UK. We used a mixed methods approach. Our extensive process evaluation looked at context, reach, recruitment, dose delivered, dose received, fidelity and experiences of participating in the trial, and included participants and trial staff. We also looked for evidence in our qualitative data to investigate whether the original causal assumptions underpinning the intervention were realised.

Results

The CHESS trial reached out to a large diverse population and recruited a representative sample. Few people with chronic tension type headaches without migraine were identified and recruited. The expected 'dose' of the intervention was delivered to participants and intervention fidelity was high. Attendance ('dose received') fell below expectation, although 261/380 (69%) received at least at least the pre-identified minimum dose. Intervention participants generally enjoyed being in the groups but there was little evidence to support the causal assumptions underpinning the intervention were realised.

Conclusions

From a process evaluation perspective despite our extensive data collection and analysis, we do not have a clear understanding of why the trial outcome was negative as the intervention was delivered as planned. However, the lack of evidence that the intervention causal assumptions brought about the planned behaviour change may provide some insight. Our data suggests only modest changes in managing headache behaviours and some disparity in how participants engaged with components of the intervention within the timeframe of the study. Moving forwards, we need a better understanding of how those who live with chronic headache can be helped to manage this disabling condition more effectively over time.

Appendix 19 Patient and public involvement in a UK National Institute for Health and Care Research Programme Grant for Applied Research: experiences from the Chronic Headache Education and Self-management Study (CHESS)

Background

Patient and public involvement (PPI) plays a crucial role in ensuring research is carried out in conjunction with the people that it will impact on. In this article, we present our experiences and reflections from working collaboratively with patients and public through the lifetime of a National Institute for Health and Care Research (NIHR) programme grant, the Chronic Headache Education and Self-management Study (CHESS), which took place between 2015 and 2020.

Patient and public involvement over the course of CHESS

We worked closely with three leading UK migraine charities and a lay advisory group throughout the programme. We followed NIHR standards and used the Guidance for Reporting Involvement of Patients and the Public checklist. We consulted our PPI contacts using a variety of methods depending on the phase of the study and the nature of the request. This included emails, discussions and face-to-face contact.

PPI members contributed throughout the study in the programme development, in the grant application, ethics documentation and trial oversight, during the feasibility study in supporting the development of a classification interview for chronic headache by participating in a headache classification conference, assessing the relevance and acceptability of patient-reported outcome measures by helping to analyse cognitive interview data, and testing the smartphone application making suggestions on how best to present the summary of data collected for participants. Due to PPI contribution, the content and duration of the study intervention were adapted and a Delphi study with consensus meeting developed a core outcome set for migraine studies.

Conclusions

The involvement of the public and patients in CHESS has allowed us to shape its overall design, intervention development and establish a core outcome set for future migraine studies. We have reflected on many learning points for the future application of PPI.

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