APPENDIX A. INTERVENTIONS FOR INCLUSION

Table A.1 Migraine Prevention Interventions Considered for Map 1 (Benefits and Harms of Migraine Prevention Treatments)

Interventions	Included (Yes/No)	Comment
Pharmacologic		
ACE inhibitors/ARBs (Lisinopril, Candesartan)	Yes	Scoping suggests evidence for efficacy for lisinopril, candesartan (probably and possibly effective, AAN/AHS guideline). Commonly used medications for hypertension. Included in Table 1.
ACE inhibitors/ARBs (Captopril, Enalapril, Telmisartan)	No	Telmisartan considered possibly ineffective by AAN/AHS guideline; captopril and enalapril without significant efficacy in SR (Jackson 2015).
Alpha-agonists (clonidine, guanfacine)	No	Considered possibly effective by AAN/AHS, but not an emerging therapy, not in common use for migraine.
Anti-thrombotics (acenocoumarol, Coumadin, picotamide)	No	Conflicting/inadequate evidence as per AAN/AHS guideline); not in clinical use
Beta-blockers (Metoprolol, propranolol)	Yes	Metoprolol, propranolol included as "effective" recommendations in AAN/AHS, propranolol recommended by SIGN guideline: Included in Table 1
Beta-blockers (Timolol)	No	Timolol listed as "effective" in AAN/AHS, but not widely used in clinical practice; also found to be equivalent to metoprolol in recent SR (Jackson 2019)
Beta-blockers (Atenolol, nadolol, nebivolol, pindolol, bisoprolol)	No	Listed as probably or possibly effective in AAN/AHS, but already evaluated along with other beta-blockers in recent SR (Jackson 2019).
Beta-blockers (acebutolol)	No	Considered possibly ineffective as per AAN/AHS guideline.
Botox (onaobotulinumtoxin A)	Yes	"Recommended" in SIGN and recent AAN guideline for chronic migraine; Scoping suggests some evidence for efficacy: Included in Table 1.
Calcium channel blockers (Nicardipine, nifedipine, nimodipine, verapamil)	No	Listed as inadequate and conflicting evidence by AAN/AHS guideline and not emerging therapy; scoping suggests large number of trials, so including could also present feasibility challenge. Evaluated in SR (Jackson 2015)

Interventions	Included (Yes/No)	Comment
Calcitonin gene-related peptide (CGRP) antagonists (Erenumab, Fremanezumab, Galcanezumab, Eptinezumab)	Yes	Considered an emerging therapy; Scoping suggests some evidence for efficacy and interventions of interest to patients: Included in Table 1
Cyclandelate	No	Conflicting, inadequate evidence as per AAN/AHS and not in clinical use.
Frovatriptan	No	Listed as "effective" by AAN/AHS but only for short-term menstrual migraine prevention, which is not a focus of this product.
Gabapentin	No	Not recommended by either AAN/AHS or SIGN guidelines) and not an emerging therapy.
Nabumetone	No	Possibly ineffective as per AAH/AHS guideline)
Naratriptan, Zolmitriptan	No	Possibly effective according to AAN/AHS, but only for short term menstrual migraine prevention which is not a focus of this product; also not emerging therapy.
Other antidepressants (fluoxetine, fluvoxamine, protryptiline, clomipramine)	No	Listed as conflicting/probably ineffective by AAN/AHS and not an emerging therapy.
Other antiepilepetics (acetazolamide, carbamazepine, clonazepam, lamotrigine, levitaracetam, oxcarbamazepine, vigabatrin, zonisamide)	No	Carbamazepine is possibly effective, but not in common use; Other drugs are not listed as effective or probably effective and also are not in common use for migraine
Topiramate	Yes	"Effective" recommendation in AAN/AHS and SIGN guideline: Included in Table 1
Tricyclics (amitriptyline, nortryptiline)	Yes	Amitriptyline considered "probably effective" by AAN/AHS, SIGN; nortriptyline recommended for inclusion by clinician stakeholders, and in common use: Included in Table 1
Valproic acid	Yes	Considered effective by AAN/AHS and SIGN guideline: Included in Table 1
Venlafaxine	Yes	Considered "probably effective" by AAN/AHS, SIGN; recommended for inclusion by clinician stakeholders: Included in Table 1.
Supplements/Nutraceuticals		
Magnesium	No	Not a high priority intervention of interest for PCORI at this time

Interventions	Included (Yes/No)	Comment
Vitamins and Minerals (including magnesium and Coenzyme Q, riboflavin)	No	Not a high priority intervention of interest for PCORI at this time
Butterbur (Petasites)	No	Not a high priority intervention of interest for PCORI at this time
Feverfew	No	Not a high priority intervention of interest for PCORI at this time
Boswelia	No	Not a high priority intervention of interest for PCORI at this time
Gingko biloba	No	Not a high priority intervention of interest for PCORI at this time
Melatonin	No	Not a high priority intervention of interest for PCORI at this time
Behavioral Therapies		
Cognitive Behavioral Therapy (CBT)	No	Not a high priority intervention of interest for PCORI at this time
Biofeedback	No	Not a high priority intervention of interest for PCORI at this time
Relaxation therapy	No	Not a high priority intervention of interest for PCORI at this time
Complementary and Alternative Medicine		
Acupuncture	No	Not a high priority intervention of interest for PCORI at this time
Devices		
Supraorbital nerve stimulator (Cefaly)	Yes	Intervention of interest for PCORI along with clinicians and patient stakeholders; commonly used in clinical practice; scoping suggests sparse data (only a single RCT); Included in Table 1.
Non invasive vagus nerve stimulator (gammaCore)	Yes	Intervention of interest for PCORI along with clinicians and patient stakeholders; commonly used in clinical practice; scoping suggests some data. Included in Table 1.
Transcranial magnetic stimulation	No	Not in common use and not available to most patients; scoping suggests limited evidence

Interventions in italics are included in Map 1 (Benefits and Harms).

Table A-2. Recommended Interventions from Guidelines

American Academy of Neurology (AAN)/ American Headache Society (AHS)		**Scottish Intercollegiate Guideline Network (SIGN)***		**Canadian Headache Society**	
Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults (2012- reaffirmed 2015)		Pharmacological Management of Migraine (2018)		Guideline for Migraine Prophylaxis (2012)	
Effective	AEDs (Divalproex, sodium valproate, topiramate), beta-blockers (metoprolol, propanolol, timolol), triptans (frovatriptan for short-term menstrual migraine prevention)	Recommended	Propanolol (60 to 180 mg), Topiramate; Botox (for chronic migraine only)	Strong recommendation (high quality of evidence)	Topiramate, Propanolol, Metoprolol, Amitriptyline
Probably effective	Antidepressants (amitriptyline, venlafaxine), beta-blockers (atenolol, nadolol), triptans (naratriptan, zolmitriptan for short term MAMs prevention)	Should be considered	Amitriptyline	Strong recommendation (moderate quality of evidence)	Nadolol, Gabapentin, Candesartan, Butterbur
Possibly effective	ACE-inhibitors (lisinopril), Angiotensive receptor blockers (candesartan), alpha-agonists (clonidine, guanfacine), AEDs (carbamazepine), beta-blockers (nebivolol, pindolol)	Can be considered	Candesartan, Valproate	Strong recommendation (low quality of evidence)	Riboflavin, CoenzymeQ, Magnesium
Conflicting, inadequate	Anti-depressants (Fluoxetine, fluvoxamine, protriptyline); anti-thrombotics (acenocoumarol, coumadin, picotamide); beta-blockers (bisoprolol), calcium channel blockers (nicardipine, nifedipine, nimodipine, verapamil), acetazolamide, cyclandelate			Weak recommendation (high quality of evidence)	Divalproex, flunarizine, pizotifen
Ineffective (should not be offered)	Lamotrigine			Weak recommendation (low quality of evidence)	Venlafaxine, verapamil, lisinopril
Probably ineffective	Clomipramine				
Possibly ineffective	Acebutolol, clonazepam, nabumetone, oxcarbazepine, telmisartan				

*Aside from Botox, all recommendations for episodic and chronic migraine

Table A-3 Guidelines on Single Interventions

Guideline	Intervention	Comment
2016 National Institute for Health and Care Excellence (NICE)	Supraorbital nerve stimulation	Current evidence on transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine raises no major safety concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
2019 European Headache Federation	CGRP antagonists	"In patients with episodic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab. In patients with chronic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab."
2016 American Academy of Neurology (AAN)	Botox	Effective for chronic migraine, ineffective for episodic migraine