# Appendix A: Review protocols

## A.1 Assessment and diagnosis

### A.1.1 Indications for consideration of additional investigation

| Component | Description |
|---|---|
| **Review question** | For young people and adults with HIV presenting with new onset headache, how common are serious intracranial abnormalities? |
| **Objectives** | To determine the occurrence of serious intracranial abnormalities in people with HIV and new onset headache, compared to people with HIV without headache. |
| **Population** | People aged 12 or over with HIV and new onset headache in isolation of other symptoms |
| **Comparisons** | People aged 12 or over with HIV without headache |
| **Presence / absence of risk factor** | Occurrence of serious intracranial abnormalities |
| **Study design** | Cohort studies<br>Case control |
| **Exclusions** | Non-English studies<br>Abstracts |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review strategy** | Minimum n=any<br>Report any serious intracranial abnormalities as reported in the studies<br>Record CD4 count if reported |

| Component | Description |
|---|---|
| **Review question** | For young people and adults with a history of malignancy presenting with new onset headache, how common are serious intracranial abnormalities? |
| **Objectives** | To determine the occurrence of serious intracranial abnormalities in people with cancer and new onset headache, compared to the occurrence in the general population. |
| **Population** | People aged 12 or over with cancer and new onset headache in isolation of other symptoms |
| **Comparisons** | People aged 12 or over with cancer, without headache |
| **Presence / absence of risk factor** | Occurrence of serious intracranial abnormalities |
| **Study design** | Cohort studies<br>Case control |
| **Exclusions** | Non-English studies<br>Abstracts |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review strategy** | Minimum n=any<br>Report any serious intracranial abnormalities as reported in the studies |

| Component | Description |
|---|---|
| **Review question** | For young people and adults presenting with early morning headache or new onset frequent headache that lasts for more than one month, how common are serious intracranial abnormalities? |
| **Objectives** | To determine the occurrence of serious intracranial abnormalities in people with early morning headache or new onset frequent headache that lasts for more than one month and is otherwise unexplained, compared to people without early morning headaches / new onset daily headache. |
| **Population** | People aged 12 or over with early morning headache or new onset frequent headache that lasts for more than 1 month, in isolation of other symptoms (unexplained) |
| **Comparisons** | People aged 12 or over without early morning headache or new onset daily headache that lasts for more than one month |
| **Presence / absence of risk factor** | Occurrence of serious intracranial abnormalities |
| **Study design** | Cohort studies<br>Case control |
| **Exclusions** | Non-English studies<br>Abstracts |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review strategy** | Minimum n=any<br>Report any serious intracranial abnormalities as reported in the studies<br>NB. Also look in search on headaches with cancer & imaging questions.<br>Report incidence figures and headache type |

### A.1.2 Identifying people with primary headache

| Component | Description |
|---|---|
| **Review question** | What is the accuracy of case finding questionnaires for diagnosing primary headache disorders and medication overuse headache? |
| **Objectives** | To examine the effectiveness of tools to aid in diagnosis of primary headaches and medication overuse headache. |
| **Population** | Females aged 12 or over with migraine<br>Subgroups:<br>• 12-18 years old |
| **Intervention** | Case finding questionnaires |
| **Comparison** | Gold standard - full assessment following ICHD-II criteria (diagnosis) |
| **Outcomes** | • Positive predictive value: True positive & false positive: TP/(TP+FP)<br>• Negative predictive value: True negative & false negative: TN/(FN+TN)<br>• Sensitivity : TP/(FN+TP)<br>• Specificity : TN/(FP+TN) |
| **Study design** | Diagnostic studies / validation studies |
| **Exclusions** | Abstracts only<br>Non English papers |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |

| Component | Description |
|---|---|
| **The review strategy** | • Minimum n=100<br>• Meta-analysis will be undertaken if >5 comparable studies are identified |

### A.1.3 Headache diaries for the diagnosis of primary headaches and medication overuse headache

| Component | Description |
|---|---|
| **Review question** | What is the clinical and cost effectiveness of using diaries for the diagnosis of people with suspected primary headaches and medication overuse headache? |
| **Objectives** | To examine the effectiveness of patient diaries as diagnostic tools in patients with suspected primary headaches and medication overuse headache. |
| **Population** | People aged 12 or over with suspected primary headache<br>Possible subgroups:<br>• 12-18 years old |
| **Interventions** | Patient diaries: paper or electronic |
| **Comparisons** | Gold standard - full assessment by headache specialist following ICHD-II criteria (diagnosis) |
| **Outcomes** | • Number of people correctly diagnosed<br>• Positive predictive value (True positive & false positive: TP/(TP+FP) )<br>• Negative predictive value (True negative & false negative: TN/(FN+TN) )<br>• Sensitivity : TP/(FN+TP)<br>• Specificity : TN/(FP+TN) |
| **Study design** | • Diagnostic studies |
| **Exclusions** | Abstracts only<br>Non-English |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | Minimum n: any<br>Review diagnosis and management separately. |

### A.1.4 Headache diaries for the management of primary headaches and medication overuse headache

| Component | Description |
|---|---|
| **Review question** | What is the clinical effectiveness, and patients' and practitioners' experience, of using diaries for the management of people with primary headaches and medication overuse headache? |
| **Objectives** | To examine the effectiveness of patient diaries as management tools in patients with primary headaches and medication overuse headache. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old |
| **Interventions** | Patient diaries: paper or electronic |
| **Comparisons** | No diary |
| **Outcomes** | • Clinical headache outcomes (for RCTs)<br>• Patients' and practitioners' experience of using diaries |
| **Study design** | • RCTs (only look at other study designs if no RCTs) |

| | |
|---|---|
| | • Qualitative studies / Systematic review |
| **Exclusions** | Abstracts only<br>Non-English |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | Minimum n: any<br>Review diagnosis and management separately. |

### A.1.5 Diagnosis of primary headaches and medication overuse headache

| Component | Description |
|---|---|
| **Review question** | For young people and adults with headache, what are the key diagnostic features of the following headaches:<br>• migraine with or without aura<br>• menstrual related migraine<br>• chronic migraine<br>• tension-type headache<br>• cluster headache<br>• medication overuse headache |
| **Objectives** | To determine the key characteristics that signify diagnosis of primary headache |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years of age |
| **Interventions** | N/A |
| **Comparisons** | N/A |
| **Outcomes** | N/A |
| **Study design** | N/A |
| **Exclusions** | N/A |
| **How the information will be searched** | ICHD-II criteria will be used so no literature search will be conducted |
| **The review strategy** | By consensus based on existing ICHD-II criteria |

### A.1.6 The role of imaging in diagnosis and management of primary headaches

#### A.1.6.1 Imaging for diagnosis in people with suspected primary headache

| Component | Description |
|---|---|
| **Review question** | Should young people and adults with suspected primary headaches be imaged to rule out serious pathology? |
| **Objectives** | To determine the utility of imaging to detect serious underlying pathology in people with headaches. |
| **Population** | People aged 12 or over with suspected primary headache.<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant women |
| **Interventions** | Imaging with CT, MRI or MRI variants |
| **Comparisons** | N/A |

| Component | Description |
|---|---|
| **Outcomes** | Percent with serious intracranial abnormalities, e.g.:<br>• Tumour/neoplasm (subdivide into types)<br>• Abscess<br>• Subdural haematoma<br>• Hydrocephalus<br>• Arterio-venous malformations |
| **Study design** | Cohort studies<br>Case control |
| **Exclusions** | Non-English studies<br>Abstracts |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review strategy** | Minimum n=any |

### A.1.6.2 Imaging as a management strategy for people with suspected primary headaches

| Component | Description |
|---|---|
| **Review question** | For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of imaging as a management strategy? |
| **Objectives** | To examine the benefits and disadvantages of imaging in reducing the impact on people with primary headaches |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• Headache type (migraine, cluster headache, tension type headache)<br>• 12-18 years old |
| **Interventions** | • MRI scan<br>• MRI variants: MRI + contrast, MR angiography<br>• CT scan |
| **Comparisons** | No imaging |
| **Outcomes** | • Resource use including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Change in headache frequency and intensity (with e.g. headache impact test or migraine disability assessment test)<br>• Percentage of responders with 25%, 50% and 75% reduction in baseline headache frequency<br>• Change in frequency of acute medication use<br>• Change in anxiety and depression (e.g. HAD)<br>• Change in health related quality of life (e.g. SF-36 or EuroQoL)<br>• Incidental radiological findings |
| **Study design** | RCTs only |
| **Exclusions** | Less than 3 months study duration<br>Non-English studies |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |

| Component | Description |
|---|---|
| **The review strategy** | Minimum n:20 in each arm for RCTs<br>Observational studies n=500<br>Outcomes to be recorded at 3 months and 1 year if reported<br>Differences between primary and secondary care to be recorded if reported<br>If RCTs are identified the results will, where appropriate, contribute to a meta-analysis. |

# A.2 Management

## A.2.1 Patient information and support

| Component | Description |
|---|---|
| **Review question** | What information and support do patients with primary headaches say they want? |
| **Objectives** | To assess what information and support patients with primary headaches say they want |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people<br>• Learning disabilities / Any vulnerable group<br>• All age bands |
| **Interventions** | Patient information and support |
| **Comparisons** | No comparison |
| **Outcomes** | • Patients' preferences |
| **Study design** | Qualitative data (e.g. interviews, focus groups) |
| **Exclusions** | Abstracts only<br>Non English studies |
| **How the information will be searched** | Databases: Medline, Embase, Cinahl<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=any |

## A.2.2 Acute pharmacological treatment of tension type headache

| Component | Description |
|---|---|
| **Review question** | In people with tension type headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with:<br>• Aspirin<br>• NSAIDs<br>• Opioids<br>• Paracetamol |
| **Objectives** | To assess the clinical and cost effectiveness of aspirin, NSAIDs, opioids and paracetamol as acute pharmacological treatment of tension type headache. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant people<br>• Route of administration |
| **Interventions** | • Aspirin |

| Component | Description |
|---|---|
| | • NSAIDs<br>• Opioids (weak and strong)<br>• Paracetamol |
| **Comparisons** | All compared to each other: Placebo, aspirin, paracetamol, NSAIDs, strong and week opioids |
| **Outcomes** | • Time to freedom from pain<br>• Headache response at up to 2 hours<br>• Pain free at 2 hours<br>• Sustained headache response at 24 hours<br>• Sustained freedom from pain at 24 hours<br>• Functional health status and health related quality of life (e.g. SF-36 or EuroQoL)<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies. |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 per arm<br>• Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available)<br>• Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available<br>• Consider dose if reported<br>• Consider route of administration if reported – see subgroups<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed |

### A.2.3 Acute pharmacological treatment of migraine

| Component | Description |
|---|---|
| **Review question** | In people with migraine with or without aura, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with:<br>• Antiemetics<br>• Aspirin<br>• NSAIDs<br>• Opioids<br>• Paracetamol<br>• Triptans<br>• Ergots<br>• Corticosteroids |
| **Objectives** | To assess the clinical and cost effectiveness of antiemetics, aspirin, NSAIDs, opioids, oxygen, paracetamol, triptans, ergots and corticosteroids as acute pharmacological treatment of migraine with or without aura. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant people |

| Component | Description |
|---|---|
| | • Route of administration |
| **Interventions** | • Antiemetics<br>• Aspirin<br>• NSAIDs<br>• Opioids (weak and strong)<br>• Paracetamol<br>• Triptans<br>• Ergots (ergotamine / dihydroergotamine)<br>• Corticosteroids |
| **Comparisons** | All compared to each other:<br>• Aspirin, paracetamol, NSAIDS, triptans, NSAIDs, weak opioids, strong opioids, triptans, ergots, corticosteroids<br>• all +/- antiemetics and antiemetics alone |
| **Outcomes** | • Time to freedom from pain<br>• Headache response at up to 2 hours<br>• Freedom from pain at up to 2 hours<br>• Sustained headache response at 24 hours<br>• Sustained freedom from pain at 24 hours Functional health status and health related quality of life (e.g. SF-36 or EuroQoL)<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies. |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 per arm (Cluster headache n=any)<br>• Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available)<br>• Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available<br>• Consider dose if reported<br>• Consider route of administration if reported – see subgroups (buccal and oral together for triptans)<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed |

### A.2.4 Acute pharmacological treatment of cluster headache

| Component | Description |
|---|---|
| **Review question** | In people with cluster headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with:<br>• Aspirin<br>• Paracetamol<br>• Oxygen<br>• Triptans<br>• Ergots<br>• NSAIDs |

| Component | Description |
|---|---|
| | • Opioids |
| **Objectives** | To assess the clinical and cost effectiveness of oxygen, triptans and ergots as acute pharmacological treatment of cluster headache |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant people<br>• Route of administration |
| **Interventions** | • Aspirin<br>• Paracetamol<br>• Oxygen (high and low flow)<br>• Triptans<br>• Ergots (ergotamine / dihydroergotamine)<br>• NSAIDs<br>• Opioids (weak and strong) |
| **Comparisons** | All compared to each other (except oxygen) or placebo:<br>• High and low flow oxygen +/- triptans or ergots vs no treatment or air |
| **Outcomes** | • Time to freedom from pain<br>• Headache response at up to 2 hours<br>• Reduction in pain at 30 minutes<br>• Functional health status and health related quality of life (e.g. SF-36 or EuroQoL)<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies. |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=any<br>• Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available)<br>• Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available<br>• Consider dose if reported<br>• Consider route of administration if reported – see subgroups (buccal and oral together for triptans)<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed |

### A.2.5 Prophylactic pharmacological treatment of tension type headache

| Component | Description |
|---|---|
| **Review question** | In people with tension type headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with:<br>• ACE inhibitors and angiotensin II receptor antagonists (ARBs)<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Antiepileptics |

| Component | Description |
|---|---|
| **Objectives** | To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers and antiepileptics as prophylactic pharmacological treatment of tension type headache. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12- 18 years old<br>• Pregnant people<br>• Dose |
| **Interventions** | • ACE inhibitors and angiotensin II receptor antagonists<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Antiepileptics |
| **Comparisons** | All compared to each other or placebo:<br>ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics. |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 per arm<br>• Minimum trial duration: 3 months<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Consider dose if reported (mg/kg in children)<br>• Consider route of administration if reported<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed<br>• Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug. |

### A.2.6 Prophylactic pharmacological treatment of migraine

| Component | Description |
|---|---|
| **Review question** | In people with migraine with or without aura and chronic migraine, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with:<br>• ACE inhibitors and angiotensin II receptor antagonists<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Calcium channel blockers |

| Component | Description |
|---|---|
| | • Antiepileptics<br>• Other serotonergic modulators |
| **Objectives** | To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers, calcium channel blockers, antiepileptics and other serotonergic modulators as prophylactic pharmacological treatment of migraine with or without aura and chronic migraine. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant people<br>• Previous treatment exposure: None, 1, 2 or 3, 4 or more<br>• Dose |
| **Interventions** | • ACE inhibitors and angiotensin II receptor antagonists<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Calcium channel blockers<br>• Antiepileptics<br>• Other serotonergic modulators (e.g. pizotifen, methysergide, cyproheptadine, dihydroergotamine) |
| **Comparisons** | All compared to each other or placebo:<br>ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics, other serotonergic modulators. |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 per arm<br>• Minimum trial duration: 3 months<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Previous treatment exposure: None, 1,2or3, 4 or more<br>• Consider dose if reported (mg/kg in children)<br>• Consider route of administration if reported<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed<br>• Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug. |

### A.2.7 Prophylactic pharmacological treatment of menstrual migraine

| Component | Description |
|---|---|
| **Review question** | In people with pure menstrual and menstrual related migraine, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with:<br>• ACE inhibitors and angiotensin II receptor antagonists<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Calcium channel blockers<br>• Antiepileptics<br>• Triptans<br>• Other serotonergic modulators<br>• NSAIDs<br>• Hormonal therapy (Contraceptives) |
| **Objectives** | To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, and hormonal therapy as prophylactic pharmacological treatment of menstrual migraine or menstrual related migraine. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-8 years old<br>• Pregnant people |
| **Interventions** | • ACE inhibitors and angiotensin II receptor antagonists<br>• Antidepressants (SNRIs, SSRIs, tricyclics)<br>• Beta blockers<br>• Calcium channel blockers<br>• Antiepileptics<br>• Triptans<br>• Other serotonergic modulators (e.g. pizotifen, methysergide, cyproheptadine, dihydroergotamine)<br>• NSAIDs<br>• Hormonal therapy (Contraceptives) |
| **Comparisons** | All compared to each other:<br>Placebo, ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, hormonal therapy. |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |

| Component | Description |
|---|---|
| **The review strategy** | • Minimum n=25 per arm<br>• Minimum trial duration: 3 months<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Previous treatment exposure: None, 1,2or3, 4 or more<br>• Consider dose if reported (mg/kg in children)<br>• Consider route of administration if reported<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed<br>• Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug. |

### A.2.8 Prophylactic pharmacological treatment of cluster headache

| Component | Description |
|---|---|
| **Review question** | In people with cluster headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with:<br>• Calcium channel blockers<br>• Corticosteroids (oral only)<br>• Lithium<br>• Melatonin<br>• Antiepileptics<br>• Triptans<br>• Other serotonergic modulators |
| **Objectives** | To assess the clinical and cost effectiveness of calcium channel blockers, corticosteroids, lithium, melatonin, antiepileptics, triptans and other serotonergic modulators as prophylactic pharmacological treatment of cluster headache. |
| **Population** | People aged 12 or over with primary headache<br>Possible subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | • Calcium channel blockers<br>• Corticosteroids (oral only)<br>• Lithium<br>• Melatonin<br>• Antiepileptics<br>• Triptans<br>• Other serotonergic modulators |
| **Comparisons** | All compared to each other or placebo:<br>Calcium channel blockers, oral corticosteroids, lithium, melatonin, antiepileptics, triptans, other serotonergic modulators (including ergots) |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |

| Component | Description |
|---|---|
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=any<br>• Outcomes to be recorded at any time point<br>• Consider dose if reported (mg/kg in children)<br>• Consider route of administration if reported<br>• Data will be meta-analysed if possible<br>• Treatment comparisons will be both direct and mixed |

### A.2.9 Prophylactic non-pharmacological management of primary headaches with acupuncture

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with acupuncture |
| **Objectives** | To assess the clinical and cost effectiveness of acupuncture, as non-pharmacological management of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Acupuncture +/- prophylactic pharmacological treatment |
| **Comparisons** | Sham acupuncture +/- prophylactic pharmacological treatment / pharmacological therapy / psychological therapy / herbal remedies / dietary supplements / manual therapy |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (per arm)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded |

| Component | Description |
|---|---|
| | • Data will be meta-analysed if possible |

### A.2.10 Prophylactic non-pharmacological management of primary headaches with manual therapies

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with manual therapies? |
| **Objectives** | To assess the clinical and cost effectiveness of manual therapies as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Manual therapies |
| **Comparisons** | Usual care |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (per arm)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.11 Prophylactic non-pharmacological management of primary headaches with psychological therapies

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with psychological therapies? |
| **Objectives** | To assess the clinical and cost effectiveness of psychological therapies as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache). |

| Component | Description |
|---|---|
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Psychological therapies (Cognitive behavioural therapy (CBT), biofeedback, controlled breathing, progressive muscle relaxation (PMR), relaxation, guided visualisation, mindfulness, attention control training (ACT), finger/hand warming) |
| **Comparisons** | Attention control |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (total)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.12 Prophylactic non-pharmacological management of primary headaches with dietary supplements

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (B2)) |
| **Objectives** | To assess the clinical and cost effectiveness of dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin(B2)) as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin(B2) +/- prophylactic pharmacological treatment |
| **Comparisons** | Placebo vs +/- prophylactic pharmacological treatment / pharmacological therapy / acupuncture / psychological therapy / herbal remedies / manual therapy |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity |

| Component | Description |
|---|---|
| | • Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (per arm)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.13 Prophylactic non-pharmacological management of primary headaches with herbal remedies

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine) what is the clinical evidence and cost-effectiveness of non-pharmacological management with herbal remedies? |
| **Objectives** | To assess the clinical and cost effectiveness of herbal remedies (e.g. feverfew and butterbur) as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Dietary supplements (e.g. feverfew, butterbur) +/- prophylactic pharmacological treatment |
| **Comparisons** | Placebo vs +/- prophylactic pharmacological treatment / pharmacological therapy / acupuncture / psychological therapy / herbal remedies / manual therapy |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies |

| Component | Description |
|---|---|
| | Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (per arm)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.14 Prophylactic non-pharmacological management of primary headaches with exercise

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with exercise programmes? |
| **Objectives** | To assess the clinical and cost effectiveness of exercise programmes as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Exercise programmes |
| **Comparisons** | Usual care |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Incidence of serious adverse events |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (per arm)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.15 Prophylactic non-pharmacological management of primary headaches with education and self management

| Component | Description |
|---|---|
| **Review question** | For people with primary headaches (migraine with or without aura, menstrual related |

| Component | Description |
|---|---|
| | migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with education and self-management programmes? |
| **Objectives** | To assess the clinical and cost effectiveness of education and self management programmes as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache). |
| **Population** | People aged 12 or over with primary headache<br>Subgroups:<br>• 12-18 years old<br>• Pregnant people |
| **Interventions** | Education and self-management programmes |
| **Comparisons** | Usual care |
| **Outcomes** | • Change in patient-reported headache days, frequency and intensity<br>• Responder rate (50% reduction)<br>• Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL)<br>• Headache specific QOL (e.g. MIDAS, HIT 6)<br>• Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Use of acute pharmacological treatment<br>• Patient's perception of the usefulness of programmes |
| **Study design** | RCTs |
| **Exclusions** | Abstracts only<br>Non English studies<br>Randomised crossover trials |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 (total)<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Randomised crossover trials excluded<br>• Data will be meta-analysed if possible |

### A.2.16 Management of medication overuse headache

| Component | Description |
|---|---|
| **Review question** | What is the clinical evidence and cost-effectiveness of withdrawal strategies (of abortive treatments), psychological therapies, corticosteroids and NSAIDs for the treatment of probable medication overuse headache? |
| **Objectives** | To identify the clinical evidence and assess the cost effectiveness of withdrawal strategies, psychological therapies, corticosteroids or NSAIDs for the treatment of probable medication overuse headache. |
| **Population** | People aged 12 or over with suspected medication overuse headache<br>Subgroups:<br>• 12-18 years old |
| **Interventions** | • Withdrawal strategies for abortive treatments (stop suddenly, withdraw gradually, inpatient, outpatient supportive packages)<br>• Psychological therapies<br>• Corticosteroids |

| | |
|---|---|
| | • NSAIDS |
| **Comparisons** | • Withdrawal strategies vs each other<br>• Psychological therapies vs attention control<br>• Corticosteroids / NSAIDS vs placebo |
| **Outcomes** | • Change in acute medication use (up to 3 months)<br>• Relapse back to MOH<br>• Responder rate (proportion who no longer have probable MOH)<br>• Change in patient reported headache days, frequency and intensity<br>• Headache specific QoL (e.g. MIDAS, HIT 6)<br>• Resource use including GP consultation, A&E attendance, investigations and referral to secondary care<br>• Functional health status and health related quality of life (e.g. SF-36 or EuroQoL) |
| **Study design** | RCTs<br>If no RCTs found, lower quality evidence will be considered |
| **Exclusions** | Abstracts only<br>Non English papers |
| **How the information will be searched** | Databases: Medline, Embase, the Cochrane Library<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=25 per arm<br>• Outcomes to be recorded at 3 months and 1 year if reported<br>• Data will be meta-analysed if possible |

# A.3 Management during pregnancy and contraceptive use

## A.3.1 Management of primary headaches during pregnancy

| Component | Description |
|---|---|
| **Review question** | What is the evidence for adverse fetal events in females with primary headaches during pregnancy using triptans? |
| **Objectives** | To determine the safety of triptans for use during pregnancy |
| **Population** | Pregnant women and girls aged 12 or over with primary headache |
| **Presence of risk factor** | Pregnant women with headache taking a triptan |
| **Absence of risk factor** | Pregnant women with or without headache, not taking a triptan |
| **Outcomes** | Fetal adverse events |
| **Study design** | Cohort studies<br>Triptan registries (published only) |
| **Exclusions** | Abstracts only<br>Non English papers |
| **How the information will be searched** | Databases: Medline, Embase, Triptan or teratology registers<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=50<br>• Consider dose if reported<br>• Consider route of administration if reported<br>• Ideally adjusted for: Age, smoking, alcohol, other drug use |

| Component | Description |
|---|---|
| **Review question** | What is the evidence for adverse fetal events in females using oxygen or verapamil during pregnancy? |
| **Objectives** | To determine the safety of oxygen or verapamil for use during pregnancy |
| **Population** | Pregnant women and girls aged 12 or over |
| **Presence of risk factor** | Pregnant women taking oxygen or verapamil |
| **Absence of risk factor** | Pregnant women not taking oxygen or verapamil |
| **Outcomes** | Fetal adverse events |
| **Study design** | Cohort studies |
| **Exclusions** | Abstracts only<br>Non English papers |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review strategy** | • Minimum n=50<br>• Consider dose if reported<br>• Consider route of administration if reported<br>• Ideally adjusted for: Age, smoking, alcohol, other drug use |

### A.3.2 Combined hormonal contraceptive use in girls and women with migraine

| Component | Description |
|---|---|
| **Review question** | What risks are associated with use of hormonal contraception in females aged 12 or over with migraine? |
| **Objectives** | To assess what adverse events are associated with the use of hormonal contraception in females ages 12 or over with migraine |
| **Population** | Females aged 12 or over with migraine<br>Subgroups:<br>• Migraine type (with and without aura) |
| **Presence of risk factor** | • Combined oral contraceptive pill<br>• Progesterone only contraceptive pill / contraceptive pill without oestrogen<br>• Progesterone implanted coil<br>• Progesterone implant<br>• Depot injection |
| **Absence of risk factor** | • Non-hormonal / other |
| **Outcomes** | • Incidence of serious adverse events<br>• Worsening effect on headache syndrome |
| **Study design** | • Prospective cohort studies<br>• Case control |
| **Exclusions** | Abstracts only<br>Non English papers |
| **How the information will be searched** | Databases: Medline, Embase<br>Language: restrict to English only |
| **The review** | Minimum n=500 for cohort |

| Component | Description |
|---|---|
| **strategy** | Ideally adjusted for: Age, smoking, familial risk |