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TITLE

What is the comparative clinical and cost-effectiveness of pharmacological treatments for adults with chronic migraine?

PROJECT TEAM

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Detailed Research Plan

What is the problem being addressed?

Migraine is the world's 3rd commonest disabling disorder[1] and the top cause of years lived with disability in those aged 15-49.[2] Migraine affects 15% of UK adults, most commonly young adults with work and family commitments.[3] It costs the UK over £1.5 billion per year.[3] Chronic migraine, defined as headaches on 15 days or more a month, for more than three months with features of migraine on at least eight of those days, is a profoundly disabling condition. Around 2-4% of the population meet an epidemiological definition of chronic headache.[4, 5] In our recent trial of supportive self-management for those living with chronic headache, 727/742 (98%) of those assessed for inclusion had migraine. This group have the potential to benefit from effective prophylactic drugs to prevent migraine attacks. Our patient-partners describe it as a condition that 'redefines, and can destroy, work and family life'.

Pharmacological treatments are available for the prevention of migraine, but the current state of the evidence is unhelpful for patients and clinicians making decisions about treatment choice. The picture regarding cost-effectiveness of different pharmacological treatments is also unclear. With the advent of expensive calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) such as erenumab, fremanezemab, and galcanezemab, there is a pressing need to compare the clinical- and cost-effectiveness of drugs to treat chronic migraine.

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

In 2011 the World Health Organisation (WHO) called for action to address the 'worldwide neglect' of headache disorders,[6] yet migraine remains a leading cause of global disease burden.[2, 7, 8] Our 2017 meta-ethnography identified the profound impact of living with the 'spectre' of headache. Key themes included loss of control over one's life, strained relationships, and social exclusion.[9] The burden on family, and the care burden for those living with a person with migraine increases with headache frequency.[10]

The direct and indirect health care costs of chronic migraine are 3-4 times as high as episodic migraine.[11] Episodic migraine is diagnosed in people with migraine who have less than 15 headache days a month. People with migraine miss, on average, 10.2 work-equivalent days per year (absent on 4.4 days and reduced productivity 11.4 days).[11] Higher work-related difficulties are associated with chronic migraine (vs. episodic migraine).[12] The burden on family, and the care burden for those living with a person with migraine increases with headache frequency.[10]

This research is timely given the increasing availability of CGRP MAbs; usually given as monthly injections.[13-16] The British National Formulary (BNF) price for typical three-month course of the CGRP MAbs erenumab, fremanezemab and galcanezemab are £1,160 to £2,319, £1,350, and £1,800 respectively. Whereas, the oral drugs recommended by National Institute for Health and Care Excellence (NICE) for migraine prophylaxis; Amitriptyline, candesartan, propranolol and topiramate cost, £3.15 to £7.98, £4.98 to £9.48, £4.08 to £12.90 and £1.34 to £9.11 for three-months treatment respectively.[17]

Evidence synthesis and an economic model is very much needed on prophylactic medications for chronic migraine. It is important for both patients and healthcare professionals to know the comparative effectiveness and cost-effectiveness of older oral drugs and newer injectable treatments.

Current treatments and existing evidence

The existing literature is of little help to clinicians and patients making decisions about which drugs to consider. Several drugs, e.g., topiramate, propranolol, amitriptyline, candesartan, and valproate are used as chronic migraine prophylactics. The first two are recommended by NICE and Scottish Intercollegiate Guidelines Network (SIGN) based on mixed quality evidence.[18, 19] Weaker evidence supports use of amitriptyline, recommended by both, and for candesartan and valproate, recommended by SIGN, but not by NICE. Overall, the available evidence base is poor quality, extrapolated almost exclusively from trials on episodic migraine. Very few studies specifically investigate chronic migraine.[18-20] Therefore, we cannot assume that drugs shown to reduce the number of headache days in people with episodic migraine will have a positive effect on the long-term disability caused by chronic migraine.

The most recent evidence on this topic was produced by Jackson et al (2015)[21] who pooled evidence from numerous randomised controlled trials (RCTs) to explore potential differences for continuous and dichotomous outcomes, for both chronic migraine and episodic migraines. Their systematic review identified thirteen trials of oral drugs (n=1,412, range 28-328, mean 101) which included people with chronic migraine (five also randomised people with chronic daily headache or chronic tension-type headache).[22-34]

Jackson and colleagues (2015) concluded that "these comparisons have been somewhat haphazard, and many important potential comparisons have not been made". This 2015 study needs to be updated using methods which are able to synthesise the overall evidence for prophylactic medications for use in people with chronic migraine, for example, using a network meta-analysis (NMA).[21]

An up-to-date overview of the relative benefits, harms, and costs of prophylactic medications to treat chronic migraine is needed. Without this, the only good evidence available to guideline producers will be for expensive CGRP MAbs, which have a modest additional effect size compared to placebo.[35, 36] A recent study by Forbes et al (2020)[37] found that compared with placebo in the seven chronic migraine RCTs (n = 5,292), the additional pooled reduction is monthly migraine days from CGRP treatment was 2.24 days (95% CI 1.79 to 2.67). They further estimated that 68% of the apparent reduction in headache days in the intervention groups was due to contextual effects. In other words, people in control group would expect an average reduction in monthly headache days of four and half days with intervention group gaining an additional reduction of two and a quarter days; six and three-quarter days in total. Thus, it can be difficult to judge clinically if treatment has been effective for an individual. It is unclear how the effect sizes for CGRP MAbs compare with the effect size of more established oral drugs or botulinum toxin type A (BTA) injections. Nevertheless, pressure is increasing on the NHS to provide these expensive treatments to people in need.[38]

Clinical effectiveness scoping review

We undertook exploratory Medline searches to assess the scale of the literature in relation to our work packages. Whilst our scoping searches suggest that a sensitive, systematic search for RCTs of migraine/headache treatments would retrieve a few thousand records, very few of these are relevant to chronic migraine specifically, and some of these are very small trials. We anticipate that no more than 40 studies would meet the inclusion criteria of our clinical effectiveness systematic review and network meta-analysis.

The evidence on oral prophylactic drugs and the most recent trials of CGRP inhibitors is mainly limited to just a single parameter: headache days. The various adverse events caused by these drugs make it unclear how to judge overall effectiveness.[21] Our recent work developing a core outcome set for headache trials indicates that quality of life (QoL) is at least as important to patients,[39] but this important parameter has not been the focus of much previous research. Reduction of headache days may not provide the anticipated improved QoL if the side-effects of prophylactic drugs are deleterious. Reducing the impact on QoL has received less attention in migraine research and is considered just as important as reducing headache days by our patient-partners.[11, 40]

Adverse events scoping review

Our decision to focus on adverse events (AEs) for WP2 came as a result of conversations with our patient-partners, who tell us that side-effects of treatment are a barrier to using otherwise effective drugs. This is supported by the literature, which shows a complex picture around side effects and patient preferences. Depression, memory loss, and weight gain are the least well accepted side-effects of migraine prophylactics (the latter especially amongst women).[41] A 2019 choice experiment identified that participants wished to avoid 10% weight gain more than they wished to avoid thinking and memory problems.[42] Published adverse event data is included in the summary of product characteristics, and elsewhere in guideline documents. For example, Valproate is usually restricted to men and post-menopausal women and is not used by a large proportion of migraine sufferers such as women of childbearing age, as children exposed to Valproate in the utero are at high risk of serious developmental disorders and congenital malformations.[19, 43] Whereas, Topiramate can reduce efficacy of hormonal contraceptives and is teratogenic. Cognitive adverse effects and depression are also common side effects of Topiramate.[19] What is less clear is the incidence of common AEs specifically when used for chronic migraine prophylaxis. In particular effects on weight and cognitive functioning that are important to people with migraine.[41] These data are needed to feed into our *de novo* economic model which we will produce in work package 4. Clinical effectiveness alone will not provide the full picture or provide useful findings for clinicians and patients making decisions about prophylactic treatment options. Apart from the recent trials of CGRP MAbs adverse events are poorly reported. Based on our scoping review few chronic migraine studies will provide any useable adverse data (n<25). For this reason, we will extend our inclusion criteria for adverse event analysis to include trials with mixed populations and episodic migraine studies, that would otherwise meet inclusion criteria for the effectiveness analysis. This will allow us to give a robust estimate of incidence of adverse events when used to prevent migraine.

Cost-effectiveness scoping review

A previous review Yu et al (2010)[44] examined the cost-effectiveness of pharmacotherapy for acute migraine prevention in a primary care setting. A decision-analytical model was constructed which added five treatments (amitriptyline, topiramate, timolol, divalproex sodium/valproate, or

propranolol) to abortive therapy compared with abortive therapy alone. Yu and colleagues (2010)[44] found that these preventive medications appeared to be cost-effective. However, this outdated study does not include CGRPs MAbs and BTA. Furthermore, the published paper did not conduct a full systematic review so potentially relevant evidence on the cost-effectiveness of prophylactic drugs for chronic migraine may have been missed and also any relevant published studies will not have been quality assessed. Moreover, the model is based on a societal perspective and not a healthcare perspective as recommended by NICE in their reference case analysis.[45] Based on our scoping review we anticipate no more than 15 cost-effectiveness studies of use of prophylactic drugs for chronic migraine. We did not identify any within trial cost-effectiveness studies.

Our study will provide high quality, robust evidence about the clinical and cost-effectiveness of, and AEs associated with, the various preventative drug treatments available for chronic migraine. The outcome of the three reviews will have direct impact on patients, clinicians, policymakers, and researchers who currently do not have this comparative information available to make informed treatment choices. We will also seek consensus about future research recommendations into drug treatment of people with chronic migraine.

Research question/aims/objectives

The overall study aim is:

- To review and compare the clinical and cost-effectiveness of drug treatments for adults with chronic migraine.

We have identified five Research Questions (RQ) which align to each component work package:

1. What is the comparative effectiveness of prophylactic drugs for chronic migraine?
2. What are the comparative incidences of adverse events of prophylactic drugs used for migraine?
3. What is known about the cost-effectiveness of prophylactic drugs for chronic migraine?
4. Which prophylactic drugs for the management of chronic migraine are the most cost-effective?
5. Based on our findings what should the research recommendations be?

Project Plan

There are five work packages (WPs) encompassing: three systematic reviews and a network meta-analysis, development of an economic model, and consensus work to develop research recommendations. This project will provide a rigorous and exhaustive assessment of the findings of the current literature and ensure that future research is relevant and meaningful to people with chronic migraine and their health and care providers.

WP1 we will conduct a systematic review and NMA of the clinical effectiveness of prophylactic medications for treatment of chronic migraine. Few syntheses of the migraine prophylaxis literature have targeted specifically at chronic migraine. No studies have produced an overall synthesis of the effect of prophylactic medications for chronic migraine using NMA. To map onto the core outcome set produced by some members of this research team, we will have two main outcomes; Headache/migraine days, and headache-related QoL. Other outcomes that may be reported include overall health-related QoL, acute treatment use, health service activity, days lost from usual activities,

health care usage, headache severity and duration.

WP2 we will conduct a systematic review of the incidence of adverse events (AEs) and use evidence from studies of both chronic and episodic migraine. Our patient-partners tell us that side-effects can be a barrier to using otherwise effective prophylactics for people with migraine. However, little attention has been given to this topic in the published literature. It is essential that the comparative incidence of AEs of prophylactic drugs is established for both the development of our economic model and to inform the treatment options for patients and healthcare professionals.

WP3 we will conduct a final systematic review assessing the cost-effectiveness of prophylactic medications used for treatment of chronic migraine. Little is known about the comparative cost-effectiveness of chronic migraine prophylaxis, but this is key for understanding the impact treatment choices have on the health service.

WP4 will be development of an economic model comparing prophylactic drugs for chronic migraine.

WP5 will bring together people with chronic migraine and clinicians in order to feedback the findings of our reviews and identify and prioritise research recommendations. This will enable translation of our research findings into useful recommendations for research priorities, grounded in the perspectives of both people with chronic migraine and headache specialists.

Systematic review methods used in WP 1-3

Search strategies will be based on the approach described in the Cochrane handbook,[46] these will be developed by an information specialist (AB), in collaboration with the health economists (RF2, HM, FA), the clinical effectiveness reviewers (RF1, AG) and the clinical experts (MM, CD, MU). For WP1 and WP2, we will systematically search the following healthcare databases: MEDLINE All (Ovid interface, 1946 to latest daily update), Embase (Ovid, 1947 to latest daily update), Cochrane CENTRAL (Wiley, current issue), Science Citation Index Expanded (Web of Science, 1970 to present) and Global Index Medicus (WHO, incorporating AIM, IMEMR, IMSEAR, LILACS and WPRO). We will also search trial registries via ClinicalTrials.gov, and the WHO ICTRP Portal, to identify relevant ongoing and/or unpublished studies. For WP3, we will search: MEDLINE All (Ovid interface, 1946 to latest daily update) Embase (Ovid, 1947 to latest daily update), EconLit with Full Text (EbscoHost), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) Database (both via CRD), International HTA database (INAHTA), Cost-Effectiveness Analysis Registry (Tufts Medical Center) and EconPapers (RePEc). Database searches will be supplemented with additional, targeted, iterative internet (Google) searches for economic evaluations and cost effectiveness studies. Furthermore, we will look at the websites of leading reimbursement agencies (e.g. NICE, Scottish Medicines Consortium (SMC), All Wales Medicine Strategy Group (AWMSG), Canadian Agency for Drugs and Technology in Health (CADTH)) for any relevant information they may have for the economic model in WP4.

We will construct a broad search strategy based on the migraine/headache population and prophylactic drug interventions of interest. Searches will combine keywords and, where appropriate, thesaurus (MeSH/EMTREE) terms, and will be tailored to the different search interfaces. A sensitive filter for RCTs will be added to the MEDLINE, Embase and Science Citation Index searches for the

clinical effectiveness and adverse effects reviews (WP1 and WP2). A filter for cost-effectiveness studies/economic evaluations will be added to the MEDLINE and Embase searches for the cost-effectiveness review (WP3). No date or language limits will be applied. Draft MEDLINE search strategies are available from the authors upon request. These will be checked by another Information Specialist (not otherwise involved in the project) for any omissions or errors in spelling, search syntax, structure and use of MeSH headings, before being adapted for the other databases. Records retrieved by database searches will be exported into EndNote X9, where duplicates will be systematically identified and removed.

Additional, pragmatic searches will be run in MEDLINE, Embase and the Cochrane Database of Systematic Reviews to identify recent systematic reviews of prophylactic migraine treatments. The reference lists of these and of the NICE, SIGN and American Headache Society guidelines will be checked for further studies meeting our inclusion criteria. Authors of key studies will be contacted and asked for details of any articles (e.g., reports, papers published and unpublished) not identified through our search strategy. We will do forward and backward citation tracking from key papers of included studies, using Science Citation Index (Web of Science), possibly supplemented by other sources and/or manual reference list checking where Science Citation Index coverage is judged to be insufficient.

On completion of the searches and removal of duplicates, two reviewers (RF1, RF2) will independently assess the retrieved citations against our inclusion/exclusion criteria for each RQ. The same set of results (identified by the search for RCTs) will be screened against the different inclusion criteria for the clinical effectiveness and adverse effects reviews (WP1 and WP2). At each screening stage, disagreements will be resolved through discussion or by a third reviewer (AG). Data extraction will be completed by the same two reviewers independently for each RQ using a pre-specified and piloted data extraction forms. We will use forward and backward citation tracking to ensure we have included outputs related to each study.

All reviews will follow the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines,[47] and we will publish protocol papers using the PRISMA-P guidelines[48] and register them on PROSPERO.

We plan to assess and communicate the degree of certainty of our synthesis findings. We will do this using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[49] Using GRADE will enable us to develop and present summaries of the evidence synthesises and generate recommendations on the certainty of our findings (very low, low, moderate, and high) which take into account risk of bias, imprecisions, inconsistency, indirectness and publication bias.

WP1: Systematic review and network meta-analysis of effectiveness. Co-leads: AG, FA

RQ: What is the comparative effectiveness of prophylactic medications (singular or in combination) for chronic migraine?

We will systematically review randomised controlled trials of selected prophylactic drugs for chronic migraine, including CGRP MAbs and BTA compared to placebo or other drugs using the review methods outlined above. Decisions about what information to include in the NMA will be informed by

its relevance to the decision problem and sufficient similarity across studies (e.g., patient characteristics and study design) to reduce the risk of violating the underlying assumptions of transitivity/coherence when pooling direct and indirect evidence across studies. We will use an iterative process and refer to the Cochrane handbook[46] to identify studies and treatments for inclusion in the NMA. We will define an initial *core set* of migraine treatments meeting the criteria for prophylactic use in chronic migraine in the UK and include trials of such treatments in a chronic migraine population. Drugs not meeting the criteria for the core set will be considered for inclusion in a *supplementary set* of treatments.[50] Only if necessary, and scientifically robust, will we extend the network to include supplementary treatments. We will derive an internally consistent set of treatment effects from this evidence base by fitting a generalised linear model NMA.[51] We will fit both fixed and random effects models and select the best fitting model based on model fit assessments and magnitude of the between-study variation in the treatment effect. Statistical heterogeneity will be quantified using the between-study standard deviation and I^2*-statistic.* The between-study standard deviation gives a direct measure of variance in the treatment effect across studies,[50, 51] whilst the I^2*-statistic* measures the proportion of variance across studies that is due to differences in population characteristics.[52, 53] Where we find evidence of substantial heterogeneity in the data, we will use network meta-regression to identify the characteristics of the study population that could explain this heterogeneity and identify subgroup of patients mostly likely to benefit from treatment. We will also test for consistency in the evidence and explore the impact of effect modifiers using subgroup analysis and network meta-regression.[54, 55]

Population: People with chronic migraine. For the main analysis, all RCTs will be included. For a sensitivity analysis, we plan to exclude studies with, an average of fewer than 100 participants per arm, in each pairwise comparison, to avoid risk of low-quality studies contributing disproportionally to our overall conclusions. With 90% follow-up, a trial with 50 participants per arm would be powered to show an implausible effect size of 0.5 indicating that any smaller trial is unlikely to have been well designed.

Just including studies where all participants meet ICHD-3 criteria for chronic migraine runs the risk of substantially reducing pool of available studies. Many older studies were performed before these criteria were developed. Even recent studies are not always clear on the definition used for chronic migraine. Trials may also include a mixture of people with chronic migraine and frequent episodic migraine. For these reasons we will include all studies that are predominately of people with symptoms consistent with chronic migraine. For each included study we will report the entry criteria as presented by the original authors, and any relevant descriptors of population included in our final report. If appropriate we will seek clarification from the original authors. Two clinical team members (MM/MU) working independently will assess RCTs for inclusion against these criteria. Any disagreement not resolved in discussion will be arbitrated by a third clinical team member (CD). If data permit, we will do a sensitivity analysis just including studies were all participants meet ICHD-3 criteria for chronic migraine.

Interventions: We will work with clinical colleagues to decide on *a final core set* of migraine prophylactic drugs. These most likely will include: CGRP MAbs, BTA, anti-depressants, ACE inhibitors and angiotensin receptor blockers, beta-blockers, calcium channel blockers, pizotifen, and anticonvulsants (topiramate, valproate/divalproex, gabapentin).

Comparators: Placebo, usual care, or other prophylactic drugs

Outcomes: Our analyses have two primary foci: Firstly, headache days / migraine days which are reported separately in many studies. Secondly, headache-related QoL. Where possible, we will use outcomes such as HIT-6, MIDAS and Migraine Specific QoL questionnaire converted to a standardised scale.

Secondary analyses: If there are sufficient data, we will use the same overall model approach for acute treatment use, headache intensity and duration, health service activity, and days lost from usual activities. If possible, we will explore if medication overuse reduces treatment response. We will report separately on any sub-group analyses in included studies.

WP2: Adverse event review. Lead: AG

RQ: What are the comparative incidences of side-effects of prophylactic medications used for migraine?

We will review all RCTs of migraine prophylactic drugs identified via the literature search for RCTs, currently prescribable in the UK, for both chronic and episodic migraine to identify comparative incidence of drug AEs. Due to the volume of literature, to make the work package more manageable we will restrict studies to 100 or more participants per arm.

We will report on the risk of bias in all studies included in WP1 but, for the additional analyses for this WP, we will only report quality assessment (using Cochrane Risk of Bias tool) and data extraction on those reporting AEs. We anticipate that identified studies would be too heterogeneous to facilitate pooling of study data and plan a narrative synthesis. If pooling is possible, we will perform a random effects meta-analyses.[46]

WP3: Cost-effectiveness review. Lead: HM

RQ: What is known about the cost-effectiveness of prophylactic drugs for chronic migraine?

We will review the literature to identify studies assessing the cost-effectiveness of prophylactic drugs for chronic migraine. We will include all full economic evaluation studies that report both costs and outcomes of at least two alternative prophylactic drugs, placebo, or no treatment in adults. Within-trial and model-based full economic evaluation studies from any country (including studies based on analysis of registry data) will be included if they report comparative cost-benefit, cost-consequence, cost-effectiveness or cost-utility. Results will be synthesised narratively and quality of included studies will be assessed using tools developed by Husereau *et al* for reporting of economic evaluations and Phillips *et al* for any model-based economic evaluations.[56, 57]

This work package will provide conclusive evidence and an assessment of the quality of the published evidence available for prophylactic drugs for chronic migraine and will also help with sourcing appropriate inputs which are required for the economic model in WP4 such as resource use, costs, utilities and probabilities.

WP4: Cost-effectiveness model. Co-leads: HM, FA

RQ: Which prophylactic drugs for the management of chronic migraine are the most cost-effective?

Clinical and cost-effectiveness evidence and AEs data identified from our reviews will inform a comprehensive decision-analytical model to estimate the comparative cost-effectiveness of prophylactic drugs used for the treatment of chronic migraine.

We will have identified all published model-based economic evaluations of chronic migraine from our systematic reviews of effectiveness and cost-effectiveness evidence. Based on this, we will determine whether development of a *de novo* economic model is required. Any such model will be based on approaches already used by NICE.[58, 59] The structure of the decision problem (e.g. choice of comparators, time horizon, perspective, type of model) will be informed by both the identified literature and the clinical expertise of the project team. We will populate the chosen model based on the evidence base we identify. We will only include drugs with some evidence of effectiveness identified from our systematic review and NMA.

Using the model, we will calculate costs and utilities for each comparator, and estimate incremental cost-effectiveness ratios to determine the recommended treatment given willingness-to-pay thresholds commonly used by NICE to inform UK adoption decisions. We will carry out probabilistic sensitivity analyses to quantify decision uncertainty based on the evidence currently available, presenting our results as cost-effectiveness acceptability curves.

We will also do value-of–information analyses (expected value of sample information) to explore the likelihood that additional evidence might alter the recommendation, and determine parameters of study design (e.g., choice of comparator(s), length of follow-up, choice of outcome measures) that maximise the value of any future RCTs. This will help inform our recommendations for future research.

WP5: Consensus findings and research recommendations. Co-leads: RP, SR

RQ: What should the research recommendations be based on our findings, and which should be highest priority?

We will work with the WP leads and our patient and clinical collaborators using consensus methodology to develop a clear and understandable set of research recommendations based on the findings of WP1-4. Throughout the study, we will meet with WP leads and our PPI partners to discuss emerging findings, to ensure that prior to the consensus meeting we have accessible and understandable summaries of each major finding.

We will invite around 15 people with chronic migraine and 10 clinicians to a consensus meeting. People with chronic migraine will be identified via communications from the National Migraine Centre who will advertise on social media and through newsletters/mailing lists. Clinicians will be identified from our networks including the Association of British Neurologists (ABN) – Headache and Pain Subsection; British Association for the Study of Headaches (BASH); and the UK Headache GPSi Network.

Participants will be provided with a summary of our findings in advance. We will use Nominal Group Technique to encourage everyone to contribute.[60-63] We used similar approaches for multiple studies, including our consensus exercises to develop a headache classification tools, a core outcome set for migraine trials.[39, 60, 62, 64] At the meeting we will do a short presentation of the findings, and present some potential research recommendations. We will then break the participants up into groups (two

clinicians and three people with migraine per group) and ask them to discuss our suggested research recommendations, identify any other recommendations themselves, and rank these in terms of priority. Each group will also be assigned a scribe and a facilitator. We will have a breakaway session, where all people with migraine meet, and all clinicians meet, to reflect on whether there were any issue sharing their perspectives in the mixed groups. If so, a spokesperson from each group will be assigned to share this with the wider group. We will then bring the participants back together and discuss their rankings as a wider group and reach a consensus using anonymous polling.

We anticipate this will take place in Month 16/17 of the project. We are hopeful that we will be able to do this face-to-face. If not, we will conduct the event virtually and utilise software which is supported by the University of Warwick such as Microsoft Teams.

Publication strategy

We aim to publish several standalone publications from this project:

- Systematic review and NMA of effectiveness of pharmacological preventive medications for chronic migraine
- Systematic review of AEs of pharmacological interventions for migraine
- Systematic review of cost-effectiveness studies for chronic migraine including an economic model assessing which drugs are cost-effective for the management of chronic migraine
- Paper setting the agenda for future research.

These will be published in relevant open access journals such as Headache: The Journal of Head and Face Pain; Journal of Headache and Pain; and Cephalagia and presented at relevant conferences such as the International Headache Society Congress and the European Headache Federation Congress. All systematic review protocols will be made available on PROSPERO.

Academic output

Informing NHS/policymakers and Impact

Links to all findings will be available via a dedicated project webpage hosted by the University of Warwick. If we show that certain drugs are cost-effective for chronic migraine, we will work with our patient-partners to highlight this information to the NHS and policy makers to directly improve patients' quality of life and reduce the financial burden on the NHS. We also have an established relationship with the National Migraine Centre and will continue to work with them to share our findings with patients. Their website gets over 2.2 million visitors per year so is an excellent way to reach our target audience.

Timelines

See attached project management plan. In brief:
Months 1-2: Protocol development and **WP1**/**WP2/WP3** literature searches
Months 2-4: **WP1/WP2/WP3** screening
Months 4-8: **WP1/WP2/WP3** data extraction
Months 8-12: **WP1/WP2/WP3** analyses
Months 11-16: **WP4** model development and analysis
Months 16-17: **WP5** meeting to develop research recommendations
Months 15-18: Writing up.

This protocol is being submitted to NETSCC MIS on 20th September.

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