PROTOCOL

Chronic Headache and Self-management Study
(CHESS)

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10		

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LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AES	Advanced Encryption Standard
APP	Application
CBT	Cognitive Behavioural Therapy
CCG	Clinical Commissioning Groups
CI	Confidence interval
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DCM	Definite Chronic Migraine
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Council for Harmonisation
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MOH	Medication Overuse Headache
MRC	Medical Research Council
NHS	National Health Service
NICE	The National Institute for Health Care Excellence
NMC	National Migraine Centre
PCM	Probable Chronic Migraine
PGP	Pretty Good Privacy (encryption)
PI	Principal Investigator
PPI	Patient & Public Involvement
PIS	Patient Information Sheet
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
SAE	Serious Adverse Event
SMART	Specific Measurable Attainable Realistic Time-based (goals)
SOP	Standard Operating Procedure
TMG	Trial Management Group
TTH	Tension Type Headache

PSC	Programme Steering Committee
QMUL	Queen Mary University of London
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Chronic headache disorders are a major cause of pain and disability. Their main impact is in young adults many of whom have both work and family commitments. The commonest chronic headache disorders are tension type (TTH), migraine, and medication overuse headaches (MOH). TTH and migraine are primary headaches. MOH is a secondary headache that can develop in people with frequent acute headaches who take analgesic, or specific anti-migraine compounds (e.g. triptans) on ≥10-15 days per month.

The management of episodic headaches is comparatively straightforward. A minority of those affected, however, develop a chronic headache syndrome; i.e. headaches on more than 15 days per month, for more than three months. Around 2-4% of the population have a chronic headache.[1,2] Approximately 25-50% of those affected also have MOH, which has a prevalence of 1%.[3-5] Around 4% of primary care consultations and 30% of neurology out-patient appointments are due to headache disorders.[6-9] TTH and migraine are the second and third most common disorders globally (after dental caries of permanent teeth).[10] The annual cost of headache disorders to the UK is £5-7 billion.[11]

A community pharmacy study found that 44% of those buying analgesics did not have a physician diagnosis, and 40% of these were positive on a screening questionnaire for migraine. Around a quarter of those recruited were overusing acute medication.[12] Many people who might benefit from prophylactic treatment for migraine have not been offered this.[13] An American survey of 120,000 households reported that migraine preventive treatments should have been considered in 39% of migraine sufferers but only 13% of those affected were on preventive treatments.[14]

NICE guidance on headaches was published in September 2012.[15] Besides recommendations to consider a course of acupuncture for people with chronic migraine or tension type headache, the guidance developers did not find suitable evidence to allow recommendations on non-pharmacological treatments for people with chronic headache.

1.2 Existing knowledge

In a scoping review we identified eight potentially relevant RCTs.[16-23] These were largely uninformative because they were too small, had only a very short follow-up, or did not report clinically relevant outcomes. Two RCTs provided useful data to inform our thinking. Matchar (N=611) tested a headache management programme added to usual care, for people with chronic headaches, based in an American headache clinic service.[16] This included a diagnostic evaluation, a headache class, and three follow-up contacts. At the six month follow-up (primary outcome) there was, compared to usual care, an additional 7.0 (95% CI 2.9 to 11.1) point reduction in the Migraine Disability Assessment score (MIDAS).[24] At 12 months this was 6.8 (95% CI -0.3 to 13.9). These results from a trial of a, principally, educational programme support the notion that educationally based interventions might improve outcome for people living with chronic headache. The data are not, however, directly transferable to a UK primary-care context because of differences in the health care system affecting content of usual care, and because participants were recruited from headache clinics rather than primary care. An economic analysis is not reported. These data were

not used to inform NICE guidance because they did not include an active control. Furthermore they included participants with different types of headaches when NICE guidance is headache-disorder specific.[25] The second, Lemstra (N=80) tested a multidisciplinary intervention, including 18 group exercise sessions for people with chronic migraine and found a positive effect on pain and quality of life after six weeks and three months.[19] Although these data are only short term they do support the notion that programmes including a behavioural component can improve outcome for people living with chronic headache. These data were not used to inform NICE guidance because multidisciplinary interventions were not part of the review protocol.[25]

Two subsequent reviews assess the effectiveness of psychological interventions. Sullivan et al [26] assessed psychological interventions for people with migraine including cognitive behavioural therapy, relaxation therapy and/or biofeedback and found these interventions to be modestly effective, however with a broad range of efficacy from 20 to 67 % and there was no evidence to indicate that one approach was superior to another. Harris et al [27] assessed the effectiveness of cognitive behavioural interventions (CBT) for people with migraine and their findings were mixed; with of their included studies providing evidence in support of the suggestion that people experiencing headaches or migraines can benefit from CBT, and that CBT can reduce the physical symptoms of headache and migraines. Patient education has also been assessed and described as moderately effective approach in people with migraine in a 2014 review.[28] In addition to this, therapies such as mindfulness are gaining popularity and there is growing evidence for their feasibility, tolerability and acceptability, and some preliminary evidence to support the use of such interventions in managing psychological comorbidities.[29-31] However none of these reviews conducted quantitative analyses and mostly are assessed a migraine-only population.

To inform the intervention design of the trial, we conducted a formal systematic literature review. For the widest feasible scope we included RCTS and non-randomised trials of any educational self-management interventions for headache. We aimed to identify and categorise components of self-management interventions, assess information regarding delivery styles and intervention providers. We searched relevant databases including the *Cochrane* library, Medline, Embase, Psychinfo and Web of knowledge from 1980 to 09/2015 and updated the search on 20/06/2016.

We identified 16,293 titles, removed 3,669 duplicates and reviewed 146 papers of which 54 were included in the review.[29,30,32-83] The included trials were testing non-pharmacological self-management and/or educational interventions. We assessed individual components of these interventions utilising an adapted version of an established framework [84] which resulted in four component categories used in self-management interventions for headache:

1. Psychological training or cognitive behavioural therapy aimed at changing attitudes and beliefs;
2. A taught or self- taught headache information component that aims to increase participants' skills and knowledge and to enable participants to deploy these enhanced skills in aspects of their lives beyond the intervention;
3. Mindfulness-based approaches, involving training patients to engage in self-regulation of attention through increasing awareness of, and accepting present thoughts, feelings and physical sensations;
4. Relaxation training components, that aim to reduce stress and anxiety in patients providing psychological resources to cope with their headaches.

The majority of interventions featured a relaxation component (n=39), alongside a psychological component (n=33). Less than half the studies also included an educational component (n=18) and the minority (n=7) of included studies used mindfulness based approaches for their intervention. Most interventions were delivered face to face, either individually (n=26) or in a group setting (n=23), with some of the included studies also delivered remote via a website or paper instructions (n=18). Most interventions were delivered by a psychologist or therapist (n=29) or other health professionals (n=11); with the remainder delivered with no contact or in a multidisciplinary team. Homework practise was part of nearly half the studies, with most trials involving an at-home relaxation task. The amount of daily home practice varied from 15 to 60 minutes across the studies and tended to use audiotapes to support at home practice and some also had the option of telephone or email support available.

To further assess the effectiveness of different components relevant for our intervention we conducted meta-analysis with all included studies that compared a self-management intervention to usual care or waiting list control. We classified the studies according to type of course delivery (group or individual and face to face or remote), who delivered intervention (psychologist/therapist or nurse/allied health professional/student), if any additional support components were used (homework or email/telephone follow up) and number and type of components (relaxation, psychological/CBT, information, mindfulness). For the analysis we grouped studies together by delivery mode and component content. We grouped outcome measures used in the trials together in the following categories: headache frequency, pain intensity, headache related disability, headache related quality of life, medication consumption, mood, stress, coping and mindfulness, locus of control and headache management self-efficacy. We limited the analysis to comparisons that included at least 10 studies per outcome. We produced a pooled effect size for each outcome category across studies by combining the final value data in the intervention and control arm for each study and calculating standardized mean differences (SMD). We included a total of 16 RCTs (n = 1770) in this quantitative synthesis.

We found a small overall effect for behavioural self-management interventions versus usual care/waiting list control, with an SMD of-0.36 (95% CI, -0.45, -0.26) on pain intensity (N=13 studies, n=1749 participants) and -0.32 (95% CI, -0.42, -0.22) on headache related disability (N=10 studies, n=1540 participants).

Studies including a psychological component found a larger effect size of -0.72 (95% CI, -0.93, -0.51) (N=5 studies, n=405 participants), compared to those without of -0.41 (95% CI, -0.58, -0.24) (N=5 studies, n=582 participants), but made no difference on intensity or headache related disability.

Studies including educational component found a larger effect size on pain intensity of 0.51 (95% CI, -0.68, -0.34) (N=4 studies, n=605 participants) compared to -0.28 (95% CI, -0.40, -0.16) those without (N=10, n=1144 participants).

Studies including a mindfulness component found a larger effect size on pain intensity of -0.50 (95% CI, -0.82, -0.18) (N=4 studies, n=168 participants), compared to those without -0.34 (95% CI, -0.44, -0.24) (N=9 studies, n=1581 participants). Including a relaxation component, face-to-

face delivery (versus remote) and the provision of additional support did not affect outcomes intensity or headache related disability.

Studies of group-delivered interventions found a larger effect on pain intensity; effect size of 0.56 (95% CI, -0.72, -0.40) (N=6 studies, n=688) participants compared to -0.39 (95% CI, -0.52, -0.27) (N=6 studies, n=1082 participants) individually delivered interventions.

Our results suggest, that consideration should be given to the development of group delivered self-management interventions that include a psychological, mindfulness and headache information component, however clinical heterogeneity amongst included studies was significant and more research is required to further investigate and confirm these findings.

1.2.1 Supportive self-management programmes

When reviewing the possible role for supportive self-management programmes the literature suggests support programmes have an established place in the management of a range of chronic diseases.[85-87] NICE did not find any relevant evidence on the use of education and self-management programmes for the treatment of chronic headaches and recommended further research in this area. There is an association between chronic headaches and chronic musculoskeletal pain.[88,89] One large community study found the odds of people with chronic headache having frequent low back pain were substantially greater than those without headache.[90] Prospective data show that chronic headaches predispose to chronic musculoskeletal pain, and vice versa.[91] Central sensitisation of the pain matrix may be a common pathway for chronic headache and other chronic pain syndromes.[92, 93] Some argue for a common explanatory model, based on either fear-avoidance or anxiety-sensitivity.[94, 95] Other work has shown a high prevalence of dysfunctional coping strategies in people with any headache type using a theoretical framework drawn from low back pain.[96] There are differences between how chronic disability arises between headaches and chronic musculoskeletal pain. Nevertheless, there is sufficient commonality that one can draw on experience from chronic pain in other areas to inform strategies to facilitate effective self-management of chronic headaches. In contrast, the management of acute headaches rightly remains within the medical model.

1.2.2 Headache diagnosis

Many patients with chronic headaches do not have an accurate diagnosis, or diagnoses (all three common headache types can co-exist), and receive inappropriate drug treatment.[97] There are deceptively simple diagnostic criteria for different headache types; for example, NICE headache guidance.[15] In reality, it can be challenging for a non-expert clinician to decide on the diagnostic classification. As part of the CHESS feasibility study we conducted a systematic review of studies that describe the validation or diagnostic accuracy of classification and diagnostic headache tools, the aim of the review was to identify any existing classification tools that could be used to stratify care for people with chronic headaches according to headache type. The review identified an unexpectedly high number of studies that validated tools used to classify or diagnose different headaches types: 8 primary headaches disorders, 20 migraine, 2 cluster headaches and 1 probable medication overuse headache.

Only two of the tools allow the diagnosis of both episodic and chronic headache disorders and differentiate between primary and secondary headaches, both are computerised diagnostic tools. The first validated in a study of 117 subjects shows good levels of agreement with an expert clinician

diagnosis, however the tool is intended to be used and interpreted by a doctor.[98] The second validated in a headache clinic population of 543 subjects shows good levels of agreement for most headache types but uses information already entered into the computerised clinical decision support as a reference test. A recent study by Lipton et al (2016) reports the validation of Identify Chronic Migraine (ID-CM) a tools to help clinicians identify patients likely to have migraine, and in particular, chronic migraine; but does not allow the classification of other chronic headache types.[99]

The findings from the review confirmed the need to develop our own telephone classification interview which can be conducted by a non-headache specialist to classify the main chronic headache disorders. The classification interview will be used for reporting and analysis purposes, and as part of the study intervention to allow targeted treatment and advice. Diagnosis will be an important component of the intervention package, as it will inform advice on medication use.
In October 2015 we held a consensus conference at the University of Warwick, the aim of the conference was to draw on evidence and expertise to reach consensus on questions to inform the design of the telephone classification interview. In total 26 delegates attended the consensus day, 5 headache specialist nurses, 13 neurologists (10 with a specialist interest in headache), 7 lay representatives (people living with headaches) and one GP with a specialist interest in headache. The day after the consensus meeting key members of the study team met to review the findings and used them to inform the development of a logic model. The purpose of the logic model is to underpin the classification interview and help ensure that the key components of the interview are addressed. Although the classification interview is based around a logic model, it is not intended to be a rigid interview schedule. Instead, the nurse conducting the interview is encouraged to use the logic model to inform their clinical reasoning and decision-making. The structure and sequence of the telephone interview will be determined by the nurse's individual consultation style, questioning, and by participants' responses. This will allow then to:

- Exclude serious pathology (secondary headaches other than medication overuse headache)
- Exclude primary headache disorders other than migraine and TTH
- Distinguish between definite chronic migraine, probable chronic migraine, and chronic TTH
- Identify medication overuse headache

1.3 Hypothesis

Amongst adults with chronic headache arising from migraine, tension type headache or medication overuse headache is the provision of a self-management support programme in addition to best usual NHS care clinically and cost effective?

1.4 Need for a trial

Chronic headaches present a major problem both for the individual and society. Previous studies on supportive self-management interventions in this population have largely been small studies with short term follow-up, they often did not report clinically relevant outcomes, or were conducted in different healthcare systems therefore difficult to translate into an NHS setting. These studies also did not necessarily focus on chronic headache but rather looked at headache with no frequency specified. Based on the results of our systematic review there may be potential for large gain through a combination of self-management education and appropriate use of prophylaxis and management of medication overuse headache in a chronic headache population.

In order to develop the evidence base needed for self-management intervention for chronic headache there needs to be a carefully developed, piloted and evaluated intervention package which has been supported by good qualitative work on understanding outcomes of interest. There is therefore the need for a robust clinical and cost-effectiveness trial within an NHS setting.

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to ICH Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018.

We will ensure that all identifiable data is anonymised and treated as confidential. Participants will be informed that they are free to withdraw at any time during any phase of the work.

Our earlier systematic review of the predictors of success of self-management interventions for chronic pain found that delivery of the intervention in the participant's mother tongue was one of the few predictors associated with success that had been identified.[100] In this study we will only recruit patients who are fluent in English since the intervention and study support materials will be delivered in English. Our previous work has demonstrated that it is very difficult to include delivery of culturally adapted versions of group self-management interventions in different languages within a definitive randomised controlled trial because of issues such as the lack of validation of outcome measures in different languages and cultures.[101]

Ethical considerations for recruitment are minimal and are predominately to do with access to patient information. For searching of GP registers only clinical staff and the Local Clinical Research Network (LCRN) along with any research staff (with appropriate permissions) will have access to such information. Patients will have the choice whether or not to participate and will be given all relevant information about the study to make an informed decision. The general risks to the participant in this study are low, however the study team are aware of implications such as emotional reactions. We will therefore ensure all facilitators are trained in recognising and managing distress should a situation occur and furthermore each group session will have two facilitators to ensure appropriate management should a patient become distressed: one facilitator can see to the patient and the other continue the group session. For additional support we will ensure a medical member of the study team is available for consultation by telephone if required. The study team will have a list of clinically qualified personnel to call on should it be necessary. Prof Underwood has a background in General Practice and Professor Taylor is a practising GP in North-east London, they both have experience of research trials, Dr Davies and Dr Mathura are the Neurologists in the trial. GCP-trained personnel will conduct the trial.

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement.[102]

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

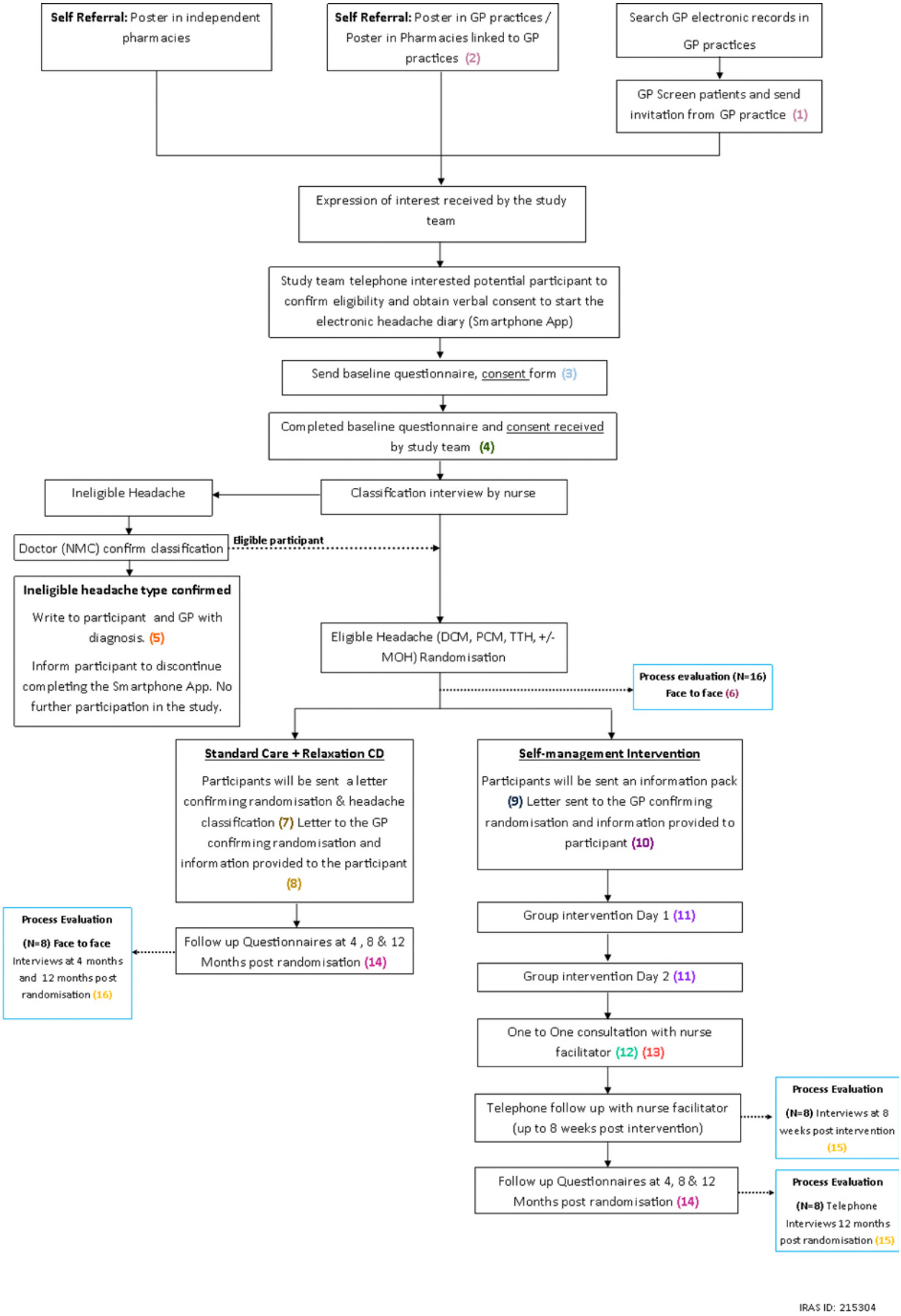
This trial is a multi-centre randomised controlled trial comparing a group education and self-management intervention with a best usual care plus relaxation control for participants living with chronic tension type headaches, probable chronic migraine or definite chronic migraine with or without medication overuse headache.

Our overarching aim is to conduct a definitive randomised controlled trial to test the effectiveness and cost effectiveness of a multicomponent education and self-management intervention targeting those with chronic headache. This intervention will be compared to best usual care and a relaxation CD for people living with chronic headaches. We will run the intervention in two locations (Midlands and Greater London). We will primarily recruit from general practices. We will adapt our existing search algorithms to identify people who have consulted with headache disorders, or received prescriptions for migraine specific drugs in the preceding two years. However, many people with chronic headaches are self-managing, usually with over the counter preparations, and not consulting their general practitioner. We will, therefore, supplement recruitment by allowing self-referral to study for people, living locally to participating practices, who are living with chronic headaches. To facilitate this we will place posters in the waiting areas of participating practices and those pharmacies that mainly serve their population. We will also advertise this on our website. Potential participants identified by either route will be screened by the study team to identify those with chronic headaches; that is people who experience headaches on 15 days or more for at least the past three months. We will seek to recruit around 689 participants from around 75 practices across the two locations (Midlands and Greater London). The clinical and cost effectiveness of the CHESS intervention will be compared to a best usual care package.

Study outcomes include: the 6 item Headache Impact Test (HIT-6), 14 item Chronic Headache Quality of Life Questionnaire (CHQLQ v1.0), SF-12 V2, EuroQol EQ-5D-5L, Hospital Anxiety and Depression Scale (HADS), Pain Self Efficacy Questionnaire (PSEQ), Social Integration Subscale of the Health Education Impact Questionnaire (heiQ), and frequency, severity and duration of headache days. Adverse events and resource use (using GP records and patient self-reported data, such as over the counter medication costs). Follow up data will be collected four, eight and 12 months post randomisation. We will carry out a process evaluation, using the MRC guidance on developing and evaluating complex interventions including an assessment of intervention fidelity.[103]

We have developed an intervention package which is an education and self-management group programme in our feasibility trial. Full details of this self-management programme are in Section 2.7.

Figure 1: Trial flow diagram



(1) Invitation Pack:

- Practice Headed paper - Invitation letter
- Participant Information Sheet - Participants identified by GP search
- Participant Information Sheet—Participant Self Referral
- Expression of interest form (Interested Green Sheet)
- Expression of interest form (Not interested Red Sheet)
- Self addressed / Pre-paid envelope
- X1 Postal Reminder (Approx. 14 days after)

(2) Posters:

- GP Practices
- Pharmacies linked with GP Practices

(3) Study Pack:

- WCTU headed paper - Covering Letter
- Consent form in triplicate
- Baseline Questionnaire
- Smartphone app instructions
- Self-addressed / Pre-paid envelope
- X1 Postal reminder (Approx. 14 days after)

(4) GP Notification (Consent):

- WCTU headed paper - Covering Letter

(5) Ineligible Headache Type:

- WCTU headed paper - Generic covering letter to participant
- WCTU headed paper— Headache specific covering letter to GP
- Information Sheet Headache specific - Participant
- Information Sheet Headache specific - GP

(6) Process Evaluation Information:

- Covering Letter
- Participant Information Sheet
- Consent Forms

(7) Participant allocation to control pack:

- WCTU headed paper- covering letter providing details of control.
- Relaxation CD and Information

(8) GP Notification of Randomisation allocation (control) and headache classification:

- WCTU headed paper - letter detailing allocation to control arm, headache classification outcome and recommendations.

(9) Participant allocation to intervention pack:

- WCTU headed paper—covering letter providing details of intervention.
- Headache Diary
- Employee letter *(if requested by participant)*

(10) GP Notification of Randomisation allocation (intervention):

- WCTU headed paper - confirmation to GP with randomisation allocation.

(11) Intervention Handouts:

- X16 Handouts to participants to supplement topics of programme
- Copy of CHESS DVD
- Copy of Mindfulness CD
- CHESS contact card
- Nurse one to one appointment card

(12) Nurse one to one Interview:

- Nurse provide participant with relevant information based on headache type (DCM, PCM, CTTH).

(13) GP Notification of Headache Classification (Intervention Arm Only):

- WCTU headed paper—letter detailing headache classification and recommendations.

(14) Follow up Pack:

- WCTU headed cover letter for each follow up month (4, 8 & 12 months)
- Follow up questionnaire (4, 8 & 12 months)
- X1 postal reminder (Approx. 14 days later)
- X1 telephone call (reminder or to capture core outcome measures)

(15) Process Evaluation/ Interview Study—Reminder:

- Reminder Letter

2.2 Aims and objectives

2.2.1 Aim

To estimate the clinical and cost-effectiveness of a group education and self-management programme for people living with chronic headache arising from migraine, tension type headache or medication overuse headache recruited from primary care when compared to a GP care plus relaxation control group.

2.2.2 Primary objective

- To test the clinical effectiveness of a group education and self-management programme for people living with chronic headaches.

2.2.3 Secondary objective

- To test the cost effectiveness of a group education and self-management programme for people living with chronic headaches.
- To quantify and draw inferences on observed general health, health-related quality of life, mood, confidence and social activity outcomes (see 2.3.1 for list of outcome measures)
- To quantify and draw inferences on the self-reported frequency, duration and severity of headaches.
- To estimate the effects of the group education and self-management programme on use of health care and broader resource use, and costs to individuals (for example, through income losses and out of pocket expenses) (see 2.3.1 for details).
- To run a parallel process evaluation of the trial which will inform interpretation of the trial findings and the implementation of the intervention across the NHS, if indicated.
- To disseminate the results. If appropriate, this will include providing materials to support roll-out of the intervention.

2.3 Outcome measures

Primary outcome:

- HIT-6 at 12 months post randomisation as the primary endpoint.
  Informed by the results of our outcome measures review, we have included two headache-specific measures - the 6-item Headache Impact Test (HIT-6) and the 14-item Chronic Headache Quality of Life Questionnaire (CHQLQ (v1.0)).[104] The CHQLQ is a headache-specific modification of Migraine Specific Quality of Life Questionnaire (MSQ v2.1).[105] There is strong evidence of acceptable psychometric properties for the HIT-6 and MSQ (v2.1) following completion by patients with headache (HIT-6) or migraine (HIT-6 and MSQ (v2.1). Re-attribution of items within the MSQ (v2.1) to 'headache' supports a broader assessment of headache than is possible with 'migraine'.

  The HIT-6 provides a short overall assessment of headache impact – with items assessing fatigue, pain, social and role functioning, emotional well-being and cognition.
  The CHQLQ assesses the role restrictions, limitations and emotional impact of headache.

There is a strong similarity of content between measures- with three of the HIT-6 items replicated from the CHQLQ. Although three of the questions in HIT-6 are not time-bound which may lead to problems in interpretation, qualitative work conducted as part of the selection process identified the greater perceived relevance of the CHQLQ to people with headache. We are assessing the comparative performance of these two measures in our feasibility study; follow-up is not complete. In the event that our analyses show that (CHQLQ (v1.0)) outperforms the HIT-6 we will consider whether changing this to be our primary outcome is appropriate.

Secondary outcomes:

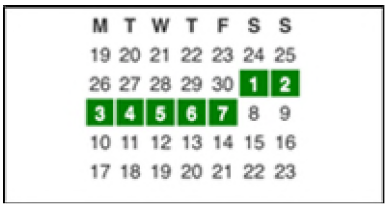
1. *Headache days:* Our primary headaches days outcome will be reported as headaches days in the preceding month reported at baseline and in follow-up questionnaires.
   We will also report estimates of total headaches days, presented as area under the curve, over whole study period derived from smartphone app/ diary records (see below)
2. *Generic health related quality of life*: We have included two standard measures of health-related quality of life – the SF-12 V2 and EQ-5D-5L.[106-108] There is limited, but acceptable, evidence supporting application of the SF-12 V2 in the headache population. Evidence for the EQ-5D is limited; we will use the EQ-5D-5L primarily for our health economic analyses.
3. *Emotional well-being:* Hospital Anxiety and Depression Scale (HADS) - Psychological distress is extremely common in people living with chronic pain. HADs has been used in many previous studies of chronic pain; including the COPERS study where we achieved positive effects on both anxiety and depression.[109]
4. *Self-Efficacy:* Pain Self-Efficacy Questionnaire (PSEQ) - Self-efficacy is an important mediator for how self-management interventions may improve patient outcomes. It is important, therefore, to measure change in self-efficacy as part of understanding the causal pathway for any change and informing our process evaluation. We have previously reviewed measure of self-efficacy and concluded that PSEQ is the most appropriate choice for studies of this nature; although all current measures have limitations.[110]
5. *Social Activity: Social Integration Subscale of the Health Education Impact Questionnaire (heiQ) - C*hronic headache can result in a disrupted lifestyle and a reduced quality of life both during and between attacks; the impact of chronic headache on an individual's ability to commit to social plans is an important aspect of quality of life. Successful treatment should seek to improve both overall quality of life, as well as an individual's quality of life during the attack, including their ability to integrate in society. Well-developed, condition-specific measure must seek to capture these distinctions. The five-item Social Integration Subscale (SIS) is one of eight domains contained within the heiQ [111], a measure of the impact of patient education programmes in chronic conditions. There is acceptable evidence of the reliability and validity of the heiQ in various chronic conditions, but it has not previously been evaluated in the chronic headache population.

We will collect follow-up data 4, 8 and 12 months after randomisation. Our primary analyses will be based on the twelve month data. We will do postal follow-up with two reminders. In the event that no response is obtained we will collect our primary clinical outcome by phone.

Headache frequency, severity and duration

A composite score for headache impact over the one year of follow up will be produced as the function of headaches days x average duration x average severity. Presenting these data graphically will allow any early benefits or harms from the intervention to be identified.

All participants will be asked to complete a smart phone app about their headaches. If they do not have access to a smart phone, or do not wish to use the app, a paper copy will be provided. Participants will initially complete the app weekly for up to six months, to cover any period of withdrawal from medication, then monthly thereafter (still requiring them to reflect over the previous 7 days) until the end of the study at 12 months after randomisation. Each time a participant completes the questions on the app the study team will receive an email notification, this will allow the study team to track response rates. Should a participant not complete the app for more than two weeks a member of the study team will telephone the participant to check they have not encountered any technical issues and to request they continue to complete. If the study team cannot make contact with the participant via telephone an email reminder will be sent. All data collection points will collect data on the preceding seven days. The app will display a calendar to indicate to the participant what period they are trying to recall information over (see example below). They will subsequently be asked to complete three questions:



1) On how many of the last 7 days have you had a headache?
   Insert number of headache days

2) On those days you had a headache, on average how long did they last?
   Insert number of hours

3) On those days you had a headache on average how severe were they?
   0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extremely Severe Pain)

2.3.1 Efficacy

Our package of secondary outcome measures are informed by our pilot study and literature reviews. All outcome measures are presented in Table 1 with data collection time points. In the event that questionnaires are not returned by the participant, two postal reminders will be sent after 10-14 day intervals. Following this, if there is still no response, they will receive a telephone call from a member of the trial coordinating team to collect the core outcomes (HIT-6 and EQ-5D-5L).

Table 1 - Outcome measures

Type of Data	Outcome measures	Time points			
		1 [a]	2 [b]	3 [c]	4 [d]
Demographic	Gender, ethnic group, age at leaving full time education, , current work status	X			
General Health	Fatigue, Sleep quality, Bodily pain [112]	X	X	X	X
General Health	Troublesomeness grid	X			
Headache Specific	*Headache Specific Information (HIT-6) [104] Chronic Headache Quality of Life Questionnaire, version1.0 (CHQLQ) Headache frequency, severity and duration over the past 7 days.	X	X	X	X
Health-related Quality of Life	Short Form 12-item Health Survey (SF12 (v2))[106, 107] EuroQoL [108], Chronic Headache Quality of Life Questionnaire, version1.0 (CHQLQ), EQ5D-5L	X	X	X	X
Mood	Hospital Anxiety and Depression Scale (HADS) [109]	X	X	X	X
Confidence	Pain Self-Efficacy Questionnaire (PSEQ) [110]	X	X	X	X
Social Activity	Social Integration Subscale (heiQ) [111]	X	X	X	X
Medication	Medication purchased in last four weeks over the counter.	X	X	X	X
Healthcare Use	Inpatient care, Admission details, NHS Day Care treatment, Community health and social care, side effects from headache medication, private treatment, Additional cost information.		X	X	X

1 [a] Baseline
2 [b] 4 month after randomisation
3 [c] 8 months after randomisation
4 [d]12 months after randomisation
*Primary outcome measure

In addition to these measures above we will collect data on headache frequency, severity and duration via a smart phone app (a paper version will be available for those who do not have access to a smartphone).

2.3.2 Safety

There will be a system for reporting adverse events and serious adverse events (see Section 4).

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

1. Able and willing to comply with the study procedures and provision of written informed consent.

2. Aged ≥18 years or above.

3. Living with chronic headache; defined as headache on 15 or more days per month for at least three months.

4. Result of nurse classification interview confirms headache type to be definite or probable chronic migraine, or chronic tension type headache, with or without medication overuse headache.

5. Fluent in written and spoken English.

2.4.2 Exclusion criteria

1. Unable to attend the group sessions.

2. No access to a telephone.

3. Has an underlying serious psychological disorder with ongoing symptoms which preclude or significantly interfere with participation in the group intervention.

4. Previous entry or randomisation in the present trial.

5. Is currently participating in another clinical trial of headache treatments, or in a trial of an unregistered medicinal product, or less than 90 days have passed since completing participation in such a trial.

N.B We will check if participants are pregnant in the one to one consultation and should this be the case they will be advised to speak to their GP with regards to medication and nurses will not discuss this with them during the consultation.

If more than one person from the same household return an expression of interest form to prevent cross-contamination the study team would offer to complete the eligibility assessment with both potential participants. If both were eligible the study team will ask the potential participants to select who they would like to proceed to participate in the study.

2.5 Informed consent

There are two consent stages:

1) Expression of interest to be part of the study

Potential participants will be sent an invitation letter, participant information sheet and an 'expression of interest' form if they are identified via the GP database search and are not screened out by the GP. If the participant is interested in the study they can return the 'expression of interest' form to the study team using a pre-addressed freepost envelope or contact the study team via phone or email. There will be a single postal reminder after 10-14 days.

Potential participants who contact the study team directly (after seeing a poster or information on the internet) will be sent the a participant information sheet and 'expression of interest' form.

2) Consent to be part of the study

Following receipt of an 'expression of interest' a member of the study team will call the potential participant. If they appear eligible (satisfying criteria 1-3 and 5) the study team will discuss with the potential participant the information sheet and consent process, the classification telephone interview, randomisation process and what will happen following randomisation. The participant will have the opportunity to ask questions and will be informed of their withdrawal rights. If the potential participant is interested in the study the member of the study team will post to the potential participant a pack containing the consent form, baseline questionnaire and the instructions for downloading the smartphone app which will capture headache frequency, severity and duration electronically. When the participant has returned the completed and signed consent form and baseline questionnaire they will formally be enrolled in the study. A copy of the fully signed consent form will be sent to the participant, their GP and a copy will be securely kept at the study office.

Participants who initially contacted the study team directly (after seeing a poster or information on the internet) will be asked to confirm their GP details when called by the study team. If the potential participant is interested they will subsequently be sent details as described above.

Willingness to continue will be monitored at all points of contact for the study including the classification interview and intervention.

During the classification interview, those participants that are classified with a headache other than those being included in this study will receive a second classification interview with a headache specialist. Should the headache specialist classify the participant with a headache type other than migraine, TTH or MOH they will be referred to their GP with details of their classification. They will not be asked to complete any further questionnaires or the smart phone app. We will confirm that anyone excluded at this stage is still happy for us to inspect their GP record at the end of the study for any confirmed headache diagnoses. If the headache specialist classifies the participant with one of our included headache types they will continue in the study.

<u>Additional consent for qualitative interviews:</u>

During the study as part of the process evaluation a sample of participants will be invited to take part in the qualitative interviews. A separate letter, information sheet and consent form will be sent by post to invite participants. These potential participants will be contacted by phone approximately 7-10 days after the information and consent form have been posted to check whether they would like to be interviewed, to answer any questions they may have, and to arrange a date for the interview to take place. The consent form for the qualitative study will be checked and countersigned by the interviewer before the interview.

2.6 Recruitment and randomisation

2.6.1 Recruitment

Potential participants will be identified via:

a) **Electronic screening of GP records**

With help from the Clinical Research Network and the study team, practices will run electronic searches on their databases, to identify people who have consulted with headaches or have been prescribed migraine specific drugs (e.g. triptans, pizotifen) in the preceding two years. Practices will screen the lists for those it would be inappropriate to approach (e.g. poorly controlled serious mental illness, terminal illness, or known secondary causes of headache such as primary or secondary brain tumours, or cluster headaches), and send approach letters on our behalf to the remainder. Those identified from the electronic search will be sent an invitation pack. Expressions of interest will be returned to the study team, who will telephone those interested in being in the study and check that they are eligible, explain the study, and obtain participant's verbal consent to start completing an electronic headache symptom severity, duration & frequency diary (or paper version where there is no access to a smartphone or computer). The electronic diary will be kept for six months with weekly data collection, thereafter monthly until the end of the study at 12 months.

b) **Posters advertising details of the study will be displayed in GP surgeries and pharmacies**

General practices will be supplied with a study poster for display in participant waiting areas, the poster will include contact details for the study office and invite participants to contact the team if they are interested in participating. Additionally we will ask practices to identify the principal pharmacies used by their patients. We will ask these pharmacies to also display CHESS trial posters. We will also ask pharmacies to display the study poster who are located in the geographical areas from which we are recruiting. Similar information about the trial will be available on the websites of the two lead academic institutions and the partner charitable organisations. This will include general locations in which the research is taking place. Together these approaches will allow people receiving GP treatment for chronic headaches who are not coded in the GP system as having headaches, and those who are self-managing headaches the opportunity to join the study. We anticipate that we will primarily recruit people registered with participating practices; however, we will not restrict recruitment to those registered with participating practices. All potential participants will need to be able to travel to the local treatment sites if randomised to the intervention group.

We will recruit from two locations; Midlands and Greater London whose populations are broadly representative of the UK as a whole. Our recruitment strategy is based on our experience of successful recruitment to multiple large community based studies of people living with chronic pain (BEAM, BEST, COPERS).[101, 113, 114]. We will seek to recruit around 75 general practices which will provide

a total practice population of 689,000. This will be supplemented by recruitment from study posters in GP practices and pharmacies. We will recruit practices in waves with clusters of practices in reasonable geographical proximity so that we can populate groups in a timely manner.

2.6.2 Classification interviews

Following receipt of baseline data and signed consent form there will be a telephone classification interview with a nurse. The purpose of this is two-fold. Firstly to ensure that participants do not have headache types other than migraine, tension type or medication overuse. Secondly to provide a classification of headache types in the study population to facilitate stratification of randomisation and reporting by headache type.

In the event that at the end of the nurse interview there is uncertainty about eligibility (i.e if the participant has another headache type) participants will be offered a second telephone interview with a doctor from the National Migraine Centre. In the event the doctor is satisfied they have an eligible headache type they will be eligible to be randomised into the study. In the event they are thought to have a different headache type they will not be eligible for the study. In the event they do not wish to have the second interview they will not be eligible for the study. We will provide information to the potential participant and their GP of the doctor's diagnostic assessment. In the event the doctor deems that urgent action is needed we will ensure the GP is informed within less than two working days. We will not collect any further questionnaire data from those excluded after consent and before randomisation. We will, however, seek data from their GP record at the end of study to identify final diagnosis of headache type.

2.6.3 Randomisation

The randomisation will be stratified by geographical locality (Midlands and Greater London) and headache type (six possible headache types; tension type headache, probable chronic migraine and definite chronic migraine with or without medication overuse headache) using minimisation. Randomisation will take place using an online application specifically developed for the CHESS Study by the Warwick CTU programming team. The study team, intervention providers and the participants cannot be masked to treatment allocation. Staff responsible for obtaining missing follow-up data will be blinded to randomisation.

We will cluster groups of 4-5 geographically close practices and aim to launch recruitment at around the same time in the practices. We will then randomise eligible participants who have provided consent in batches of around 20 so that we have sufficient participants to populate a group. This will help reduce any delay between randomisation and start of the intervention.

Participants will be randomised to either the relaxation group or self-management group and will be informed of randomisation allocation via a telephone call from the study team. Participants will also receive written notification of the randomisation outcome. The same information will also be sent to the participant's GP to notify them of randomisation into the study and a copy of the information provided to the participant to be filed in the patient notes.

In the event that, in error, two participants from the same household are randomised then to prevent cross-contamination one participant will be withdrawn from the study. This will be the second participant randomised. The study team will notify the participants via telephone and will still provide the second withdrawn participant with headache information based on the classification telephone interview completed prior to randomisation.

2.6.2.1 Post-randomisation withdrawals and exclusions

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the research study at any time (including follow-up) without providing a reason and without prejudice, if they so wish. Participants are informed of this in the participant information sheet. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. Data recorded up to the point of withdrawal will be included in the analysis. Should a participant decide to withdraw after the intervention commences, or should the investigator(s) decide to withdraw the participant, all efforts are made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete and final evaluation at the time of the participant's withdrawal will be recorded in the Case Report Form (CRF). If the reason for withdrawal is an Adverse Event (AE), monitoring of the participant will continue until the outcome is evident. The specific event must be recorded in CRF.

2.7 Trial treatments / intervention

2.7.1 Trial treatment(s) / intervention

The CHESS intervention is a group education and self-management programme (around 10 participants per group) facilitated by a trained CHESS nurse and allied health professional.

Those randomised to the intervention arm will be asked to complete a paper headache diary for a period of up to eight weeks to help the nurse understand their headache pattern during the one to one sessions. They will be booked in to attend the structured group sessions which will be run over two days, over two weeks followed by a nurse one to one consultation. The sessions will take place on weekdays and where possible, these sessions will run during school hours to accommodate those with children. The start time of group sessions one and two will be 10:00am and the finish time will be 3:00pm. The group sessions will be held in easily accessible venues in the community which have parking and/or near to public transport to allow participants easy access. Refreshments (tea and coffee) will be provided.

Following the second group session each participant will be booked in to attend a one to one appointment lasting up to two hours with the CHESS trained nurse to classify their headache type, discuss medication and lifestyle factors and finally to explore SMART goals. This discussion will be backed up by written information (for patient and GP), consistent with NICE guidance, to support shared informed decision making between the patient and their GP, about medication choices. All participants will be offered telephone follow-up for up to eight weeks. The frequency of these follow-up calls will be individually negotiated and agreed with participants. This will be discussed and agreed during the one to one session. The course structure is described in table 2.

The group intervention will be delivered using a range of methods including: group discussions, brainstorming, sharing narratives and experiences, problem solving, watching an educational DVD, role play and taster sessions. The detailed components of the intervention are highlighted in Table 3. The programme includes a range of behavioural change techniques including; barrier identification, general encouragement, instruction from the group facilitators, provision of feedback, and allowing opportunities for social comparison in the group.

Process for organising groups

Eligibility phase:

- As part of the eligibility call participants will be given the dates of the course and asked to confirm they can make both of the days. They will only be eligible if they can make both dates and agree to attend the sessions. If they are unable to make either of the days they will, where possible, be offered further course dates.

Post randomisation but pre course:

- Those that call to say they cannot attend day 1 of the course will be offered up to two further chance to attend another course. After this they will be advised to contact the research team should they wish to attend. The research team will then offer a course if it is within a suitable timeframe and one is available locally.

- If the participant informs the research team that they do not wish to attend because they have changed their mind then they will remain in the study as intention to treat and still receive questionnaires. The research team will send the participant the relaxation CD, mindfulness CD and the Living with Chronic Headaches DVD with a covering letter and instructions of use.

Day 1 of course:

- Those that have been booked in and do not attend will be classed as a DNA. The research team will attempt to call these participants to find out why they were unable to attend. Where possible the team will attempt to call those due to attend and then DNA in the first hour of the course starting, just in case they may have forgotten and can make the rest of the course.
- Those that call and cancel on the day will be offered up to two further opportunities to attend.
- If the participant informs the research team that they do not wish to attend because they have changed their mind then they will remain in the study as intention to treat and still receive questionnaires. The research team will send the participant the relaxation CD, mindfulness CD, the Living with Chronic Headaches DVD, and confirmation of the participant's headache classification including the relevant headache classification information sheet.

Day 2 of course:

- Those that have been booked in and do not attend will be classed as a DNA for that day. They will be contacted by the research team to see if they would like to be booked in for a one to one consultation with the nurse. If they are happy to be booked in they will be provided with the missed material from day 2 at that consultation and have the opportunity to ask any questions.
- If we are unable to contact the participants they will be classed as DNA.
- If a participant does not attend day 1 but turns up to day 2 they will be advised that they need to complete the first day of the course in order for the material on the second day to make sense. They will be encouraged to contact they research team to see if there are any forthcoming courses. If they are insistent on staying we will allow them to do so and the missed material will be covered during the one to one consultation.

Group size:

Where possible we will try and book groups to fill 12 confirmed participants. We anticipate a couple will cancel or not turn up on the day giving us our anticipated group of 10. Should there be any

difficulty with recruitment in a particular area we would still run the group if we had a minimum of 6 confirmed participants.

Table 2 - Course Structure

Approximate weeks	Course
1-8	Paper headache diary Participants complete a paper headache diary; as recommended by NICE ahead of their first appointment for a duration of up to eight weeks.[15]
8-9	CHESS Day one 10.00am – 3.00pm
9-10	CHESS Day two 10.00am – 3.00pm
11-13	One to one nurse consultation and follow-up For this population continuing support may be important, particularly for those with MOH who may find that their pain becomes much worse over the first few weeks after stopping regular analgesics. Nurses will agree with participants during the one to one if, when and how often they would like a follow-up call. Calls will be offered for up to eight weeks after the nurse consultation. During this time if the participants wishes to contact the nurse they will be instructed to contact the research team at the University of Warwick who will pass on their message.

Table 3 - Intervention components

Day	Modules	Content of sessions
1. Living, understanding and dealing with chronic headaches	1. Introduction to the course and each other	**Session 1**: Welcome and introductions **Session 2**: Course overview
	2. Understanding chronic headaches and acceptance	**Session 3**. Headache information and mechanisms **Session 4**. Acceptance of chronic headaches
	Taster activity – Relaxation and breathing	
	Lunch	
	3. Mind, body and pain link	**Session 5**. Impact of thoughts, mood and emotions on headaches **Session 6**. Headache cycle and breaking the cycle
	4. Dealing with unhelpful thought patterns	**Session 7**. Unhelpful thinking patterns: recognising and finding alternatives
	5. Summary	**Session 8:** Summary and reminders from day 1
2. Learning how to adapt and take control of your life with chronic headaches	1. Reflections	**Session 9**. Reflections from Day 1
	2. Back to basics	**Session 10**. Identifying barriers to change and exploring problem solving and goal setting **Session 11**. Lifestyle factors and impact on headaches
	3. Making headaches more manageable	**Session 12**. Managing stress and anxiety **Session 13**. Manging sleep better **Session 14**. Mindfulness and relaxation for headaches
	Lunch	
	Taster activity – Mindfulness practice	
	5. Treatment options	**Session 15**. Medication management
	6. Communication – explaining your headaches to others	**Session 16**. Relationships and communication with family, carers and friends **Session 17**. Communicating better with Health Professionals
	7. Future management	**Session 18**. Managing setbacks – what to do when things don't go to plan
	8. Summary	**Session 19**. Summary of course
3. One to one session with nurse	Session covers: • Classification assessment with headache diary • Discussion around medication • Lifestyle factors and personalised goal setting	

2.7.2 Control intervention

The control participants will be provided with a relaxation CD to use. The CD comprises of a progressive muscle relaxation track. It will be available in both CD format as well as an MP3 download from the CHESS website: www.warwick.ac.uk/chess. Additionally those in the control arm of the study, and their GPs, will be provided with the final outcome of the classification interview/s. Participants will also receive a brief advice sheet on treatment options that is consistent with NICE guidance. We note here that we are seeking to make broad classifications and not aiming to produce a final diagnosis and that our suggestions are purely advisory.

2.7.3 Compliance/contamination

We will record the number of sessions each individual attended including the follow up calls completed and their duration.

The researchers based at Warwick will have responsibility for quality control of the interventions. A checklist for fidelity of delivery and quality assessment will be developed and agreed by the study team. Members of the CHESS team will periodically make quality control visits to observe some of the group sessions. Quality assurance checks will be undertaken by the WCTU to ensure the integrity of randomisation, study entry procedures and data collection.

2.8 Process Evaluation

We have completed a formative process evaluation as part of the pilot study which has helped to shape and refine trial processes and recruitment. In the main study the process evaluation will be summative as well as explanatory. The intent is to report the process evaluation results prior to the main results in order to allow the team to assess if the analysis plan should be added to.

Understanding the content of an intervention is insufficient to understand why an intervention works. The context in which the intervention is delivered, including the process of delivery, and the physical and social environments influence its effectiveness.[115] This process evaluation examines the intervention in use and its initial impact. A number of authors have described the use of process evaluation in complex intervention trials, pointing out the value of being able to place findings into context, understanding both how the interventions are delivered, and how the social, political and physical context influences effectiveness.[115-118] In a recent large trial, which reported a negative outcome, a comprehensive, mixed method, process evaluation helped us to explain the outcome and place the results in context.[119,120]

We will adopt a mixed methods approach for this process evaluation.[115,121,122] The principal data collection method will be quantitative, whilst the qualitative data, will complement and illuminate the quantitative data, providing a depth and breadth of understanding. We will use the framework for process evaluation proposed by Steckler and Linnan including, context, reach, dose delivered, dose received, fidelity, and recruitment.[123] We will add to this an exploration of the experience of delivering and receiving the intervention to inform any future roll out of the intervention, and exploration of early impact of the intervention on participants.

The process evaluation will be independent of the main trial and it is good practice to provide results prior to the reporting of the effectiveness so as not to be influenced by them.[115] The initial report will be hypothesis forming suggesting areas where things have gone well or not so well.

Additional analyses may be carried out on the trial data informed by findings from the process evaluation.

The aims of the process evaluation are

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

Much of the process evaluation data will be based on routinely collected trial data (e.g. intervention registers). A measure of fidelity will be developed specifically for this trial.[124] In addition we will carry out observations, interviews and focus groups.

We will evaluate the following:

- Context: We will assess the context of the practices within the trial: rural/urban; demographics and socioeconomic indicators of the locality they serve; local health services relevant to headache (e.g. GP with special interest, specialist clinic access)
- Reach: Is the trial recruiting from the diversity of the population with headache within each practice?
- Dose delivered: How many interventions have we run? Why have interventions not been delivered?
- Dose received: Are participants attending? If not why not? What is the level attrition?
- Fidelity: Are we delivering the intervention as the protocol intended? Are the facilitators adhering to the protocol and are they doing this competently?
- Recruitment: Barriers and facilitators to the recruitment of practices and patients

Key components	Potential source of data	Type of data
Context	Census data Initial site visit	Demographic and socioeconomic characteristics of population served by the practice Qualitative data from site visit
Reach	Trial screening logs	Routine trial data e.g. numbers recruited, number declined, eligibility, classification categories, baseline characteristics
Dose delivered	Intervention team research diaries	Numbers of groups delivered/not delivered and why, location of groups
Dose received	Trial intervention attendance sheets	Attendance data
Fidelity	Intervention group observation Group audio recordings Intervention staff interviews /focus groups Participant interviews	Observation data Interview data

Recruitment	Recruitment staff research diaries Recruitment staff interviews	Text and verbal accounts of barriers and facilitators to recruitment
Experience of participating in the trial	Staff interview/focus groups Participant interviews GPs	Verbal accounts of the experience of; delivering or receiving the intervention and participating in the trial GP feedback form
Early impact	Participant interviews	Verbal accounts of impact on participant

Data collection process

Data for context, reach, dose delivered and dose received will be collected as part of the main trial data collection processes.

We will interview a purposive sample of up to 30 trial participants to explore the experience of; living with frequent headaches and its management, taking part in the trial and its initial impact. We aim to follow up the same people at three time points; baseline (prior to randomisation), after 4 month questionnaire (and completion of the 8 week telephone follow up period post intervention) and at 12 months (after the 12 month questionnaire). To ensure we attain a representative sample, if interview participants are not available for interview at follow up we will approach new participants.

To assess fidelity, we will audio record all group intervention sessions and one to one session from which we will take a sample of 10-15%. We will also observe up to 10% of the groups.

We will hold focus groups or individual interviews with members of the recruitment team and intervention team (separately) to explore their perceptions of the trial and its delivery.

Data analysis

Quantitative data will be entered onto the study database and appropriate descriptive statistics, charts, tables or figures will be produced. Qualitative data, all interviews and focus groups will be audio recorded and where necessary transcribed verbatim. Analysis will be by the framework method proposed by Richie and Spencer [125] and comparative analysis of the participant interviews across time.

2.8 Blinding

2.8.1 Methods for ensuring blinding

Allocation concealment will be maintained by using Warwick CTU's centralised randomisation service. All baseline data will be collected prior to randomisation.

Blinding will be impossible for participants and facilitators. However, where possible we will ensure that the intervention delivery team is separate from the data collection team.

Our primary outcome is a participant completed outcome. Participants will, inevitably be aware of their treatment allocation. We will develop and sign off a detailed pre-specified statistical analysis plan before any outcome data are accessed for analysis.

2.9 Concomitant illness and medication

2.9.1 Concomitant illness

At the point of searching practice databases the GP will screen participants to identify those whom it would be inappropriate to approach. If an illness influences the potential participant's eligibility to continue in the trial the investigator will be informed and they will be excluded from further participation.

2.10 End of trial

Although the study is low risk the Sponsor and CIs reserve the right to terminate the research on safety grounds at any time. Before terminating the research, the sponsor and investigators will ensure that a review of the overall benefit-risk analysis confirms the balance to be no longer acceptable. Should termination be necessary both parties will arrange the relevant procedures which include informing the Research Ethics Committee. On termination of the research, the sponsor and CI's will ensure that adequate consideration is given to the protection of enrolled participants interests.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing if the trial has been concluded or terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection.

Table 4 - Trial assessments

	Contact points: enrolment, intervention and data collection									
Contact	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window (No. Weeks ± No. Days)	**Initial Contact**	**Eligibility**	**Consent**	**Baseline**	**Classification**	**Randomisation**	**Intervention**	**4 month follow up**	**8 month follow up**	**12 month follow up**
PIS + expression of interest following GP screen	✓									
Inclusion/exclusion criteria		✓	✓							
Telephone Classification Interview					✓					
Start electronic headache severity diary (mobile app)		✓								

	Contact points: enrolment, intervention and data collection									
Contact	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window (No. Weeks ± No. Days)	**Initial Contact**	**Eligibility**	**Consent**	**Baseline**	**Classification**	**Randomisation**	**Intervention**	**4 month follow up**	**8 month follow up**	**12 month follow up**
Finish electronic headache severity diary (mobile app)										✓
Written Information						✓				
Intervention							✓			
Adverse events							✓	✓	✓	✓
Questionnaire				✓				✓	✓	✓
GP records										✓

4. ADVERSE EVENT MANAGEMENT

Our experience across multiple studies of group interventions is that adverse events directly attributable to interventions of this type are rare. This includes events during the session, e.g. severe psychological disturbance, or a fall during travel to and from the venue. We will manage any suspected adverse events during group or one to one sessions in line with Warwick CTU's standard operating procedures.

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with this treatment/intervention. An adverse event can be any unfavourable and unintended sign, symptom, or disease that occurs during the time a participant is involved in the research (i.e. 12 month research period) *whether or not* it is considered to be related to the intervention.

We have all necessary measures in place to handle adverse events appropriately. The facilitators' manual will include an adverse events flow diagram to assist. Where possible the facilitators will make necessary adjustments to accommodate participants experiencing an adverse event. We will conduct risk assessments for the suitability of the venues.

Any mild or moderate levels of emotional distress as a result of discussing experiences of living with chronic headache during the delivery of the intervention will be recorded in the Case Report Form (CRF).

Any short term increase in headaches as a consequence of medication withdrawal will be captured using the smartphone app (or paper diary if appropriate).

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

For ay SAEs which occur during the research study we will follow the appropriate CTU SOPs.

4.2 Reporting SAEs and SUSARs

Any SAEs which occur as a result of attending or travelling directly to / from the study intervention, must be reported by the facilitator to WCTU via email or telephone within 24 hours of becoming aware of its occurrence. SAEs will be reported using the SAE form provided with the intervention materials. The trial manager will liaise with the facilitator to compile all the necessary information. The trial coordinating centre is responsible to reporting serious adverse events that are deemed to be at least a possibly related and unexpected to the sponsor and REC within required timelines. All SAEs will be recorded for inclusion in annual reports to REC.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Relationship to trial medication	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

5. DATA MANAGEMENT

Submitted data will be reviewed for completeness and entered onto a secure, backed-up bespoke database held at WCTU which will be accessible only by authorised members of the team. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 2018. Participants will be identified by a unique trial identification number, and their initials in order to maintain anonymity. Handling of personal data by the research team will be clearly documented in the participant information sheet and consent obtained.

Participant trial identification numbers will be generated by the WCTU programming team prior to the mail out from the GP practice and a unique trial identification number will be assigned to each patient on the mail out list following the GP screen. The participant trial identification number is

documented in the bottom right hand corner of the 'expression of interest' form marked 'for office use only'. This trial identification number will be recorded on all CRFs throughout the study.

Personal identifying information will be held securely at WCTU, when received in response to invitation. This will include a copy of the participant 'expression of interest' form and personal contact details of trial participants will be needed to communicate confirmation of randomisation allocation and to send out follow up questionnaires. This information will be filed separately from all other trial information.

In the unlikely event a disclosure is made which jeopardises the safety of the participant or another person, this will be reported to the CI who will decide on the appropriate action. In such circumstances the participant should be informed that the information will be shared with another party and the nature of the information to be shared, unless the CI considers it to be unsafe.

5.1 Data collection and management

The Case Report Forms (CRFs) will be developed to collect all required study data. These will be returned to the study team at Warwick Clinical Trials Unit. A member of the team will check the data and input into a study specific database designed by the Programming Team at the WCTU. We will email participants a week prior to sending out follow up study questionnaires to notify them that the questionnaire is due to arrive. Follow up study questionnaires at four and eight months will be posted to participants with a £5 high street voucher. The 12 month questionnaires will be posted to participants with a £10 high street voucher as a token of our appreciation. A CHESS Study pen will be sent with the reminder postal questionnaires at all three time points as an incentive to complete. A third and final reminder will be posted out to participants, this questionnaire will be the key clinical outcomes only. If there are missing data (for our key clinical outcomes), this will be followed up with the participant who completed the form, as soon as possible. We will phone the participant and enter the correct information onto the form, this will be initialled and dated.
Particular procedures will be followed to resolve missing/unreturned questionnaires as detailed in the study Data Management Plan.

Follow ups are classed as 'closed cases' when either a questionnaire is received from the participant or the above procedure has been followed to the end without collection of data, in which case the participant is classed as a 'non-responder' and the case is closed.

All (paper) data will be held securely in locked cupboards by a member of the research team at WCTU or QMUL for the baseline questionnaires, intervention evaluation sheets, postal questionnaires at four, eight and 12 months. After all the data have been entered onto the database and main analyses completed, the original of the CRF will be securely stored in archiving facilities approved and overseen by the Unit Quality Assurance manager.

5.2 Electronic headache severity diary

We are working with Clinvivo Ltd a University of Warwick spin-out Company specialising in electronic data collection, to capture data on headache frequency, duration and severity electronically using a smartphone App. The data from the questions in the electronic diary will be numerical and downloaded into a WCTU database.

Data are transferred from the client device to the server via an SSL connection. The server immediately encrypts the data using a randomly generated 256-bit AES (Advanced Encryption Standard) key. The AES key is then encrypted using a public key that is specific to the study. The server only stores the encrypted data and the encrypted 256-bit key. The AES key can only be decrypted using the study-specific private key, which is never stored on the server.

When the data are transferred to the study manager, it is decrypted on a separate computer by a Clinvivo employee using the study-specific private key. It is then exported to the agreed file format (e.g., Excel, CSV, etc.) and is then encrypted using the OpenPGP standard (with a 2048-bit public key provided by the study manager) before being transferred to the study manager.

5.3 Paper headache diary

Data from the paper headache diary will be entered into the WCTU database.

5.4 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.5 Data storage

All essential documentation and study records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Data will be stored on University secure servers. Any data transfer would be in accordance with SOPs and require data sharing agreements to be in place. Study related document will be made available for internal monitoring and audit activities. Access to the datasets will be restricted to authorised personnel only.

5.6 Data access and quality assurance

All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with participant-information will be held in secure, locked filing cabinets within a restricted area of WCTU. Participants will be identified by a trial ID number only. Direct access to source data/documents will be required for trial-related monitoring. For quality assurance, the data and results will be statistically checked. A full data management plan will be produced by the Trial Coordinator and statistician to outline the data monitoring checks required.

5.7 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

5.8 Power and sample size

For the purposes of our sample size calculation the primary clinical outcome is the mean HIT-6 score at 12 months post randomisation between the self-management group programme and the relaxation therapy (control arm). The HIT-6 outcome measure is in a continuous scale with higher value indicates more severe impact on daily life. From our systematic reviews we anticipate a worthwhile difference to be 2.0, i.e. mean outcome in the control arm is 2.0 units higher than for the intervention.[44] From our feasibility trial (114 participants), the standard deviation of HIT-6 at baseline was 6.87.

Participants are randomised to either the self-management group or relaxation therapy. In this design, there may a clustering effect in the self-management group and not in the control arm. Therefore, the sample size calculation has to consider the feature of these partially nested data. Based on similar trials [101] we assume that the intra-class correlation coefficient (ICC) is 0.01. As stated in Section 2.7.1, the average size of the self-management programme is 10.
The required sample size was estimated using Moerbeek's method to account for grouping in one arm.[126] To detect a between group difference of 2 with standard deviation of 6.9, equivalently the standardised effect size is 0.29, and assuming that the ratio of the total variance in the self-management group to the relaxation therapy is 1 at two-sided 5% significance level and at least 90% power, the sample size required is 523 participants (253 in the relaxation group and 270 in the self-management group).

To account for a loss to follow-up of 20% the sample size required is 654 with 316 to the relaxation arm and 338 to the self-management programme.

Based on the feasibility study results the overwhelming majority of those recruited, approximately 95%, will have either definite or probable chronic migraine and 5% will have chronic tension type headache only. We want to be able to draw definite conclusion on this specific subgroup of chronic migraine. Therefore, we will base our sample size and primary clinical outcome on the population with probable or definite chronic migraine. Therefore, based on 95% of our sampled population with probable or definite chronic migraine and accounting for a 20% loss to follow-up, the sample size we would require is 689 with 333 to the relaxation arm and 356 to the self-management programme.

In consultation with the DMC we would like to review the sample size around halfway through recruitment to ensure we have recruited sufficient participants with probable or definite chronic migraine and with within trial data on the variance of our primary outcome at baseline. This review will be based on the headache classification and actual baseline standard deviation of our sampled population. We might also need to recruit some additional participants to ensure that the final group sessions at each site are adequately populated.

5.9 Statistical analysis of effectiveness and harms

Participants' characteristics and reported outcomes will be summarised as mean and standard deviation (for continuous data) or frequency and percentage (for categorical data) by treatment arms. Difference between baseline and the three follow-up time points (4-, 8- and 12-month post randomisation) will be computed for the primary and secondary outcomes by treatment arms.

The primary analysis approach will be intention to treat i.e. the data will be analysed according to the treatment the participant was originally allocated to, irrespective of what they actually received. We will explore the possibility of carrying out a complier averaged causal effect (CACE) analysis as a sensitivity analysis. Our primary clinical analysis will be the overall difference between the self-management therapy (intervention) and the relaxation therapy (control) groups with a 95% confidence interval (CI) in the population with either probable or definite chronic migraine – if the proportion of participants with tension type headache is ≤ 15%. The hypothesis testing of the primary outcome will be two-sided at the 5% level and the main analysis will estimate the treatment effect using a multilevel model (the model used to design this main trial). We will also present overall results for those with all headache types. Our experience is that NICE, was specifically interested in data on specific headache types; rejecting data that reported data on mixed population of people with chronic headaches. We will, therefore in addition to our primary analyses present the results (mean difference and 95% CI) for each of the three headache types with or

without medication overuse headache separately, and present results for those with or without medication overuse separately to facilitate future meta-analyses and inform future condition specific guidelines. All analyses will be adjusted by the baseline stratification factors (types of headache and geographical locality), sex and age.

Similar analyses will be performed for all the other secondary outcomes. Pre-specified subgroup analyses using formal statistical tests for interaction will examine whether baseline anxiety, depression and severity are moderators of treatment effect.[127] We will assess the level of missingness in the primary outcome and if required, we will use appropriate multiple imputation techniques to impute data and estimate the treatment effect as a form of sensitivity analysis. A full analysis plan, including all primary and secondary analyses, will be written and signed off prior to conducting the final analyses.

5.10 Health Economic Evaluation

Our economic evaluation will be conducted alongside the trial and we will initially adopt a one year time horizon from both an NHS and personal social services perspective and a broader societal perspective to estimate the cost-utility of the intervention. Resource use data will be collected to explore the costs of the delivery of the intervention and to estimate the key cost drivers. This will mainly consist of visits to the GP practice, medication usage and any adverse events or length of stay in the hospital. In terms of costs to society, we will estimate time off work and any productivity losses associated with chronic headaches. Resource use information will be collected using self-completed postal questionnaires completed at four, eight and 12 months after randomisation, as well as the use of routine health service data collected from general practice records. Resources will be valued using national estimates of unit costs such as the Prescription Cost Analysis database or the Unit Costs of Health and Social Care. [128] Preference-based health-related quality of life outcomes will primarily be assessed through the completion of the EQ-5D-5L at each follow-up point.[129] Quality-adjusted life-years (QALYs) will be calculated as the area under the baseline-adjusted utility curve, and will be calculated using linear interpolation between baseline and follow-up utility scores.

The results of the economic evaluation will be presented using incremental cost-effectiveness ratios, expressed in terms of incremental cost per QALY gained, and cost-effectiveness acceptability curves generated via non-parametric bootstrapping.

More extensive economic modelling using decision-analytic methods will extend the target population, the time horizon to 5 years as the long-term natural history is unclear and the decision context, drawing on best available information from the literature together with stakeholder consultations to supplement the trial data. Longer-term costs and consequences will be discounted to present values using nationally recommended discount rates recommended for health technology appraisal. We will use probabilistic sensitivity analysis to estimate the impact of uncertainty over model parameters. We will also use simple sensitivity analysis to assess the robustness of the results to changes in deterministic parameters such as medication dosages, costs, discount rate and time horizon for patients presenting with chronic headaches. We will also explore cost-effectiveness of the intervention by conducting subgroup analyses for the different headache types.

6. TRIAL ORGANISATION AND OVERSIGHT

6.1 Sponsor and governance arrangements

The University of Warwick will act as Sponsor for the study. University policies and SOPs will be adhered to.

6.2 Regulatory authorities/ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by Warwick Clinical Trials Unit/CHESS Study team.

Any substantial protocol amendments will be notified to all relevant parties for approval.

6.3 Trial Registration

This trial will be registered with an International Standard Randomised Controlled Trial Number (ISRCTN) Register.

6.4 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol. Confirmation of Public Liability Insurance will be required for all non NHS venues used for the delivery of the intervention.

6.5 Trial timetable and milestones

	Year 3				Year 4				Year 5			
	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
Main RTC												
Practice Recruitment												
Participant Recruitment												
Intervention Delivery												
Follow-up												
Analysis and write up												

6.6 Administration

The trial co-ordination will be based at WCTU, University of Warwick. Trial coordination for the London area will be based at QMUL.

6.7 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from

management meetings will be referred to the Programme Steering Committee or Investigators, as appropriate.

6.8 Programme Steering Committee (PSC)

The trial will be guided by a group of respected and experienced personnel and trialists.

as well as at least one 'lay' representative. The PSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial.

The membership of the PSC is shown on page 7.

6.9 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the PSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 8.

DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

6.10 Essential Documentation

A Trial Master File will be set up according to WCTU SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

We will perform a risk assessment and produce a monitoring plan in line with the level of risk identified.

8. PATIENT AND PUBLIC INVOLVMENT (PPI)

We have had substantial patient and public involvement in the feasibility phase of this study. Lay members were involved in the development of the classification interview, development of the intervention and steering of the study via the independent programme steering and trial management group.

Our trial management group comprises of our lay co-applicants who are representatives of three leading UK migraine charities (The Migraine Trust, Migraine Action, and National Migraine Centre).

We have developed a lay steering group who are and will be collaboratively involved during the study. At key points in the programme we will approach the lay steering group for input.

9. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Programme Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses, academics and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

Scientific presentation and publications:

The findings from this trial will inform clinical practice on the identification and management of patients with chronic headache. In addition to the main NIHR report publication, we aim to present findings to the professional community at scientific meetings and relevant international conferences. We will publish the results in high quality peer-reviewed journals and have requested funding for open access publishing.

Research impact: Participating centres/healthcare professionals:

The study team will work with the CCGs and CRN, to ensure effective dissemination of our findings to healthcare professionals. For the healthcare professionals involved in the study we will disseminate results of the study through the study website. We will also host a meeting to present the trial results to commissioners and clinicians. This process has been used in previous clinical trials and has proved a very popular format, allowing two-way communication between clinicians and researchers. These meetings ensure that clinical teams are informed of trial results and thanked for their valuable contribution. Importantly, it also allows for implementation of clinical changes based on trial findings prior to formal peer review publication.

Research impact: participants, patients and general public:

For the participants, we will provide a written lay summary of the findings and also publish these on a study specific website; with contact information should they wish to discuss the findings. Our charity partners will be involved with feedback to the organisations they represent.

Research impact: NHS and development of training to support roll-out of the intervention:

To facilitate the implementation of the intervention within the NHS the study findings and intervention will be made available to NHS healthcare professionals, managers, policy makers and commissioners. In addition to the NIHR report, a summary of the study findings will be available via a study specific website so that health care professionals can provide evidence to NHS managers and commissioners of the clinical and cost-effectiveness of the intervention.

To enable roll-out of the intervention the facilitators' manual will become a resource.

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