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eTable 1: Summary of medications at baseline

		Standard care				Self-management			
Drug (n=727)	**Median Dose mg/28 days (range, IQR)**	**Drug group (n= 351)**	**Median DDDs Median (IQR)**	**Type (n=351)**	**Median DDDs Median (IQR)**	**Drug group (n=376)**	**Median DDDs Median (IQR)**	**Type (n=376)**	**Median DDDs Median (IQR)**
Acute									
Aspirin (n=86)	6250 (500-39600, 2400-16200)	Analgesic (n=244)	6 (2.3-14)	Acute (n=321)	14 (6.6-28)	Analgesic (n=251)	4.8 (1.8-11)	Acute (n=341)	12 (5.3-25)
Paracetamol (n=481)	15000 (250-224000, 5000-36000)								
Cyclizine (n=1)	100	Anti-emetic (n=18)	2.7 (2-3)			Anti-emetic (n=13)	2 (1-6.7)		
Domperidone (n=7)	80 (40-300, 50-250)								
Metoclopramide (n=11)	80 (10-840, 60-100)								
Prochlorperazine (n=13)	25 (3-225, 12-50)								
Diclofenac (n=8)	975 (50-2400, 450-1925)	NSAID (n=136)	4.7 (2-13)			NSAID (n=159)	5.3 (2-11)		
Ibuprofen (n=258)	5200 (200-67200, 2400-12000)								
Indometacin (n=2)	475 (200-750, 200-750)								
Mefenamic acid (n=3)	2500 (2000-3000, 2000-3000)								
Meloxicam (n=0)	-								
Naproxen (n=41)	4000 (250-56000, 1500-14000)								
Tolefenamic acid (n=1)	800								
Fentanyl patches (n=0)	-	Opioids* (n=114)	2.4 (0.96-9)			Opioids* (n=86)	1.9 (0.67-5.8)		
Morphine (n=2)	70 (20-120, 20-120)								
Tramadol (n=16)	2450 (50-11200, 300-4900)								
Codeine (n=176)	192 (8-6944, 68-720)								
Dihydrocodeine (n=16)	254 (40-1600, 95-404)								

Tapentadol (n=0)	-								
Almotriptan (n=2)	100 (75-125, 75-125)	Triptan (n=174)	8 (3-16)			Triptan (n=178)	8 (4-16)		
Eletriptan (n=4)	400 (280-960, 300-720)								
Frovatriptan (n=12)	26 (13-160, 16-38)								
Naratriptan (n=33)	15 (2.5-120, 10-35)								
Rizatriptan (n=41)	50 (10-360, 20-90)								
Sumatriptan injection (n=7)	24 (6-72, 6-60)								
Sumatriptan oral (n=204)	450 (50-4800, 200-800)								
Sumatriptan spray (n=8)	80 (40-400, 80-200)								
Zolmitriptan oral (n=48)	20 (0-360, 8.8-40)								
Zolmitriptan spray (n=12)	25 (5-75, 7.5-45)								
Prophylaxis									
Candesartan (n=9)	168 (40-448, 56-224)	Angiotensin receptor blocker (n=4)	32 (6-56)	Prophylaxis (n=114)	14 (5.3-32)	Angiotensin receptor blocker (n=6)	18 (14-28)	Prophylaxis (n=121)	14 (6.9-28)
Losartan (n=1)	700								
Sodium valproate (n=8)	19600 (11200-39200, 11200-25200)	Anti-epileptic (n=18)	9.3 (4.7-15)			Anti-epileptic (n=33)	9.3 (4.7-14)		
Topiramate (n=43)	2800 (275-19600, 1400-4200)								
Atenolol (n=1)	700	Beta blocker (n=31)	14 (7-28)			Beta blocker (n=35)	14 (7-28)		
Metoprolol (n=1)	2800								
Propranolol (n=64)	2240 (0-13440, 1120-4480)								
Flunarizine (n=3)	150 (140-310, 140-310)	Calcium channel blocker (n=1)	14			Calcium channel blocker (n=2)	23 (15-31)		
Gabapentin (n=15)	27000 (16800-75600, 16800-50400)	Gabapentinoid (n=13)	24 (14-37)			Gabapentinoid (n=12)	14 (9.3-23)		
Pregabalin (n=10)	6400 (700-33600, 4200-16800)								
Citalopram (n=5)	560 (280-4480, 280-560)	Other antidepressant (n=16)	25 (14-29)			Other antidepressant (n=12)	21 (14-42)		
Duloxetine (n=3)	560 (560-1120, 560-1120)								
Escitlaopram (n=1)	280								
Fluoxetine (n=2)	700 (280-1120, 280-1120)								

Mirtazepine (n=7)	420 (420-1260, 420-450)								
Sertraline (n=8)	1400 (700-2800, 1400-2150)								
Venlafaxine (n=3)	2100 (2100-2100, 2100-2100)								
Pizotifen (n=18)	42 (7-126, 14-56)	Serotonergic antagonist (n=12)	28 (14-47)			Serotonergic antagonist (n=6)	23 (9.3-28)		
Amitriptyline (n=76)	560 (30-5600, 280-1085)	Tricyclic antidepressant (n=47)	7.5 (3.7-15)			Tricyclic antidepressant (n=42)	7.5 (3.7-15)		
Dosulepin (n=2)	3150 (2100-4200, 2100-4200)								
Imipramine (n=0)	-								
Nortriptyline (n=11)	560 (100-2800, 280-1400)								
Anxiolytic/sedative									
Diazepam (n=6)	35 (2-112, 6-84)	Benzodiazepine (n=3)	2 (0.6-11)	Anxiolytic/ sedative (n=3)	2 (0.6-11)	Benzodiazepine (n=4)	3.3 (0.9-6.7)	Anxiolytic/sedative (n=5)	5 (1.6-8.4)
Lorazepam (n=1)	4								
Zopiclone (n=1)	210	Cyclopyrrolone sedative (n=0)	-			Cyclopyrrolone sedative (n=1)	28		

* Opioids reported as morphine equivalent quantities standardised to codeine DDDs to make dosage appropriate for non-malignant pain.

eTable 2: Daily defined dose (DDD) summarised by drug group and drug type across treatments arms at baseline.

Medications	Standard care N; Median DDD (IQR)	Self-management N; Median DDD (IQR)
Drug group		
Analgesic	244; 6 (2.3-14)	251; 4.8 (1.8-11)
Anti-emetic	18; 2.7 (2-3)	13; 2 (1-6.7)
NSAID	136; 4.7 (2-13)	159; 5.3 (2-11)
Opioids	114; 2.4 (0.96-9)	86; 1.9 (0.67-5.8)
Triptan	174; 8 (3-16)	178; 8 (4-16)
Angiotensin receptor block	4; 32 (6-56)	6; 18 (14-28)
Anti-epileptic	18; 9.3 (4.7-15)	33; 9.3 (4.7-14)
Beta blocker	31; 14 (7-28)	35; 14 (7-28)
Calcium channel blocker	1; 14	2; 23 (15-31)
Gabapentinoid	13; 24 (14-37)	12; 14 (9.3-23)
Other antidepressant	16; 25 (14-29)	12; 21 (14-42)
Serotonergic antagonist	12; 28 (14-47)	6; 23 (9.3-28)
Tricyclic antidepressant	47; 7.5 (3.7-15)	42; 7.5 (3.7-15)
Benzodiazepine	3; 2 (0.6-11)	4; 3.3 (0.9-6.7)
Cyclopyrrolone sedative	-	1; 28
Drug type		
Acute	321; 14 (6.6-28)	341; 12 (5.3-25)
Prophylaxis	114; 14 (5.3-32)	121; 14 (6.9-28)
Anxiolytic/Sedative	3; 2 (0.6-11)	5; 5 (1.6-8.4)

eTable 3: Summary of medications at 4 months.

		Standard care				Self-management			
Drug (n=495)	**Median Dose mg/28 days (range, IQR)**	**Drug group (n= 243)**	**Median DDDs Median (IQR)**	**Type (n=243)**	**Median DDDs Median (IQR)**	**Drug group (n=252)**	**Median DDDs Median (IQR)**	**Type (n=252)**	**Median DDDs Median (IQR)**
Acute									
Aspirin (n=47)	4800 (600-36000, 2400-7200)	Analgesic (n=161)	4.3 (1.3-8)	Acute (n=226)	9.3 (4.7-20)	Analgesic (n=173)	3.2 (1.3-6.7)	Acute (n=232)	8.3 (3.3-16)
Paracetamol (n=324)	10000 (250-234000, 4000-22500)								
Cyclizine (n=0)	-	Anti-emetic (n=9)	1 (0.75-2.7)			Anti-emetic (n=6)	1.7 (0.5-6)		
Domperidone (n=1)	60								
Metoclopramide (n=5)	180 (80-840, 140-200)								
Prochlorperazine (n=9)	9 (6-40, 6-12)								
Diclofenac (n=3)	300 (100-300, 100-300)	NSAID (n=90)	4 (1.7-8)			NSAID (n=74)	2.8 (1.3-6.7)		
Ibuprofen (n=145)	3200 (200-39200, 1600-8000)								
Indometacin (n=1)	400								
Mefenamic acid (n=0)	-								
Meloxicam (n=0)	-								
Naproxen (n=21)	4000 (500-84000, 1750-10000)								
Tolefenamic acid (n=1)	1000								
Fentanyl patches (n=1)	34	Opioids* (n=63)	2.9 (1-7.6)			Opioids* (n=51)	2 (0.64-9.6)		
Morphine (n=2)	135 (30-240, 30-240)								
Tramadol (n=7)	2800 (150-8400, 1000-7200)								
Codeine (n=96)	224 (10-6720, 64-640)								
Dihydrocodeine (n=10)	530 (22-6720, 40-1120)								
Tapentadol (n=0)	-								
Almotriptan (n=2)	75 (75-75, 75-75)	Triptan (n=116)	6.5 (4-13)			Triptan (n=130)	6 (4-12)		
Eletriptan (n=4)	260 (160-560, 180-440)								
Frovatriptan (n=7)	23 (7.5-45, 15-34)								
Naratriptan (n=20)	15 (2.5-28, 8.8-21)								

Rizatriptan (n=28)	35 (5-240, 20-60)								
Sumatriptan injection (n=3)	24 (18-90, 18-90)								
Sumatriptan oral (n=141)	400 (0-3900, 200-800)								
Sumatriptan spray (n=7)	80 (10-300, 20-160)								
Zolmitriptan oral (n=37)	18 (2.5-140, 10-30)								
Zolmitriptan spray (n=8)	15 (0-50, 7.5-30)								
Prophylaxis									
Candesartan (n=7)	168 (56-448, 112-448)	Angiotensin receptor blocker (n=3)	56 (21-56)	Prophylaxis (n=80)	14 (7.2-28)	Angiotensin receptor blocker (n=5)	21 (14-28)	Prophylaxis (n=86)	14 (4.7-28)
Losartan (n=1)	4200								
Sodium valproate (n=4)	22400 (11200-28000, 16800-25200)	Anti-epileptic (n=10)	7.2 (4.7-15)			Anti-epileptic (n=28)	5.8 (3.5-11)		
Topiramate (n=34)	1750 (175-8400, 1400-2800)								
Atenolol (n=2)	2450 (700-4200, 700-4200)	Beta blocker (n=25)	14 (11-28)			Beta blocker (n=24)	28 (14-28)		
Metoprolol (n=0)	-								
Propranolol (n=47)	2240 (320-8960, 2240-4480)								
Flunarizine (n=2)	140 (140-140, 140-140)	Calcium channel blocker (n=2)	14 (14-14)			Calcium channel blocker (n=0)	-		
Gabapentin (n=14)	21000 (2100-75600, 8400-25200)	Gabapentinoid (n=10)	12 (7-37)			Gabapentinoid (n=13)	9.3 (4.7-14)		
Pregabalin (n=9)	2800 (1050-33600, 2100-16800)								
Citalopram (n=4)	420 (240-560, 260-560)	Other antidepressant (n=11)	28 (20-28)			Other antidepressant (n=7)	21 (14-28)		
Duloxetine (n=3)	3360 (1680-3360, 1680-3360)								
Escitlaopram (n=0)	-								
Fluoxetine (n=3)	560 (400-560, 400-560)								
Mirtazepine (n=1)	420								
Sertraline (n=5)	1400 (700-1400, 700-1400)								
Venlafaxine (n=2)	3150 (2100-4200, 2100-4200)								
Pizotifen (n=11)	28 (7-84, 14-42)	Serotonergic antagonist (n=6)	14 (9.3-28)			Serotonergic antagonist (n=5)	19 (9.3-21)		
Amitriptyline (n=49)	560 (20-6300, 280-1120)		9.3 (3.7-17)				4.7 (3.7-11)		

Dosulepin (n=3)	2100 (1400-4200, 1400-4200)	Tricyclic antidepressant (n=35)				Tricyclic antidepressant (n=25)			
Imipramine (n=1)	840								
Nortriptyline (n=7)	840 (210-2800, 280-1240)								
Anxiolytic/sedative									
Diazepam (n=3)	112 (4-180, 4-180)	Benzodiazepine (n=1)	11	Anxiolytic/sedative (n=1)	11	Benzodiazepine (n=2)	9.2 (0.4-18)	Anxiolytic/sedative (n=2)	9.2 (0.4-18)
Lorazepam (n=0)	-								
Zopiclone (n=0)	-	Cyclopyrrolone sedative (n=0)	-			Cyclopyrrolone sedative (n=0)	-		

* Opioids reported as morphine equivalent quantities standardised to codeine DDDs to make dosage appropriate for non-malignant pain

eTable 4: Daily defined dose (DDD) summarised by drug group and drug type across treatments arms at 4 months (based on eTable 3).

Medications	Standard care N; Median DDD (IQR)	Self-management N; Median DDD (IQR)	P-value*
Drug group			
Analgesic	161; 4.3 (1.3-8)	173; 3.2 (1.3-6.7)	0.094
Anti-emetic	9; 1 (0.75-2.7)	6; 1.7 (0.5-6)	0.634
NSAID	90; 4 (1.7-8)	74; 2.8 (1.3-6.7)	0.199
Opioids	63; 2.9 (1-7.6)	51; 2 (0.64-9.6)	0.486
Triptan	116; 6.5 (4-13)	130; 6 (4-12)	0.841
Angiotensin receptor block	3; 56 (21-56)	5; 21 (14-28)	0.500
Anti-epileptic	10; 7.2 (4.7-15)	28; 5.8 (3.5-11)	0.324
Beta blocker	25; 14 (11-28)	24; 28 (14-28)	0.005
Calcium channel blocker	2; 14 (14-14)	-	-
Gabapentinoid	10; 12 (7-37)	13; 9.3 (4.7-14)	0.435
Other antidepressant	11; 28 (20-28)	7; 21 (14-28)	0.248
Serotonergic antagonist	6; 14 (9.3-28)	5; 19 (9.3-21)	0.905

Tricyclic antidepressant	35; 9.3 (3.7-17)	25; 4.7 (3.7-11)	0.289
Benzodiazepine	1; 11	2; 9.2 (0.4-18)	1.00
Cyclopyrrolone sedative	-	-	-
Drug type			
Acute	226; 9.3 (4.7-20)	232; 8.3 (3.3-16)	0.165
Prophylaxis	80; 14 (7.2-28)	86; 14 (4.7-28)	0.921
Anxiolytic/Sedative	1; 11	2; 9.2 (0.4-18)	1.00

* P-value computed using a non-parametric test.

eTable 5: Summary of medications at 8 months.

		Standard care				Self-management			
Drug (n=486)	**Median Dose mg/28 days (range, IQR)**	**Drug group (n= 229)**	**Median DDDs Median (IQR)**	**Type (n=229)**	**Median DDDs Median (IQR)**	**Drug group (n=257)**	**Median DDDs Median (IQR)**	**Type (n=257)**	**Median DDDs Median (IQR)**
Acute									
Aspirin (n=48)	5000 (325-50400, 2650-8700)	Analgesic (n=136)	3.4 (1.3-8)	Acute (n=203)	10 (4-17)	Analgesic (n=155)	2.7 (1.2-6.4)	Acute (n=225)	7.7 (3-16)
Paracetamol (n=276)	9000 (250-126000, 3175-19750)								
Cyclizine (n=3)	500 (300-500, 300-500)	Anti-emetic (n=10)	3.7 (2.5-6.7)			Anti-emetic (n=5)	1.3 (1-5)		
Domperidone (n=1)	40								
Metoclopramide (n=5)	200 (100-2520, 150-210)								
Prochlorperazine (n=6)	24 (12-75, 18-48)								
Diclofenac (n=3)	3000 (800-4200, 800-4200)	NSAID (n=78)	3.3 (1.5-8)			NSAID (n=76)	3 (1.3-7.6)		
Ibuprofen (n=132)	3200 (200-33600, 1600-7000)								
Indometacin (n=1)	400								
Mefenamic acid (n=1)	3000								
Meloxicam (n=1)	210								
Naproxen (n=20)	3000 (500-56000, 1750-10250)								
Tolefenamic acid (n=1)	800								
Fentanyl patches (n=0)	-	Opioids* (n=54)	2.6 (0.96-9)			Opioids* (n=46)	1.4 (0.6-3.6)		
Morphine (n=2)	1260 (840-1680, 840-1680)								

Tramadol (n=7)	1600 (100-6300, 200-5600)								
Codeine (n=86)	174 (0-3360, 64-480)								
Dihydrocodeine (n=7)	240 (0-6720, 60-1120)								
Tapentadol (n=0)	-								
Almotriptan (n=2)	106 (63-150, 63-150)	Triptan (n=106)	7.8 (4-12)			Triptan (n=127)	6 (4-12)		
Eletriptan (n=3)	80 (40-300, 40-300)								
Frovatriptan (n=8)	16 (5-30, 11-23)								
Naratriptan (n=23)	10 (2.5-75, 5-18)								
Rizatriptan (n=33)	60 (5-280, 40-120)								
Sumatriptan injection (n=4)	18 (6-36, 9-30)								
Sumatriptan oral (n=124)	300 (50-8000, 200-613)								
Sumatriptan spray (n=5)	120 (20-240, 20-180)								
Zolmitriptan oral (n=36)	21 (2.5-101, 10-33)								
Zolmitriptan spray (n=7)	20 (0-125, 5-45)								
Prophylaxis									
Candesartan (n=5)	112 (44-224, 56-224)	Angiotensin receptor blocker (n=1)	28	Prophylaxis (n=73)	14 (7-28)	Angiotensin receptor blocker (n=5)	14 (7-28)	Prophylaxis (n=84)	12 (4.3-27)
Losartan (n=1)	1400								
Sodium valproate (n=5)	12000 (11200-22400, 11200-16800)	Anti-epileptic (n=11)	9.3 (4.7-18)			Anti-epileptic (n=25)	4.7 (2.3-12)		
Topiramate (n=32)	1400 (0-16800, 700-4025)								
Atenolol (n=1)	700	Beta blocker (n=24)	14 (8.2-28)			Beta blocker (n=25)	14 (14-28)		
Metoprolol (n=0)	-								
Propranolol (n=48)	2240 (360-8960, 1680-4480)								
Flunarizine (n=1)	140	Calcium channel blocker (n=1)	14			Calcium channel blocker (n=0)	-		
Gabapentin (n=5)	33600 (19600-67200, 25200-44800)	Gabapentinoid (n=7)	14 (9.3-37)			Gabapentinoid (n=4)	12 (7-19)		
Pregabalin (n=6)	2800 (600-14700, 1400-4200)								
Citalopram (n=5)	560 (280-1120, 560-560)	Other antidepressant (n=11)	14 (7-28)			Other antidepressant (n=9)	42 (28-56)		
Duloxetine (n=3)	420 (140-560, 140-560)								

Escitlaopram (n=0)	-								
Fluoxetine (n=2)	570 (20-1120, 20-1120)								
Mirtazepine (n=4)	420 (300-1260, 360-840)								
Sertraline (n=6)	2800 (1400-5600, 1400-4200)								
Venlafaxine (n=0)	-								
Pizotifen (n=11)	42 (14-84, 14-42)	Serotonergic antagonist (n=8)	28 (9.3-28)			Serotonergic antagonist (n=3)	19 (9.3-28)		
Amitriptyline (n=49)	560 (0-4200, 280-840)	Tricyclic antidepressant (n=30)	8.9 (3.7-15)			Tricyclic antidepressant (n=34)	7.5 (3.7-11)		
Dosulepin (n=3)	800 (700-2800, 700-2800)								
Imipramine (n=1)	840								
Nortriptyline (n=11)	840 (100-2800, 160-1120)								
Anxiolytic/sedative									
Diazepam (n=2)	77 (42-112, 42-112)	Benzodiazepine (n=1)	11	Anxiolytic/ sedative (n=1)	11	Benzodiazepine (n=1)	4.2	Anxiolytic/ sedative (n=1)	4.2
Lorazepam (n=0)	-								
Zopiclone (n=0)	-	Cyclopyrrolone sedative (n=0)	-			Cyclopyrrolone sedative (n=0)	-		

* Opioids reported as morphine equivalent quantities standardised to codeine DDDs to make dosage appropriate for non-malignant pain

eTable 6: Daily defined dose (DDD) summarised by drug group and drug type across treatments arms at 8 months (based on eeTable).

Medications	Standard care N; Median DDD (IQR)	Self-management N; Median DDD (IQR)	P-value*
Drug group			
Analgesic	136; 3.4 (1.3-8)	155; 2.7 (1.2-6.4)	0.095
Anti-emetic	10; 3.7 (2.5-6.7)	5; 1.3 (1-5)	0.140
NSAID	78; 3.3 (1.5-8)	76; 3 (1.3-7.6)	0.562
Opioids	54; 2.6 (0.96-9)	46; 1.4 (0.6-3.6)	0.020
Triptan	106; 7.8 (4-12)	127; 6 (4-12)	0.636
Angiotensin receptor block	1; 28	5; 14 (7-28)	1.00
Anti-epileptic	11; 9.3 (4.7-18)	25; 4.7 (2.3-12)	0.056
Beta blocker	24; 14 (8.2-28)	25; 14 (14-28)	0.872
Calcium channel blocker	1; 14	-	-
Gabapentinoid	7; 14 (9.3-37)	4; 12 (7-19)	0.612
Other antidepressant	11; 14 (7-28)	9; 42 (28-56)	0.140
Serotonergic antagonist	8; 28 (9.3-28)	3; 19 (9.3-28)	0.727
Tricyclic antidepressant	30; 8.9 (3.7-15)	34; 7.5 (3.7-11)	0.603
Benzodiazepine	1; 11	1; 42	1.00
Cyclopyrrolone sedative	-	-	-
Drug type			
Acute	203; 10 (4-17)	225; 7.7 (3-16)	0.162
Prophylaxis	73; 14 (7-28)	84; 12 (4.3-27)	0.170
Anxiolytic/Sedative	1; 11	1; 4.2	1.000

* P-value computed using a non-parametric test.

eTable 7: Summary of medications at 12 months.

		Standard care				Self-management			
Drug (n=504)	**Median Dose mg/28 days (range, IQR)**	**Drug group (n=236)**	**Median DDDs Median (IQR)**	**Type (n=236)**	**Median DDDs Median (IQR)**	**Drug group (n=268)**	**Median DDDs Median (IQR)**	**Type (n=268)**	**Median DDDs Median (IQR)**
Acute									
Aspirin (n=49)	4000 (600-39000, 2400-9600)	Analgesic (n=143)	3 (1.3-10)	Acute (n=212)	9.8 (3.1-18)	Analgesic (n=171)	3.3 (1.3-7.8)	Acute (n=247)	8 (3.3-16)
Paracetamol (n=301)	9000 (400-90000, 4000-22000)								
Cyclizine (n=2)	325 (200-450, 200-450)	Anti-emetic (n=9)	4.5 (1.7-6)			Anti-emetic (n=12)	2 (0.5-2.8)		
Domperidone (n=3)	60 (10-200, 10-200)								
Metoclopramide (n=8)	120 (0-460, 35-210)								
Prochlorperazine (n=8)	24 (3-72, 15-60)								
Diclofenac (n=4)	500 (150-3600, 225-2150)	NSAID (n=81)	3.3 (1.3-9)			NSAID (n=85)	3 (1.7-8)		
Ibuprofen (n=148)	3400 (200-50400, 1600-9600)								
Indometacin (n=1)	450								
Mefenamic acid (n=0)	-								
Meloxicam (n=0)	-								
Naproxen (n=17)	3500 (250-51000, 1500-14000)								
Tolefenamic acid (n=1)	1000								
Fentanyl patches (n=0)	-	Opioids* (n=57)	1.9 (0.64-5.1)			Opioids* (n=45)	1.9 (1.1-6.3)		
Morphine (n=1)	3640								
Tramadol (n=6)	1250 (100-9200, 200-5600)								
Codeine (n=86)	186 (0-4800, 72-576)								
Dihydrocodeine (n=8)	155 (10-1120, 45-760)								
Tapentadol (n=1)	700								
Almotriptan (n=3)	63 (50-88, 50-88)	Triptan (n=106)	8 (3-15)			Triptan (n=137)	6 (4-12)		
Eletriptan (n=3)	320 (160-840, 160-840)								
Frovatriptan (n=8)	7.5 (2.5-60, 5-23)								
Naratriptan (n=21)	18 (5-100, 10-25)								
Rizatriptan (n=25)	50 (10-300, 30-100)								

Sumatriptan injection (n=4)	36 (18-672, 21-360)								
Sumatriptan oral (n=141)	300 (50-27200, 150-600)								
Sumatriptan spray (n=5)	40 (20-240, 20-240)								
Zolmitriptan oral (n=36)	20 (2.5-140, 11-41)								
Zolmitriptan spray (n=6)	20 (5-50, 10-40)								
Prophylaxis									
Candesartan (n=7)	112 (4-224, 28-224)	Angiotensin receptor blocker (n=2)	21 (14-28)	Prophylaxis (n=69)	14 (7-28)	Angiotensin receptor blocker (n=6)	11 (3.5-28)	Prophylaxis (n=84)	14 (7.5-28)
Losartan (n=1)	1400								
Sodium valproate (n=4)	22400 (11200-33600, 16800-28000)	Anti-epileptic (n=10)	7.2 (4.7-14)			Anti-epileptic (n=20)	8.2 (3.5-17)		
Topiramate (n=26)	2100 (350-6300, 1400-4200)								
Atenolol (n=0)	-	Beta blocker (n=22)	28 (14-28)			Beta blocker (n=31)	14 (14-28)		
Metoprolol (n=0)	-								
Propranolol (n=53)	2520 (160-8960, 2240-4480)								
Flunarizine (n=1)	140	Calcium channel blocker (n=1)	14			Calcium channel blocker (n=0)	-		
Gabapentin (n=6)	30800 (16800-67200, 25200-67200)	Gabapentinoid (n=5)	14 (14-20)			Gabapentinoid (n=6)	12 (4.7-28)		
Pregabalin (n=5)	1400 (700-8400, 1400-4200)								
Citalopram (n=3)	280 (135-560, 135-560)	Other antidepressant (n=9)	19 (9.3-28)			Other antidepressant (n=7)	21 (14-28)		
Duloxetine (n=4)	490 (140-1120, 280-840)								
Escitlaopram (n=0)	-								
Fluoxetine (n=2)	560 (560-560, 560-560)								
Mirtazepine (n=2)	1050 (420-1680, 420-1680)								
Sertraline (n=3)	1400 (1400-1400, 1400-1400)								
Venlafaxine (n=2)	2100 (2100-2100, 2100-2100)								
Pizotifen (n=12)	28 (11-42, 14-42)	Serotonergic antagonist (n=8)	28 (14-28)			Serotonergic antagonist (n=4)	14 (9.3-19)		
Amitriptyline (n=44)	560 (30-4200, 280-840)	Tricyclic antidepressant (n=29)	7.5 (3.7-11)			Tricyclic antidepressant (n=27)	7.5 (3.7-15)		
Dosulepin (n=2)	3150 (2100-4200, 2100-4200)								
Imipramine (n=1)	1120								

Nortriptyline (n=9)	560 (210-1400, 560-800)								
Anxiolytic/sedative									
Diazepam (n=1)	16	Benzodiazepine (n=1)	1.6	Anxiolytic/sedative (n=1)	1.6	Benzodiazepine (n=0)	-	Anxiolytic/sedative (n=0)	-
Lorazepam (n=0)	-								
Zopiclone (n=0)	-	Cyclopyrrolone sedative (n=0)	-			Cyclopyrrolone sedative (n=0)	-		

* Opioids reported as morphine equivalent quantities standardised to codeine DDDs to make dosage appropriate for non-malignant pain

eTable 8: Daily defined dose (DDD) summarised by drug group and drug type across treatments arms at 12 months (based on eeTable).

Medications	Standard care N; Median DDD (IQR)	Self-management N; Median DDD (IQR)	P-value*
Drug group			
Analgesic	142; 3 (1.3-10)	171; 3.3 (1.3-7.8)	0.637
Anti-emetic	9; 4.5 (1.7-6)	12; 2 (0.5-2.8)	0.239
NSAID	81; 3.3 (1.3-9)	85; 3 (1.7-8)	0.754
Opioids	57; 1.9 (0.64-5.1)	45; 1.9 (1.1-6.3)	0.344
Triptan	106; 8 (3-15)	137; 6 (4-12)	0.585
Angiotensin receptor block	2; 21 (14-28)	6; 11 (3.5-28)	0.643
Anti-epileptic	10; 7.2 (4.7-14)	20; 8.2 (3.5-17)	0.940
Beta blocker	22; 28 (14-28)	31; 14 (14-28)	0.539
Calcium channel blocker	1; 14	-	-
Gabapentinoid	5; 14 (14-20)	6; 12 (4.7-28)	0.623
Other antidepressant	9; 19 (9.3-28)	7; 21 (14-28)	0.811
Serotonergic antagonist	8; 28 (14-28)	4; 14 (9.3-19)	0.186
Tricyclic antidepressant	29; 7.5 (3.7-11)	27; 7.5 (3.7-15)	0.709
Benzodiazepine	1; 1.6	-	-
Cyclopyrrolone sedative	-	-	-
Drug type			
Acute	212; 9.8 (3.1-18)	247; 8 (3.3-16)	0.614
Prophylaxis	69; 14 (7-28)	84; 14 (7.5-28)	0.860
Anxiolytic/Sedative	1; 1.6	-	-

* P-value computed using a non-parametric test.

eTable 9: Screening of potential participants summarised by clinical commissioning groups (CCGs).

CCG/Practice name	Practice population	Number identified by search	Total Number Excluded	Total Number Mail Out	EOI entered	Not interested	Interested	Not eligible	Eligible	Consented	Randomised
NHS Berkshire West CCG	11637	218	25	193	56	39	17	10	4	2	2
NHS Birmingham and Solihull CCG	164665	3431*	78*	3338*	523	352	171	52	78	43	41
NHS Birmingham Crosscity CCG	15490	603	0	603	108	90	18	7	8	6	6
NHS Cannock Chase CCG	8104	174	10	164	48	33	15	6	9	6	4
NHS Coventry and Rugby CCG	95078	1974	204	1761	386	237	149	42	91	58	53
NHS East Leicestershire and Rutland CCG	11119	297	30	267	69	48	21	4	11	10	10
NHS East Staffordshire CCG	53524	1009	82	927	321	213	108	38	65	45	42
NHS Herefordshire and Worcestershire CCG	130457	2592	67	2519	787	516	271	85	125	91	83
NHS Hounslow CCG	49311	1522	35	1487	254	176	78	41	32	25	25
NHS Leicester City CCG	24278	1242	8	1223	144	94	50	7	21	10	9
NHS Milton Keynes CCG	30844	1376	43	1333	269	195	74	11	37	23	20
NHS Newham CCG	54483	859	25	834	99	50	49	20	24	18	16
NHS North Central London CCG	106936	2114	167	1947	343	227	116	55	58	40	39
NHS Nottingham and Nottinghamshire CCG	69075	2251	70	1906	313	225	88	30	44	30	27
NHS Oxfordshire CCG	170890	3513	360	3148	859	604	255	77	136	78	72
NHS South East London CCG	197575	3602	154	3448	623	386	237	98	125	87	81
NHS South East Staffordshire and Seisdon Peninsula CCG	28595	360	47	313	158	112	46	14	31	25	25
NHS South Warwickshire CCG	98303	1738	125	1607	552	394	158	48	94	69	67
NHS South West London CCG	35446	587	27	560	125	83	42	19	20	14	13
NHS Southwark CCG	21488	303	3	300	46	28	18	6	9	8	7
NHS Tower Hamlets CCG	86463	1868	49	1819	199	110	89	47	39	29	28

CCG/Practice name	Practice population	Number identified by search	Total Number Excluded	Total Number Mail Out	EOI entered	Not interested	Interested	Not eligible	Eligible	Consented	Randomised
NHS Warwickshire North CCG	65923	1365	42	1323	380	271	109	29	64	41	39
Self-referral	**	**	**	**	**	0	41	7	34	27	27
Total	**1529684**	**32998**	**1651**	**31020**	**6703**	**4483**	**2220**	**753**	**1159**	**785**	**736**

* Missing data from two practices
** Not applicable

eTable 10: Number and percentage of participants randomised to standard care and self-management by geographical location.

Region	Standard care	Self-management	Total
Midlands	249 (48.4%)	266 (51.6%)	515
Greater London	107 (48.4%)	114 (51.6%)	221
TOTAL:	356	380	736

eTable 11: Baseline demographic characteristics of all randomised participants with migraine by treatment group

	Standard care (N=351)	Self-management (N=376)	TOTAL (N=727)
Headache classification			
Definite chronic migraine *with MOH*	191 (54%) *122 (35%)*	*205 (55%)* *131 (35%)*	*396 (54%)* *253 (34%)*
Chronic tension type headache and episodic migraine *with MOH*	160 (46%) *74 (21%)*	171 (45%) *80 (21%)*	331 (46%) *154 (21%)*
Age (years)			
Mean (SD)	47·9 (15·0)	47·0 (14·9)	47·5 (15·0)
Gender			
Female	284 (81%)	320 (85%)	604 (83%)
Male	67 (19%)	54 (14%)	121 (17%)
Missing	0	2 (1%)	2 (<1%)
Race and Ethnicity[a]			
Asian	29 (8%)	31 (8%)	60 (8%)
Black	24 (7%)	18 (5%)	42 (6%)
White	282 (80%)	304 (80%)	586 (80%)
Multiracial or multiethnic	8 (2%)	13 (3%)	21 (3%)
Other	2 (1%)	6 (2%)	8 (1%)
Missing	6 (2%)	4 (1%)	10 (1%)
Employment status			
Employed	192 (55%)	221 (59%)	413 (57%)
Unemployed	9 (3%)	14 (4%)	23 (3%)

At school or full-time education	10 (3%)	13 (3%)	23 (3%)
Unable to work due to long term sickness	36 (10%)	33 (9%)	69 (9%)
Looking after home/family	21 (6%)	22 (6%)	43 (6%)
Retired from paid work	60 (17%)	57 (15%)	117 (16%)
Other	16 (4%)	11 (3%)	27 (4%)
Missing	7 (2%)	5 (1%)	12 (1%)
Age left full time education			
Did not receive formal education	2 (1%)	2 (1%)	4 (1%)
Age 12 or less	3 (1%)	2 (1%)	5 (1%)
Age 13 to 16	92 (26%)	82 (22%)	174 (24%)
Age 17 to 19	90 (26%)	108 (29%)	198 (27%)
Age 20 or over	144 (41%)	163 (43%)	307 (42%)
Still in full time education	12 (3%)	15 (4%)	27 (4%)
Missing	8 (2%)	4 (1%)	12 (2%)
Headache/migraine days over the last 4 weeks			
N	349	372	721
Median (IQR)	16 (10, 20)	16 (12, 20)	16 (11, 20)
Headache/migraine days over the last 4 weeks			
N	349	372	
<15	137 (39%)	137 (37%)	274 (38%)
≥15	212 (61%)	235 (63%)	447 (62%)
Number of days pain killers or triptans were used as acute medications for headache/migraine over the last 4 weeks			
N	346	371	717
Median (IQR)	12 (8, 16)	12 (6, 17)	12 (7, 17)
Number of hours the headache/migraine lasted on the days they had it			
N	236	255	491
Median (IQR)	7 (4, 15)	8 (4, 14)	7 (4, 15)
Average severity (0-10; No pain to Extremely severe pain) on the headache/migraine Days			
N	242	264	506
Median (IQR)	7 (6, 8)	7 (6, 8)	7 (6, 8)
How fatigued were you on average in the past seven days			
Not at all	3 (1%)	6 (2%)	9 (1%)
A little bit	43 (12%)	41 (11%)	84 (12%)
Somewhat	83 (27%)	79 (21%)	162 (22%)
Quite a bit	138 (39%)	147 (39%)	285 (39%)
Very much	82 (23%)	99 (26%)	181 (25%)

Missing	2 (1%)	4 (1%)	6 (1%)
Sleep quality in the past seven days			
Very poor	45 (13%)	57 (15%)	102 (14%)
Poor	113 (32%)	128 (34%)	241 (33%)
Fair	132 (38%)	134 (36%)	266 (37%)
Good	54 (15%)	47 (13%)	101 (14%)
Very good	6 (2%)	7 (2%)	13 (2%)
Missing	1 (<1%)	3 (1%)	4 (1%)
Average pain (other than headache) in the past seven days (0-10; No pain to Worst imaginable pain)			
N	346	369	715
Mean (SD)	4·5 (2·7)	4·4 (2·7)	4·5 (2·7)

eTable 12: Baseline outcome measures by treatment group

Baseline outcome measure	Standard care (N=351)	Self-management (N=376)	TOTAL (N=727)
HIT-6			
N	350	374	724
Mean (SD)	64.6 (5.5)	64.4 (5.4)	64.5 (5.5)
Median (IQR)	64.5 (61, 68)	64 (62, 68)	64 (61, 68)
Missing	1	2	3
CH-QLQ – role restrictive			
N	351	374	725
Mean (SD)	54.5 (17.3)	54.4 (16.9)	54.4 (17.1)
Median (IQR)	57.1 (42.9, 66.7)	54.8 (42.9, 66.7)	54.8 (42.9, 66.7)
Missing	0	2	2
CH-QLQ – role preventive			
N	351	374	725
Mean (SD)	69.4 (21.2)	69.4 (20.5)	69.4 (20.8)
Median (IQR)	75 (54.2, 87.5)	70.8 (54.2, 87.5)	70.8 (54.2, 87.5)
Missing	0	2	2
CH-QLQ – emotional function			
N	351	373	724
Mean (SD)	57.2 (22.3)	57.0 (22.4)	57.1 (22.3)
Median (IQR)	55.6 (38.9, 77.8)	61.1 (38.9, 77.8)	61.1 (38.9, 77.8)
Missing	0	3	3
SF-12 Physical			
N	347	370	717
Mean (SD)	43.7 (10.9)	44.9 (10.0)	44.4 (10.5)
Median (IQR)	44.1 (36.9, 52.1)	45.7 (38.6, 52.7)	45.3 (37.6, 52.5)
Missing	4	6	10
SF-12 Mental			
N	348	370	718

Mean (SD)	39.6 (10.3)	39.8 (10.6)	39.7 (10.5)
Median (IQR)	39.5 (32.2, 47.1)	39.3 (32.2, 48.5)	39.5 (32.2, 47.8)
Missing	3	6	9
EQ-5D			
N	346	372	718
Mean (SD)	0.62 (0.25)	0.64 (0.26)	0.63 (0.26)
Median (IQR)	0.71 (0.53, 0.77)	0.72 (0.53, 0.78)	0.71 (0.53, 0.77)
Missing	5	4	9
EQ-5D VAS			
N	350	371	721
Mean (SD)	62.2 (19.6)	62.9 (20.5)	62.6 (20.0)
Median (IQR)	65 (50, 75)	67 (50, 80)	65 (50, 80)
Missing	1	5	6
HADS Anxiety			
N	349	373	722
Mean (SD)	10.9 (2.7)	10.5 (2.7)	10.7 (2.7)
Median (IQR)	11 (9, 13)	10 (9, 13)	11 (9, 13)
Missing	2	3	5
HADS Depression			
N	349	373	722
Mean (SD)	8.9 (2.0)	9.2 (1.8)	9.1 (1.9)
Median (IQR)	9 (8, 10)	9 (8, 10)	9 (8, 10)
Missing	2	3	5
HADS Anxiety - categorised			
0-7	34 (9.7%)	53 (14.1%)	87 (12.0%)
8-10	115 (32.8%)	138 (36.7%)	253 (34.8%)
11-21	200 (57.0%)	182 (48.4%)	382 (52.5%)
Missing	2 (0.5%)	3 (0.8%)	5 (0.7%)
HADS Depression - categorised			
0-7	76 (21.6%)	59 (15.7%)	135 (18.5%)
8-10	199 (56.7%)	229 (60.9%)	428 (58.9%)
11-21	74 (21.1%)	85 (22.6%)	159 (21.9%)
Missing	2 (0.6%)	3 (0.8%)	5 (0.7%)
PSEQ			
N	348	371	719
Mean (SD)	32.9 (13.3)	32.5 (13.8)	32.7 (13.5)
Median (IQR)	34 (24, 43)	34 (22, 44)	34 (23, 43)
Missing	3	5	8
HeiQ			
N	348	373	721
Mean (SD)	2.8 (0.6)	2.8 (0.7)	2.8 (0.7)
Median (IQR)	2.8 (2.4, 3.2)	3 (2.4, 3.2)	3 (2.4, 3.2)
Missing	3	3	6

eTable 13: Baseline pain grid summarised for participants in the standard care arm.

Pain symptom	No pain experienced	Not at all troublesome	Slightly troublesome	Moderately troublesome	Very troublesome	Extremely troublesome
Headache	2 (0.6%)	0	28 (8.2%)	91 (26.6%)	145 (42.4%)	76 (22.2%)
Neck pain	58 (17.4%)	18 (5.4%)	65 (19.5%)	96 (28.7%)	77 (23.0%)	20 (6.0%)
Shoulder pain	89 (27.1%)	20 (6.1%)	85 (25.8%)	68 (20.7%)	50 (15.2%)	17 (5.2%)
Elbow pain	231 (73.1%)	30 (9.5%)	21 (6.7%)	22 (7.0%)	8 (2.5%)	4 (1.3%)
Wrist / hand pain	165 (51.6%)	25 (7.8%)	60 (18.8%)	34 (10.6%)	24 (7.5%)	12 (3.8%)
Chest pain	205 (64.9%)	26 (8.2%)	48 (15.2%)	22 (7.0%)	10 (3.2%)	5 (1.6%)
Abdominal pain	142 (44.5%)	29 (9.1%)	71 (22.3%)	40 (12.5%)	29 (9.1%)	8 (2.5%)
Upper back pain	149 (46.3%)	22 (6.8%)	70 (21.7%)	39 (12.1%)	32 (9.9%)	10 (3.1%)
Lower back pain	86 (26.1%)	27 (8.2%)	77 (23.4%)	56 (17.0%)	55 (16.7%)	28 (8.5%)
Hip / thigh pain	176 (54.7%)	29 (9.0%)	38 (11.8%)	35 (10.9%)	26 (8.1%)	18 (5.6%)
Knee pain	161 (50.6%)	25 (7.9%)	45 (14.2%)	37 (11.6%)	27 (8.5%)	23 (7.2%)
Ankle / foot pain	183 (56.3%)	20 (6.2%)	51 (15.7%)	34 (10.5%)	18 (5.5%)	19 (5.9%)
Other pains	181 (68.6%)	17 (6.4%)	20 (7.6%)	13 (4.9%)	18 (6.8%)	15 (5.7%)

eTable 14: Baseline pain grid summarised for participants in the self-management arm.

Pain symptom	No pain experienced	Not at all troublesome	Slightly troublesome	Moderately troublesome	Very troublesome	Extremely troublesome
Headache	2 (0.5%)	1 (0.3%)	21 (5.7%)	102 (27.7%)	156 (42.4%)	86 (23.4%)
Neck pain	67 (19.0%)	18 (5.1%)	85 (24.2%)	96 (27.3%)	58 (16.5%)	28 (8.0%)
Shoulder pain	95 (27.5%)	25 (7.3%)	92 (26.7%)	66 (19.1%)	42 (12.2%)	25 (7.3%)
Elbow pain	241 (72.8%)	28 (8.5%)	29 (8.8%)	21 (6.3%)	10 (3.0%)	2 (0.6%)
Wrist / hand pain	171 (50.6%)	24 (7.1%)	77 (22.8%)	35 (10.4%)	22 (6.5%)	9 (2.7%)
Chest pain	219 (66.4%)	29 (8.8%)	46 (13.9%)	19 (5.8%)	14 (4.2%)	3 (0.9%)
Abdominal pain	168 (49.7%)	36 (10.7%)	71 (21.0%)	34 (10.1%)	22 (6.5%)	7 (2.1%)
Upper back pain	150 (45.3%)	34 (10.3%)	64 (19.3%)	44 (13.3%)	26 (7.9%)	13 (3.9%)
Lower back pain	84 (24.1%)	33 (9.5%)	94 (26.9%)	66 (18.9%)	51 (14.6%)	21 (6.0%)
Hip / thigh pain	168 (49.9%)	30 (8.9%)	53 (15.7%)	48 (14.2%)	25 (7.4%)	13 (3.9%)
Knee pain	169 (49.0%)	22 (6.4%)	74 (21.5%)	38 (11.0%)	28 (8.1%)	14 (4.1%)
Ankle / foot pain	184 (55.1%)	28 (8.4%)	51 (15.3%)	38 (11.4%)	28 (8.4%)	5 (1.5%)
Other pains	190 (66.9%)	21 (7.4%)	25 (8.8%)	23 (8.1%)	14 (4.9%)	11 (3.9%)

eTable 15: Summary of intervention data.

	Self-management
Time from randomisation to Session 1 (days)	
N	375
Mean (SD)	26.9 (31.7)
Median (IQR)	15 (11, 23)
Missing	1
Time from randomisation to Session 2 (days)	
N	375
Mean (SD)	34.1 (32.6)
Median (IQR)	22 (18, 30)
Missing	1
Session attendance	
Session 1 only	17 (4.5%)
Session 1 & 2 only	10 (2.7%)
Session 1 and one-to-one only	43 (11.5%)
Session 1 and 2 and one-to-one	216 (57.6%)
Did not attend session 1 (hence no other groups)	89 (23.7%)
Adherence	
Minimum adherence (Session 1 and one-to-one as a minimum)	259 (69.1%)
Full adherence (Session 1, session 2 and one-to-one)	216 (57.6%)
Group size as randomised	
Number of groups	42
Mean (SD)	9.0 (3.4)
Median (IQR)	9 (7, 12)
Missing	0
Group attendance on Day 1	
Number of groups	42
Mean (SD)	6.8 (2.7)
Median (IQR)	6.5 (5, 9)
Missing	0

eTable 16: Longitudinal analysis for the number of headache days as captured by headache diary summarised by treatment group.

	Unadjusted mean difference (95% CI); p-value (N = 492)	Adjusted mean difference (95% CI); p-value (N = 490)
On how many of the last 7 days have you had a headache, days	0.2 (-0.12, 0.46); 0.239	0.2 (-0.11, 0.46); 0.234
On the days you had a headache on average how long did they last, hours	0.4 (-0.52, 1.26); 0.418	0.4 (-0.47, 1.28); 0.361
On the days you had a headache on average how severe were they	0.2 (-0.09, 0.46); 0.181	0.2 (-0.08, 0.46); 0.163

eTable 17: Study outcomes at 4 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
HIT-6					
N	275	276	551	-1.3 (-2.47, -0.11); 0.033	-1.0 (-1.91, -0.006); 0.049
Mean (SD)	62.3 (7.1)	61.0 (7.0)	61.7 (7.1)		
Median (IQR)	63 (59, 66)	62 (58, 65)	62 (58, 66)		
Missing	1	1	2		
CH-QLQ – role restrictive					
N	244	251	495	2.5 (-0.86, 5.80); 0.146	1.5 (-1.01, 3.97); 0.243
Mean (SD)	61.6 (18.3)	64.1 (17.6)	62.9 (18.0)		
Median (IQR)	61.9 (50, 75)	66.7 (52.4, 76.2)	64.3 (50, 76.2)		
Missing	32	26	58		
CH-QLQ – role preventive					
N	244	251	495	2.5 (-1.20, 6.17); 0.187	1.6 (-0.84, 4.02); 0.199
Mean (SD)	75.9 (20.5)	78.6 (18.7)	77.3 (19.6)		
Median (IQR)	81.3 (62.5, 91.7)	83.3 (66.7, 91.7)	83.3 (66.7, 91.7)		
Missing	32	26	58		
CH-QLQ – emotional function					
N	244	251	495	1.7 (-2.45, 5.76); 0.429	1.0 (-2.07, 4.01); 0.531
Mean (SD)	64.8 (23.4)	66.5 (23.0)	65.7 (23.2)		
Median (IQR)	66.7 (44.4, 83.3)	72.2 (50, 88.9)	66.7 (50, 83.3)		
Missing	32	26	58		
SF-12 Physical					
N	242	251	493	0.2 (-1.58, 2.07); 0.793	-0.2 (-1.49, 1.06); 0.739
Mean (SD)	46.1 (10.7)	46.3 (10.0)	46.2 (10.4)		
Median (IQR)	48.8 (38.7, 54.5)	48.4 (40.8, 53.9)	48.5 (40.1, 54.3)		
Missing	34	26	60		
SF-12 Mental					
N	243	251	494	1.6 (-0.32, 3.46); 0.103	0.7 (-0.80, 2.19); 0.361
Mean (SD)	41.2 (10.8)	42.8 (10.2)	42.0 (10.5)		
Median (IQR)	41.7 (32.3, 50.4)	42.7 (35.2, 51.3)	42.3 (34.5, 50.9)		
Missing	33	26	59		
EQ-5D					
N	275	274	549	0.04 (-0.01, 0.09); 0.113 Non-parametric test: P=0.011	0.02 (-0.008, 0.05); 0.150
Mean (SD)	0.63 (0.28)	0.68 (0.26)	0.66 (0.27)		
Median (IQR)	0.72 (0.55, 0.80)	0.74 (0.64, 0.84)	0.74 (0.58, 0.84)		
Missing	1	3	4		
EQ-5D VAS					

N	241	250	491	1.7 (-2.37, 5.71); 0.417	0.8 (-2.27, 3.79); 0.622
Mean (SD)	65.0 (20.7)	67.1 (20.6)	66.0 (20.6)		
Median (IQR)	70 (50, 80)	70 (56, 85)	70 (50, 80)		
Missing	35	27	62		
HADS Anxiety					
N	244	251	495	-0.2 (-0.65, 0.30); 0.472	0.2 (-0.22, 0.55); 0.393
Mean (SD)	10.5 (2.7)	10.3 (2.7)	10.4 (2.7)		
Median (IQR)	10 (8, 12)	10 (8, 12)	10 (8, 12)		
Missing	32	26	58		
HADS Depression					
N	244	251	495	-0.07 (-0.41, 0.27); 0.682	-0.1 (-0.43, 0.20); 0.477
Mean (SD)	9.1 (1.8)	9.0 (1.7)	9.1 (1.8)		
Median (IQR)	9 (8, 10)	9 (8, 10)	9 (8, 10)		
Missing	32	26	58		
PSEQ					
N	244	250	494	2.4 (-0.04, 4.84); 0.054	2.3 (0.51, 4.00); 0.011
Mean (SD)	35.4 (14.2)	37.8 (13.5)	36.6 (13.9)		
Median (IQR)	37.5 (24, 46)	39 (28, 48)	38 (26, 47)		
Missing	32	27	59		
HeiQ					
N	244	251	495	0.09 (-0.04, 0.22); 0.171	0.04 (-0.07, 0.15); 0.452
Mean (SD)	2.9 (0.70)	3.0 (0.70)	2.9 (0.7)		
Median (IQR)	3 (2.4, 3.2)	3 (2.6, 3.4)	3 (2.4, 3.4)		
Missing	32	26	58		

* Models adjusted for age, gender, the baseline value of the dependent variable and baseline stratification factors (type of headache and geographical locality).

eTable 18: Study outcomes at 8 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
HIT-6					
N	263	283	546	-0.3 (-1.45, 0.93); 0.672	0.07 (-0.95, 1.09); 0.888
Mean (SD)	61.1 (7.2)	60.8 (6.4)	61.0 (6.8)		
Median (IQR)	62 (57, 66)	61 (58, 65)	61 (57, 65)		
Missing	1	1	2		
CH-QLQ – role restrictive					
N	228	254	482	0.7 (-2.81, 4.29); 0.683	-0.09 (-2.87, 2.69); 0.949
Mean (SD)	65.3 (19.6)	66.3 (17.8)	65.8 (18.7)		
Median (IQR)	66.7 (52.4, 81.0)	66.7 (54.8, 78.6)	66.7 (52.4, 81.0)		
Missing	36	30	66		
CH-QLQ – role preventive					
N	228	254	482	1.8 (-2.09, 5.62); 0.369	1.2 (-1.47, 3.97); 0.368
Mean (SD)	77.2 (22.1)	79.2 (19.2)	78.3 (20.6)		
Median (IQR)	83.3 (66.7, 95.8)	83.3 (70.8, 95.8)	83.3 (66.7, 95.8)		
Missing	36	30	66		
CH-QLQ – emotional function					
N	228	253	481	0.07 (-4.05, 4.20); 0.972	-0.5 (-3.74, 2.80); 0.778
Mean (SD)	69.2 (23.3)	69.3 (22.6)	69.2 (22.9)		
Median (IQR)	75 (55.6, 88.9)	72.2 (55.6, 88.9)	72.2 (55.6, 88.9)		
Missing	36	31	67		
SF-12 Physical					

N	226	253	479	0.5 (-1.36, 2.35); 0.602	-0.06 (-1.31, 1.18); 0.918
Mean (SD)	46.8 (10.7)	47.3 (9.9)	47.0 (10.3)		
Median (IQR)	49.2 (39.9, 54.8)	48.5 (41.6, 54.8)	48.8 (41.3, 54.8)		
Missing	38	31	69		
SF-12 Mental					
N	226	253	479	1.4 (-0.55, 3.28); 0.161	0.9 (-0.55, 2.44); 0.215
Mean (SD)	41.5 (10.1)	42.9 (10.4)	42.3 (10.3)		
Median (IQR)	41.3 (35.0, 49.3)	43.1 (35.5, 51.2)	42.1 (35.2, 50.4)		
Missing	38	31	69		
EQ-5D					
N	261	280	541	0.05 (-0.002, 0.09); 0.059 Non-parametric test: P=0.037	0.03 (-0.002, 0.06); 0.069
Mean (SD)	0.65 (0.27)	0.70 (0.24)	0.67 (0.26)		
Median (IQR)	0.74 (0.56, 0.80)	0.74 (0.65, 0.84)	0.74 (0.64, 0.84)		
Missing	3	4	7		
EQ-5D VAS					
N	224	253	477	2.9 (-0.93, 6.67); 0.138	2.3 (-0.57, 5.27); 0.115
Mean (SD)	66.1 (21.3)	69.0 (20.1)	67.7 (20.7)		
Median (IQR)	70 (50, 80)	75 (55, 85)	70 (55, 85)		
Missing	40	31	71		
HADS Anxiety					
N	226	252	478	-0.5 (-0.94, -0.03); 0.067	-0.2 (-0.63, 0.23); 0.355
Mean (SD)	10.5 (2.7)	10.0 (2.7)	10.2 (2.7)		
Median (IQR)	10 (8, 12)	10 (8, 12)	10 (8, 12)		
Missing	38	32	70		
HADS Depression					
N	226	252	478	-0.04 (-0.37, 0.28); 0.789	-0.1 (-0.41, 0.17); 0.416
Mean (SD)	9.1 (1.9)	9.0 (1.6)	9.1 (1.8)		
Median (IQR)	9 (8, 10)	9 (8, 10)	9 (8, 10)		
Missing	38	32	70		
PSEQ					
N	226	253	479	1.7 (-0.86, 4.17); 0.198	1.5 (-0.31, 3.34); 0.103
Mean (SD)	37.0 (14.8)	38.7 (13.2)	37.9 (14.0)		
Median (IQR)	39.5 (28, 49)	40 (28, 50)	40 (28, 49)		
Missing	38	31	69		
HeiQ					
N	224	253	477	0.06 (-0.07, 0.19); 0.340	0.04 (-0.06, 0.14); 0.395
Mean (SD)	2.9 (0.7)	3.0 (0.69)	2.9 (0.7)		
Median (IQR)	3 (2.4, 3.3)	3 (2.6, 3.4)	3 (2.6, 3.4)		
Missing	40	31	71		

* Model adjusted for age, gender, the baseline value of the dependent variable and baseline stratification factors (type of headache and geographical locality).

eTable 19: Study outcomes at 12 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
HIT-6					
N	282	300	582	-0.6 (-1.72, 0.54); 0.303	-0.3 (-1.23, 0.67); 0.560
Mean (SD)	60.7 (7.0)	60.1 (6.9)	60.4 (7.0)		
Median (IQR)	62 (57, 65)	61 (55.5, 64.5)	61 (56, 65)		
Missing	1	3	4		
CH-QLQ – role restrictive					

N	235	268	503	0.9 (-2.33, 4.16); 0.582	0.3 (-2.25, 2.94); 0.794
Mean (SD)	66.0 (19.0)	66.9 (18.1)	66.5 (18.5)		
Median (IQR)	66.7 (54.8, 81.0)	66.7 (57.1, 81.0)	66.7 (54.8, 81.0)		
Missing	48	35	83		
CH-QLQ – role preventive					
N	235	268	503	2.5 (-0.92, 5.84); 0.153	2.3 (-0.35, 4.88); 0.090
Mean (SD)	77.5 (20.3)	80.0 (18.4)	78.8 (19.3)		
Median (IQR)	83.3 (66.7, 95.8)	83.3 (70.8, 95.8)	83.3 (66.7, 95.8)		
Missing	48	35	83		
CH-QLQ – emotional function					
N	235	268	503	1.7 (-2.27, 5.69); 0.399	1.2 (-2.06, 4.40); 0.477
Mean (SD)	68.7 (23.3)	70.5 (22.1)	69.7 (22.7)		
Median (IQR)	72.2 (50, 88.9)	72.2 (55.6, 88.9)	72.2 (55.6, 88.9)		
Missing	48	35	83		
SF-12 Physical					
N	234	265	499	0.9 (-0.86, 2.72); 0.308	0.5 (-0.81, 1.77); 0.465
Mean (SD)	46.0 (10.8)	46.9 (9.4)	46.5 (10.1)		
Median (IQR)	47.3 (37.5, 54.5)	48.4 (40.8, 54.4)	48.1 (40.3, 54.5)		
Missing	49	38	87		
SF-12 Mental					
N	234	267	501	1.5 (-0.54, 3.48); 0.151	0.9 (-0.84, 2.58); 0.318
Mean (SD)	42.2 (10.9)	43.9 (10.5)	43.1 (10.7)		
Median (IQR)	41.6 (34.2, 50.7)	44.5 (37.1, 52.2)	43.4 (35.6, 51.4)		
Missing	49	36	85		
EQ-5D					
N	282	301	583	0.03 (-0.02, 0.07); 0.216 Non-parametric test: P=0.107	0.003 (-0.03, 0.03); 0.875
Mean (SD)	0.67 (0.26)	0.69 (0.25)	0.68 (0.25)		
Median (IQR)	0.74 (0.60, 0.81)	0.74 (0.64, 0.84)	0.74 (0.63, 0.84)		
Missing	1	2	3		
EQ-5D VAS					
N	227	264	491	4.1 (0.10, 8.19); 0.045	3.9 (0.90, 6.88); 0.011
Mean (SD)	65.3 (22.5)	69.7 (20.7)	67.7 (21.6)		
Median (IQR)	70 (50, 80)	75 (60, 85)	75 (51, 85)		
Missing	56	39	95		
HADS Anxiety					
N	234	266	500	-0.1 (-0.61, 0.36); 0.610	0.2 (-0.21, 0.61); 0.337
Mean (SD)	10.3 (2.8)	10.2 (2.7)	10.2 (2.7)		
Median (IQR)	10 (8, 12)	10 (8, 12)	10 (8, 10)		
Missing	49	37	86		
HADS Depression					
N	234	266	500	-0.001 (-0.31, 0.31); 0.993	-0.03 (-0.33, 0.26); 0.818
Mean (SD)	9.1 (1.8)	9.1 (1.7)	9.1 (1.8)		
Median (IQR)	9 (8, 10)	9 (8, 10)	9 (8, 10)		
Missing	49	37	86		
PSEQ					
N	234	267	501	2.2 (-0.36, 4.81); 0.091	2.1 (0.17, 3.96); 0.033
Mean (SD)	37.1 (14.6)	39.4 (13.6)	38.3 (14.1)		
Median (IQR)	40 (27, 48)	41 (31, 50)	40 (29, 49)		
Missing	49	36	85		
HeiQ					
N	233	267	500	0.04 (-0.10, 0.18); 0.558	0.001 (-0.10, 0.10); 0.988
Mean (SD)	2.9 (0.70)	3.0 (0.7)	3.0 (0.7)		

Median (IQR)	3 (2.6, 3.4)	3 (2.6, 3.4)	3 (2.6, 3.4)		
Missing	50	36	86		

eTable 20: General health outcomes at 4 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
Headache/migraine days over the last 4 weeks					
N	239	248	487	1.1 (-0.31, 2.44); 0.127	1.5 (0.48, 2.56); 0.004
Mean (SD)	12.3 (7.5)	13.4 (7.6)	12.9 (7.5)		
Median (IQR)	10 (7, 16)	13 (7, 18.5)	12 (7, 18)		
Missing	37	29	66		
Number of days pain killers or triptans were used for headache/migraine over the last 4 weeks					
N	241	249	490	-0.09 (-1.34, 1.61); 0.889	0.2 (-0.91, 1.23); 0.769
Mean (SD)	9.5 (7.3)	9.4 (6.9)	9.5 (7.1)		
Median (IQR)	8 (4, 12)	8 (4, 13)	8 (4, 13)		
Missing	35	28	63		
Average number of hours the headache/migraine lasted on the days they had it					
N	223	220	443	0.2 (-1.09, 1.49); 0.758 Non-parametric test: P=0.335	0.1 (-1.14, 1.43); 0.825
Mean (SD)	8.4 (7.0)	8.6 (6.6)	8.5 (6.8)		
Median (IQR)	6 (4, 12)	6 (4, 12)	6 (4, 12)		
Missing	53	57	110		
Average severity (0-10; No pain to Extremely severe pain) on the days you had a headache/migraine					
N	224	222	446	-0.08 (-0.48, 0.31); 0.677	-0.1 (-0.47, 0.26); 0.569
Mean (SD)	6.1 (2.1)	6.0 (1.9)	6.0 (2.0)		
Median (IQR)	6 (5, 8)	6 (5, 7)	6 (5, 8)		
Missing	52	55	107		
How fatigued were you on average in the past seven days					
Not at all	4 (1.4%)	11 (4.0%)	15 (2.7%)	OR: 0.9 (-0.63, 1.11); 0.378	OR: 0.9 (0.65, 1.27); 0.562
A little bit	53 (19.2%)	52 (18.8%)	105 (19.0%)		
Somewhat	53 (19.2%)	52 (18.8%)	105 (19.0%)		
Quite a bit	75 (27.2%)	86 (31.0%)	161 (29.1%)		
Very much	59 (21.4%)	49 (17.7%)	108 (19.5%)		
Missing	32 (11.6%)	27 (9.7%)	59 (10.7%)		
Sleep quality in the past seven days					
Very poor	38 (13.8%)	33 (11.9%)	71 (12.8%)	OR: 0.9 (0.66, 1.30); 0.665	OR: 1.0 (0.72, 1.42); 0.951
Poor	61 (22.1%)	81 (29.2%)	142 (25.7%)		
Fair	103 (37.3%)	90 (32.5%)	193 (34.9%)		
Good	37 (13.4%)	40 (14.4%)	77 (13.9%)		
Very good	5 (1.8%)	6 (2.2%)	11 (2.0%)		
Missing	32 (11.6%)	27 (9.8%)	59 (10.7%)		
Average pain (other than headache) in the past seven days (0-10; No pain to Worst imaginable pain)					
N	243	250	493	-0.3 (-0.80, 0.27); 0.331	-0.2 (-0.64, 0.16); 0.241
Mean (SD)	4.3 (2.8)	4.0 (2.6)	4.1 (2.7)		
Median (IQR)	4 (2, 6)	4 (2, 6)	4 (2, 6)		
Missing	33	27	60		

eTable 21: General health outcomes at 8 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
Headache/migraine days over the last 4 weeks					
N	226	252	478	-0.01 (-1.44, 1.42); 0.990	0.3 (-0.86, 1.49); 0.598
Mean (SD)	11.8 (8.1)	11.8 (7.4)	11.8 (7.7)		
Median (IQR)	10 (5, 18)	10 (6, 16)	10 (5, 17)		
Missing	38	32	70		
Number of days pain killers or triptans were used for headache/migraine over the last 4 weeks					
N	226	252	478	-0.4 (-1.73, 0.90); 0.532	-0.1 (-1.27, 1.05); 0.852
Mean (SD)	9.3 (7.5)	8.9 (7.2)	9.1 (7.3)		
Median (IQR)	8 (3, 14)	7.5 (3.5, 12)	7 (3, 13)		
Missing	38	32	70		
Average number of hours the headache/migraine lasted on the days they had it					
N	223	246	469	1.5 (0.06, 2.90); 0.041 Non-parametric test: P=0.021	2.0 (0.55, 3.42); 0.007
Mean (SD)	8.0 (6.9)	9.2 (7.3)	8.6 (7.1)		
Median (IQR)	6 (3, 10)	7 (4, 12)	6 (4, 11)		
Missing	41	38	79		
Average severity (0-10; No pain to Extremely severe pain) on the days you had a headache/migraine					
N	222	246	468	0.2 (-0.22, 0.53); 0.436	0.3 (-0.06, 0.65); 0.101
Mean (SD)	6.0 (2.1)	6.1 (2.0)	6.0 (2.0)		
Median (IQR)	6 (5, 7)	6 (5, 7)	6 (5, 7)		
Missing	42	38	80		
How fatigued were you on average in the past seven days					
Not at all	14 (5.3%)	9 (3.2%)	23 (4.3%)	OR: 0.8 (0.60, 1.20); 0.357	OR: 0.9 (0.63, 1.22); 0.429
A little bit	35 (13.3%)	58 (20.4%)	93 (17.0%)		
Somewhat	56 (21.2%)	64 (22.5%)	120 (21.9%)		
Quite a bit	80 (30.3%)	81 (28.5%)	161 (29.4%)		
Very much	41 (15.5%)	41 (14.5%)	82 (15.0%)		
Missing	38 (14.4%)	31 (10.9%)	69 (12.6%)		
Sleep quality in the past seven days					
Very poor	35 (13.3%)	25 (8.8%)	60 (10.9%)	OR: 1.2 (0.86, 1.65); 0.296	OR: 1.3 (0.91, 1.84); 0.153
Poor	62 (23.5%)	71 (25.0%)	133 (24.3%)		
Fair	81 (30.7%)	106 (37.3%)	187 (34.1%)		
Good	40 (15.1%)	44 (15.5%)	84 (15.3%)		
Very good	7 (2.6%)	7 (2.5%)	14 (2.6%)		
Missing	39 (14.8%)	31 (10.9%)	70 (12.8%)		
Average pain (other than headache) in the past seven days (0-10; No pain to Worst imaginable pain)					
N	226	253	479	-0.4 (-0.90, 0.13); 0.139	-0.3 (-0.68, 0.17); 0.234
Mean (SD)	4.3 (2.8)	3.9 (2.7)	4.1 (2.7)		
Median (IQR)	4 (2, 6)	4 (2, 6)	4 (2, 6)		
Missing	38	31	69		

eTable 22: General health outcomes at 12 months follow-up.

Outcome	Standard care	Self-management	TOTAL	Unadjusted mean difference (95% CI); p-value	Adjusted mean difference* (95% CI); p-value
Headache/migraine days over the last 4 weeks					
N	233	268	501	0.5 (-0.94, 1.87); 0.517	0.9 (-0.29, 2.05); 0.141
Mean (SD)	11.4 (7.8)	11.8 (7.8)	11.6 (7.8)		
Median (IQR)	10 (4, 15)	10 (6, 17)	10 (5, 16)		
Missing	50	35	85		
Number of days pain killers or triptans were used for headache/migraine over the last 4 weeks					
N	233	266	499	0.4 (-0.88, 1.66); 0.546	0.7 (-0.39, 1.80); 0.209
Mean (SD)	9.0 (7.1)	9.4 (7.3)	9.2 (7.2)		
Median (IQR)	8 (3, 12)	8 (3, 14)	8 (3, 13)		
Missing	50	37	87		
Average number of hours the headache/migraine lasted on the days they had it					
N	230	265	495	1.1 (-0.17, 2.41); 0.089 Non-parametric test: P=0.054	1.1 (-0.10, 2.30); 0.072
Mean (SD)	8.5 (7.1)	9.6 (7.4)	9.1 (7.3)		
Median (IQR)	6 (4, 12)	7 (4, 12)	6 (4, 12)		
Missing	53	38	91		
Average severity (0-10; No pain to Extremely severe pain) on the days you had a headache/migraine					
N	234	267	501	-0.03 (-0.36, 0.30); 0.869	-0.02 (-0.34, 0.29); 0.886
Mean (SD)	6.1 (1.9)	6.0 (1.8)	6.1 (1.9)		
Median (IQR)	6 (5, 7)	6 (5, 7)	6 (5, 7)		
Missing	49	36	85		
How fatigued were you on average in the past seven days					
Not at all	14 (4.9%)	11 (3.6%)	25 (4.3%)	OR: 1.0 (0.67, 1.38); 0.831	OR: 0.9 (0.63, 1.29); 0.561
A little bit	63 (22.3%)	70 (23.1%)	133 (22.7%)		
Somewhat	59 (20.8%)	89 (29.4%)	148 (25.3%)		
Quite a bit	67 (23.7%)	65 (21.4%)	132 (22.5%)		
Very much	32 (11.3%)	32 (10.6%)	64 (10.9%)		
Missing	48 (17.0%)	36 (11.9%)	84 (14.3%)		
Sleep quality in the past seven days					
Very poor	28 (9.9%)	26 (8.6%)	54 (9.2%)	1.0 (0.72, 1.36); 0.962	1.0 (0.75, 1.45); 0.793
Poor	58 (20.5%)	74 (24.4%)	132 (22.5%)		
Fair	94 (33.2%)	105 (34.6%)	199 (34.0%)		
Good	46 (16.2%)	56 (18.5%)	102 (17.4%)		
Very good	9 (3.2%)	6 (2.0%)	15 (2.6%)		
Missing	48 (17.0%)	36 (11.9%)	84 (14.3%)		
Average pain (other than headache) in the past seven days (0-10; No pain to Worst imaginable pain)					
N	234	267	501	-0.1 (-0.63, 0.37); 0.614	-0.1 (-0.51, 0.32); 0.651
Mean (SD)	4.1 (2.8)	4.0 (2.7)	4.0 (2.8)		
Median (IQR)	4 (2, 6)	4 (2, 6)	4 (2, 6)		
Missing	49	36	85		

eTable 23: Treatment effectiveness estimates for the primary outcome (HIT-6 at 12 months) for each of the headache types and medication overuse.

Headache type	Standard care	Self-management	Adjusted mean difference (95% CI); p-value
Definite chronic migraine			
N	149	159	-0.7 (-1.97, 0.65); 0.325
Mean (SD)	62.7 (6.1)	61.4 (6.8)	
Median (IQR)	63 (60, 66)	62 (59, 66)	
Missing	0	0	
Probable chronic migraine			
N	133	141	-0.1 (-1.46, 1.35); 0.943
Mean (SD)	58.4 (7.3)	58.6 (6.7)	
Median (IQR)	60 (55, 63)	59 (54, 63)	
Missing	1	3	
Medication overuse – No			
N	120	134	-0.4 (-1.85, 0.95); 0.532
Mean (SD)	60.4 (6.8)	59.3 (7.2)	
Median (IQR)	61 (57, 65)	60.5 (55, 64)	
Missing	1	3	
Medication overuse - Yes			
N	162	166	-0.03 (-1.31, 1.26); 0.967
Mean (SD)	60.9 (7.2)	60.7 (6.6)	
Median (IQR)	62 (57, 66)	62 (56, 65)	
Missing	0	0	

eTable 24: Sensitivity analysis - treatment effectiveness estimate based on the primary outcome (at 12-month follow-up) having excluded those participants reporting less than 15 days of headache at baseline**.**

	Standard care	Self-management	Estimate (95% CI); p-value
HIT-6			
N	172	186	-0.2 (-1.45, 0.97); 0.696
Mean (SD)	60.9 (7.0)	60.6 (6.7)	
Median (IQR)	62 (57, 65.5)	62 (56, 65)	
Missing	0	1	

eTable 25 Intention To treat (ITT) and Complier Averaged Causal Effect (CACE) model estimates of treatment difference at each time point whole population including those with tension type headache

	ITT model		CACE model (minimum adherence)		CACE model (full adherence)	
	Mean difference (95% CI)*	p-value	Mean difference (95% CI)†	p-value	Mean difference (95% CI)†	p-value
HIT-6						
4 months	-0·9 (-1·88, -0·004)	0·049	-1·3 (-2·54, -0·02)	0·046	-1·5 (-3·08, -0·01)	0·048
8 months	0·09 (-0·93, 1·11)	0·860	0·07 (-1·19, 1·34)	0·910	0·09 (-1·42, 1·59)	0·910

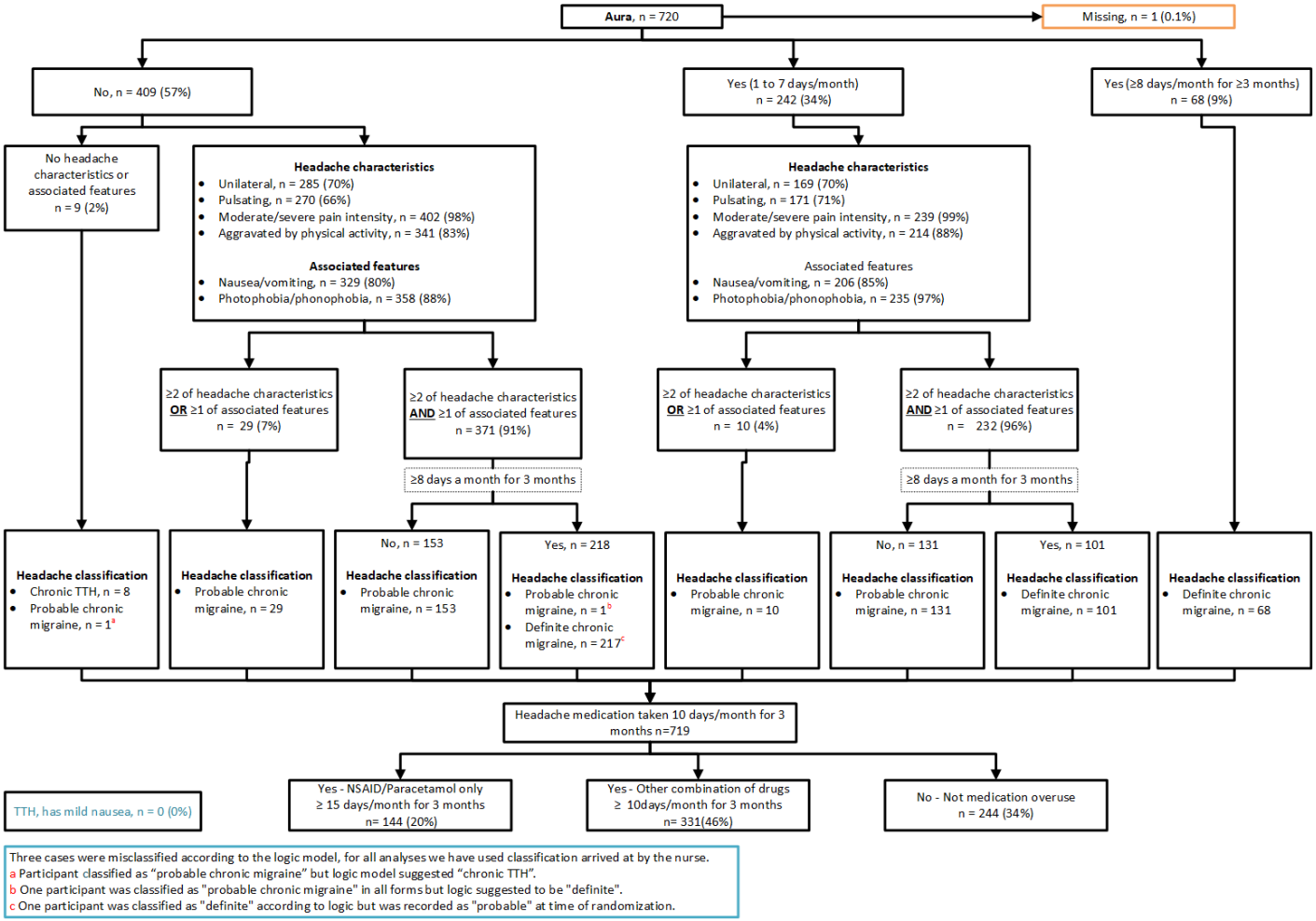
12 months	-0·3 (-1·22, 0·66)	0·555	-0·4 (-1·66, 0·86)	0·533	-0·5 (-2·00, 1·03)	0·533

** Based on a multi-level model adjusted for age, gender, headache type, geographical locality and baseline measure of the outcome. The intervention group was included as a random effect to account for partial clustering in one arm.*
† Based on a single equation instrumental variable regression model with outcome adjusted for age, gender, headache type, geographical locality and baseline measure of the outcome.
Note: Compliance will be of two levels - Minimal compliance with the intervention is defined as the participant attending day 1 of the intervention plus the one-to-one session. Full compliance is defined as the participant attending both days, plus individualised contact with the nurse.

eTable 26: Adverse events (AE) and serious adverse events (SAE) summarised by treatment group.

Event details	Standard care (N=351)	Self-management (N=376)	Total (N=727)
AE's			
Number of AE's reported	1 (0.3%)	6 (1.6%)	7 (1.0%)
SAE's			
Number of SAE's reported	1 (0.3%)	0	1 (0.1%)
Reason Serious Adverse Event deemed serious			
Death	1 (0.3%)	0	1 (0.1%)
Life-threatening	0	0	0
Hospitalisation or prolongation of existing hospitalisation	0	0	0
Persistent or significant disability or incapacity	0	0	0
Congenital anomaly/birth defect	0	0	0
Other	0	0	0
SAE severity assessment			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0
Fatal/life threatening	1 (0.3%)	0	1 (0.1%)

eFigure 1 Headache classification by nurse flow chart.



Protocol

Chronic Headache and Self-management Study (CHESS)

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10		

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LIST OF ABBREVIATIONS/GLOSSARY

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

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

1. BACKGROUND

1.1 Epidemiology and burden of the condition

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

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

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

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

1.2 Existing knowledge

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1.2.1 Supportive self-management programmes

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

1.2.2 Headache diagnosis

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

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

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

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

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

1.3 Hypothesis

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

1.4 Need for a trial

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

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

1.5 Ethical considerations

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

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

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

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

1.6 CONSORT

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

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

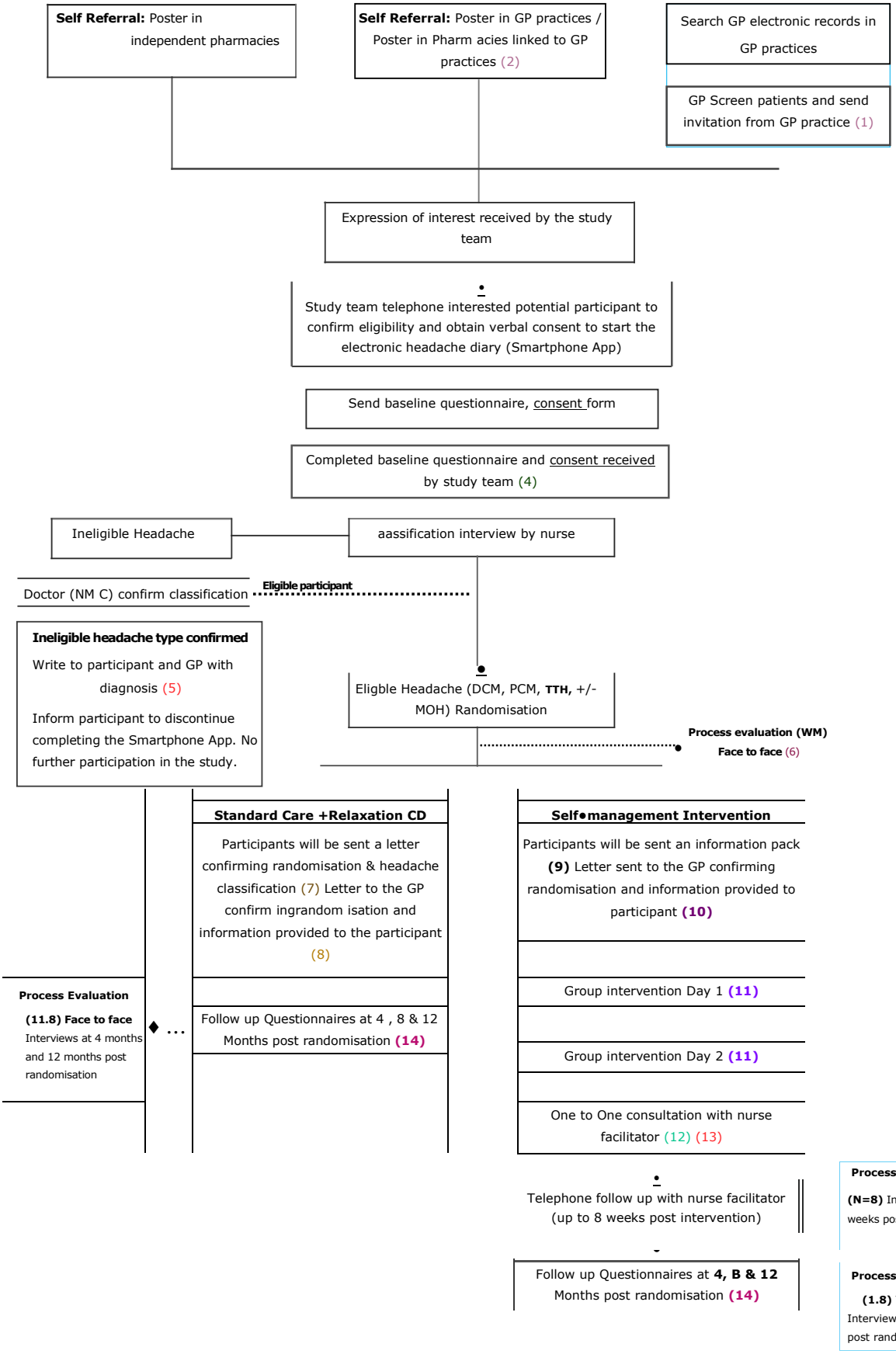
This trial is a multi-centre randomised controlled trial comparing a group education and self-management intervention with a best usual care plus relaxation control for participants living with chronic tension type headaches, probable chronic migraine or definite chronic migraine with or without medication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

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

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

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

Figure 1: Trial flow diagram



IRAS ID: 215304

(1) Invitation Pack:

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

(2) Posters:

- GP Practices
  Pharmacies linked with GP Practices

(3) Study Pack:

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

(4) GP Notification (Consent):

- WCTU headed paper- Covering Letter

(5) Ineligible Headache Type:

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

(6) Process Evaluation Information:

- Covering Letter
- Participant Information Sheet
  Consent Forms

(7) Participant allocation to control pack:

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

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

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

(9) Participant allocation to intervention pack:

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

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

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

(11) Intervention Handouts:

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

(12) Nurse one to one Interview:

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

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

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

(14) Follow up Pack:

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

(15) Process Evaluation/ Interview Study—Reminder:

- Reminder Letter

2.2 Aims and objectives

2.2.1 Aim

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

2.2.2 Primary objective

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

2.2.3 Secondary objective

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

2.3 Outcome measures

Primary outcome:

- HIT-6 at 12 months post randomisation as the primary endpoint.

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

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

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

Secondary outcomes:

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

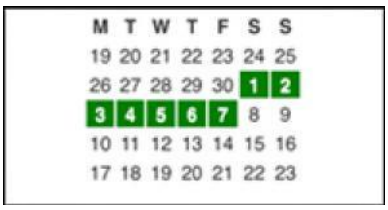
We will collect follow-up data 4, 8 and 12 months after randomisation. Our primary analyses will be based on the twelve month data. We will do postal follow-up with two reminders. In the event that no response is obtained we will collect our primary clinical outcome by phone.

Headache frequency, severity and duration

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

All participants will be asked to complete a smart phone app about their headaches. If they do not have

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



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

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

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

2.3.1 Efficacy

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

Table 1 - Outcome measures

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

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

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

2.3.2 Safety

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

2.4 Eligibility criteria

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

2.4.1 Inclusion criteria

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

2. Aged ≥18 years or above.

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

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

5. Fluent in written and spoken English.

2.4.2 Exclusion criteria

1. Unable to attend the group sessions.

2. No access to a telephone.

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

4. Previous entry or randomisation in the present trial.

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

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

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

2.5 Informed consent

There are two consent stages:

1) Expression of interest to be part of the study

Potential participants will be sent an invitation letter, participant information sheet and an 'expression of interest' form if they are identified via the GP database search and are not screened out by the GP. If the participant is interested in the study they can return the 'expression of interest' form to the study team using a pre-addressed freepost envelope or contact the study team via phone or email. There will be a single postal reminder after 1014 days.

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

2) Consent to be part of the study

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

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

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

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

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

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

2.6 Recruitment and randomisation

2.6.1 Recruitment

Potential participants will be identified via:

a) **Electronic screening of GP records**

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

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

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

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

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

2.6.2 Classification interviews

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

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

2.6.3 Randomisation

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

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

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

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

2.6.2.1 Post-randomisation withdrawals and exclusions

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the research study at any time (including follow-up) without providing a reason and without prejudice, if they so wish. Participants are informed of this in the participant information sheet. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. Data

recorded up to the point of withdrawal will be included in the analysis. Should a participant decide to withdraw after the intervention commences, or should the investigator(s) decide to withdraw the participant, all efforts are made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete and final evaluation at the time of the participant's withdrawal will be recorded in the Case Report Form (CRF). If the reason for withdrawal is an Adverse Event (AE), monitoring of the participant will continue until the outcome is evident. The specific event must be recorded in CRF.

2.7 Trial treatments / intervention

2.7.1 Trial treatment(s) / intervention

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

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

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

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

Process for organising groups

Eligibility phase:

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

Post randomisation but pre course:

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

- If the participant informs the research team that they do not wish to attend because they have changed their mind then they will remain in the study as intention to treat and still receive questionnaires. The research team will send the participant the relaxation CD, mindfulness CD and

the Living with Chronic Headaches DVD with a covering letter and instructions of use.

Day 1 of course:

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

Day 2 of course:

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

Group size:

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

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

Table 2 - Course Structure

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

Table 3 - Intervention components

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

2.7.2 Control intervention

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

2.7.3 Compliance/contamination

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

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

2.8 Process Evaluation

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

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

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

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

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

The aims of the process evaluation are

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

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

We will evaluate the following:

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

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

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

Data collection process

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

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

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

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

Data analysis

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

2.8 Blinding

2.8.1 Methods for ensuring blinding

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

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

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

2.9 Concomitant illness and medication

2.9.1 Concomitant illness

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

2.10 End of trial

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

The trial will be stopped prematurely if:

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

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

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection.

Table 4 - Trial assessments

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

Finish electronic headache severity diary (mobile app)										✓
Written Information						✓				
Intervention							✓			
Adverse events							✓	✓	✓	✓
Questionnaire				✓				✓	✓	✓
GP records										✓

4. ADVERSE EVENT MANAGEMENT

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

4.1 Definitions

4.1.1 Adverse Events (AE)

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

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

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

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

4.1.2 Serious Adverse Events (SAEs)

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

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

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

4.2 Reporting SAEs and SUSARs

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

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

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

5. DATA MANAGEMENT

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

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

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

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

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

5.1 Data collection and management

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

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

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

5.2 Electronic headache severity diary

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

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

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

5.3 Paper headache diary

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

5.4 Database

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

5.5 Data storage

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

5.6 Data access and quality assurance

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

5.7 Archiving

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

5.8 Power and sample size

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

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

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

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

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

5.9 Statistical analysis of effectiveness and harms

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

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

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

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

5.10 Health Economic Evaluation

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

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

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

6. TRIAL ORGANISATION AND OVERSIGHT

6.1 Sponsor and governance arrangements

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

6.2 Regulatory authorities/ethical approval

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

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

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

6.3 Trial Registration

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

6.4 Indemnity

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

6.5 Trial timetable and milestones

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

6.6 Administration

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

6.7 Trial Management Group (TMG)

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

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

6.8 Programme Steering Committee (PSC)

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

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

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

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

The membership of the PSC is shown on page 7.

6.9 Data Monitoring Committee (DMC)

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

The membership of the DMC is shown on page 8.

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

6.10 Essential Documentation

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

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

7. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

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

8. PATIENT AND PUBLIC INVOLVMENT (PPI)

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

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

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

9. DISSEMINATION AND PUBLICATION

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

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

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

Scientific presentation and publications:

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

Research impact: Participating centres/healthcare professionals:

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

Research impact: participants, patients and general public:

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

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

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

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

10. REFERENCES

1. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA: The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia : an international journal of headache 2007, 27(3):193-210.
2. Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G: Prevalence of migraine and non-migrainous headache--head-HUNT, a large population-based study. Cephalalgia: an international journal of headache 2000, 20(10):900-906.
3. Lu SR, Fuh JL, Chen WT, Juang KD, Wang SJ: Chronic daily headache in Taipei, Taiwan: prevalence, follow-up and outcome predictors. Cephalalgia: an international journal of headache 2001, 21(10):980-986.
4. Castillo J, Munoz P, Guitera V, Pascual J: Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. Headache 1999, 39(3):190-196.
5. Wang SJ, Fuh JL, Lu SR, Liu CY, Hsu LC, Wang PN, Liu HC: Chronic daily headache in Chinese elderly: prevalence, risk factors, and biannual follow-up. Neurology 2000, 54(2):314- 319.
6. Latinovic R, Gulliford M, Ridsdale L: Headache and migraine in primary care: consultation, prescription, and referral rates in a large population. Journal of neurology, neurosurgery, and psychiatry 2006, 77(3):385-387.
7. Hopkins A, Menken M, DeFriese G: A record of patient encounters in neurological practice in the United Kingdom. Journal of neurology, neurosurgery, and psychiatry 1989, 52(4):436438.
8. Gahir KK, Larner AJ: Primary headache disorder in the emergency department: perspective from a general neurology outpatient clinic. Emergency medicine journal: EMJ 2006, 23(2):135-136.
9. UK audit of the care of common Neurological disorders. Association of British Neurologists (Services Committe); 1991.
10. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V et al: Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013, 380(9859):2163-2196.
11. Steiner T: The economic cost of migraine and other headache disorders in the UK: A Report of the All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD): House of Commons; 2010: 1-3.
12. Mehuys E, Paemeleire K, Van Hees T, Christiaens T, Van Bortel LM, Van Tongelen I, De Bolle L, Remon JP, Boussery K: Self-medication of regular headache: a community pharmacy-based survey. European journal of neurology: the official journal of the European Federation of Neurological Societies 2012, 19(8):1093-1099.
13. Zielman R, Veenstra P, Zwet E, Berg J: How general practitioners treat migraine patients: evaluation of a headache guideline. Cephalalgia: an international journal of headache 2012, 32(12):908-915.

14. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, Group AA: Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007, 68(5):343-349.
15. Carville S, Padhi S, Reason T, Underwood M: Diagnosis and management of headaches in young people and adults: summary of NICE guidance. BMJ 2012, 345:e5765.
16. Matchar DB, Harpole L, Samsa GP, Jurgelski A, Lipton RB, Silberstein SD, Young W, Kori S, Blumenfeld A: The headache management trial: a randomized study of coordinated care. Headache 2008, 48(9):1294-1310.
17. Bromberg J, Wood ME, Black RA, Surette DA, Zacharoff KL, Chiauzzi EJ: A randomized trial of a web-based intervention to improve migraine self-management and coping. Headache 2012, 52(2):244-261.
18. Winkler R, Underwood P, Fatovich B, James R, Gray D: A clinical trial of a self-care approach to the management of chronic headache in general practice. Soc Sci Med 1989, 29(2):213219.
19. Lemstra M, Stewart B, Olszynski WP: Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. Headache 2002, 42(9):845-854.
20. Martin PR, Nathan PR, Milech D, van Keppel M: Cognitive therapy vs. self-management training in the treatment of chronic headaches. The British journal of clinical psychology / the British Psychological Society 1989, 28 (Pt 4):347-361.
21. Andersson G, Lundstrom P, Strom L: Internet-based treatment of headache: does telephone contact add anything? Headache 2003, 43(4):353-361.
22. Thorn BE, Pence LB, Ward LC, Kilgo G, Clements KL, Cross TH, Davis AM, Tsui PW: A randomized clinical trial of targeted cognitive behavioral treatment to reduce catastrophizing in chronic headache sufferers. The journal of pain: official journal of the American Pain Society 2007, 8(12):938-949.
23. Devineni T, Blanchard EB: A randomized controlled trial of an internet-based treatment for chronic headache. Behaviour research and therapy 2005, 43(3):277-292.
24. Stewart WF, Lipton RB, Dowson AJ, Sawyer J: Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology 2001, 56(6 Suppl 1):S20-28.
25. Headaches. Diagnosis and management of headaches in young people and adults. Clinical Guideline 150 Methods, evidence and recommendations. In. London; 2012.
26. Sullivan A, Cousins S, Ridsdale L. Psychological interventions for migraine: a systematic review. Journal of Neurology. 2016:1-9.
27. Harris P, Loveman E, Clegg A, Easton S, Berry N. Systematic review of cognitive behavioural therapy for the management of headaches and migraines in adults. British journal of pain. 2015;9(4):213-24.
28. Kindelan-Calvo P, Gil-Martinez A, Paris-Alemany A, Pardo-Montero J, Munoz-Garcia D, Angulo-Diaz-Parreno S, et al. Effectiveness of therapeutic patient education for adults with migraine. A systematic review and meta-analysis of randomized controlled trials. Pain Med. 2014;15(9):1619-36.
29. Day MA, Thorn BE, Ward LC, Rubin N, Hickman SD, Scogin F, et al. Mindfulness-based cognitive therapy for the treatment of headache pain: a pilot study. The Clinical journal of pain. 2014;30:152-61.
30. Dindo LN. One-day behavioral intervention for depression and impairment in patients with comorbid depression and migraine. Headache. 2014;54 (8):1431-2.
31. Grazzi L, Sansone E, Raggi A, Leonardi M, D'Amico D, Andrasik F. Mindfulness versus Pharmacological Preventative Treatment for Chronic Migraine (CM) with Medication Overuse (MO): Preliminary Findings (P2.204). Neurology. 2016;86(16 Supplement).
32. Andersson G, Lundstrom P, Strom L. Internet-based treatment of headache: Does telephone contact add anything? Headache. 2003;43:353-61.

33. Bakhshani NM, Amirani A, Amirifard H, Shahrakipoor M. The Effectiveness of Mindfulness-Based Stress Reduction on Perceived Pain Intensity and Quality of Life in Patients With Chronic Headache. Glob J Health Sci. 2016;8(4):142-51.
34. Basler HD, Jakle C, Kroner-Herwig B. Cognitive-behavioral therapy for chronic headache at German pain centers. International Journal of Rehabilitation and Health. 1996;2:235-52.
35. Bell NW, Abramowitz SI, Folkins CH. Biofeedback, brief psychotherapy and tension headache. Headache. 1983;23:162-73.
36. Bhombal ST, Usman A, Ghufran M. Effectiveness of behavioural management on migraine in adult patients visiting family practice clinics: a randomized controlled trial. JPMA - Journal of the Pakistan Medical Association. 2014;64:900-6.
37. Blanchard EBl, Andrasik Fl, Evans DDl, Neff DFl, Appelbaum KAl, Rodichok LDp. CASE STUDIES AND CLINICAL REPLICATION SERIES - BEHAVIORAL TREATMENT OF 250 CHRONIC HEADACHE PATIENTS - A CLINICAL REPLICATION SERIES\par } {\f1\fs18. Behavior Therapy\par } {\f1\fs18.16\par } {\f1\fs18:308-27\par } {\f1\fs18.
38. Blanchard EB, Andrasik F, Neff DF, Saunders NL, Arena JG, Pallmeyer TP, Teders SJ, Jurish SE, Rodichok LD. Four process studies in the behavioral treatment of chronic headache. Behav Res Ther. 1983;21(3):209-20.
39. Blanchard EB, Appelbaum KA, Radnitz CL, Michultka D, Morrill B, Kirsch C, Hillhouse J, Evans DD, Guarnieri P, Attanasio V, et al. Placebo-controlled evaluation of abbreviated progressive muscle relaxation and of relaxation combined with cognitive therapy in the treatment of tension headache. J Consult Clin Psychol. 1990 Apr;58(2):210-5.
40. Bromberg J, Wood ME, Black RA, Surette DA, Zacharoff KL, Chiauzzi EJ. A randomized trial of a web-based intervention to improve migraine self-management and coping. Headache. 2012;52:244-61.
41. Burton WN, Chen CY, Li X, McCluskey M, Erickson D, Schultz AB. Evaluation of a Workplace-Based Migraine Education Program. J Occup Environ Med. 2016;58(8):790-5.
42. Cathcart S, Galatis N, Immink M, Proeve M, Petkov J. Brief mindfulness-based therapy for chronic tension-type headache: a randomized controlled pilot study. Behavioural and cognitive psychotherapy. 2014;42:1-15.
43. Christiansen S, Jürgens TP, Klinger R. Outpatient Combined Group and Individual Cognitive-Behavioral Treatment for Patients With Migraine and Tension-Type Headache in a Routine Clinical Setting. Headache. 2015 Sep;55(8):1072-91. doi: 10.1111/head.12626. Epub 2015 Aug 12.
44. Cousins S, Ridsdale L, Goldstein LH, et al. A pilot study of cognitive behavioural therapy and relaxation. J Neurol. 2015.
45. D.Tobin KH, A. Baker, J.E. Holm. Development and clinical trial of a minimal contact, cognitive-behavioral treatment for tension headache. Cognitive Therapy and Research. 1988;12(4):325-39.
46. D'Souza PJ, Lumley MA, Kraft CA, Dooley JA. Relaxation training and written emotional disclosure for tension or migraine headaches: A randomized, controlled trial. Annals of Behavioral Medicine. 2008;36:21-32.
47. Devineni T, Blanchard EB. A randomized controlled trial of an internet-based treatment for chronic headache. Behaviour Research & Therapy. 2005;43:277-92.
48. Ezra Y, Gotkine M, Goldman S, Adahan HM, Ben-Hur T. Hypnotic relaxation vs amitriptyline for tension-type headache: Let the patient choose. Headache. 2012;52:785-91.
49. Feuille M, Pargament K. Pain, mindfulness, and spirituality: A randomized controlled trial comparing effects of mindfulness and relaxation on pain-related outcomes in migraineurs. J Health Psychol. 2015 Aug;20(8):1090-106. doi: 10.1177/1359105313508459. Epub 2013 Nov 7.
50. Figueroa JL. Group treatment of chronic tension headaches. A comparative treatment study. Behavior Modification. 1982;6:229-39.

51. Gaul C, Bromstrup J, Fritsche G, Diener HC, Katsarava Z. Evaluating integrated headache care: A one-year follow-up observational study in patients treated at the Essen headache centre. BMC Neurology. 2011;11.
52. Grazzi Ll, Andrasik Fl, Usai Sp. Behavioral plus pharmacological treatment vs pharmacological treatment for chronic headache with medication overuse and disability assessment: Results at two year follow-up\par } {\f1\fs18. Applied Psychophysiology and Biofeedback\par } {\f1\fs18.31\par } {\f1\fs18:342-3\par } {\f1\fs18.
53. Gunreben-Stempfle B, Griessinger N, Lang E, Muehlhans B, Sittl R, Ulrich K. Effectiveness of an intensive multidisciplinary headache treatment program: Research submission. Headache. 2009;49:990-1000.
54. H.T. Mosley CG, W.M. Meeks. Treatment of Tension Headache in the elderly: a controlled evaluation of relaxation training and relaxation training combinded with cognitive-behavoural therapy. Journal of Clinical Geropsychology. 1995(1):175-88.
55. Harpole LH, Samsa GP, Jurgelski AE, Shipley JL, Bernstein A, Matchar DB. Headache Management Program Improves Outcome for Chronic Headache. Headache: The Journal of Head and Face Pain. 2003;43(7):715-24.
56. Holroyd KA, Cottrell CK, O'Donnell FJ, Cordingley GE, Drew JB, Carlson BW, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ. 2010;341:c4871.
57. Holroyd KA, Nash JM, Pingel JD, Cordingley GE, Jerome A. A comparison of pharmacological (amitriptyline HCL) and nonpharmacological (cognitive-behavioral) therapies for chronic tension headaches. Journal of Consulting and Clinical Psychology. 1991;59:387-93.
58. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: A randomized controlled trial. Journal of the American Medical Association. 2001;285:2208-15.
59. Jensen R, Peter Z, Christian Dehlendorff a. Predictors of outcome of the treatment programme in a multidisciplinary headache centre. Cephalalgia.30(10) 1214–24.
60. Kohlenberg RJ, Cahn T. Self-help treatment for migraine headaches: a controlled outcome study. Headache. 1981 Sep;21(5):196-200.
61. Lemstra M, Stewart B, Olszynski WP. Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. Headache. 2002;42:845-54.
62. Magnusson JE, Riess CM, Becker WJ. Effectiveness of a multidisciplinary treatment program for chronic daily headache. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2004;31(1):72-9.
63. Mahmoudzadeh Zarandi F, Raiesifar A, Ebadi A. The Effect of Orem's Self-Care Model on Quality of Life in Patients with Migraine: a Randomized Clinical Trial. Acta medica Iranica. 2014;54(3):159-64.
64. Marcus DA, Scharff L, Mercer S, Turk DC. Nonpharmacological treatment for migraine: incremental utility of physical therapy with relaxation and thermal biofeedback. Cephalalgia. 1998;18:266-72; discussion 42.
65. Martin PR, Aiello R, Gilson K, Meadows G, Milgrom J, Reece J. Cognitive behavior therapy for comorbid migraine and/or tension-type headache and major depressive disorder: An exploratory randomized controlled trial. Behaviour research and therapy. 2015;73:8-18.
66. Martin PR, Nathan PR, Milech D, Van K. Cognitive therapy vs. self-management training in the treatment of chronic headaches. British Journal of Clinical Psychology. 1989;28:347-61.
67. Martin PR, Reece J, Callan M, MacLeod C, Kaur A, Gregg K, et al. Behavioral management of the triggers of recurrent headache: A randomized controlled trial. Behaviour Research and Therapy. 2014;61:1-11.
68. Matchar DB, Harpole L, Samsa GP, Jurgelski A, Lipton RB, Silberstein SD, et al. The headache management trial: a randomized study of coordinated care. Headache. 2008;48:1294-310.

69. Melis PM, Rooimans W, Spierings EL, Hoogduin CA. Treatment of chronic tension-type headache with hypnotherapy: a single-blind time controlled study. Headache. 1991 Nov;31(10):686-9.
70. Mo'Tamedi H, Rezaiemaram P, Tavallaie A. The effectiveness of a group-based acceptance and commitment additive therapy on rehabilitation of female outpatients with chronic headache: Preliminary findings reducing 3 dimensions of headache impact. Headache. 2012;52:1106-19.
71. Motoya R, Oda K, Ito E, Ichikawa M, Sato T, Watanabe T, et al. Effectiveness of cognitive behavioral therapy based on the pain sustainment/exacerbation model in patients with tension-type headache: a pilot study. Fukushima journal of medical science. 2014;60(2):13340.
72. Nicholson R, Nash J, Andrasik F. A self-administered behavioral intervention using tailored messages for migraine. Headache. 2005;45:1124-39.
73. Omidi A, Zargar F. Effects of mindfulness-based stress reduction on perceived stress and psychological health in patients with tension headache. Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences. 2015;20(11):105863.
74. Richardson GM, McGrath PJ. Cognitive-behavioral therapy for migraine headaches: a minimal-therapist-contact approach versus a clinic-based approach. Headache. 1989 Jun;29(6):352-7.
75. Smith TR, Nicholson RA, Banks JW. Migraine education improves quality of life in a primary care setting. Headache. 2010 Apr;50(4):600-12. doi: 10.1111/j.1526- 610.2010.01618.x. Epub 2010 Feb 9.
76. Sorbi MJ, van der Vaart R. User acceptance of an Internet training aid for migraine self-management. J Telemed Telecare. 2010;16(1):20-4. doi: 10.1258/jtt.2009.001007.
77. Spinhoven P, Linssen AC, Van Dyck R, Zitman FG. Autogenic training and self-hypnosis in the control of tension headache. Gen Hosp Psychiatry. 1992 Nov;14(6):408-15.
78. Strom Ll, Pettersson Rl, Andersson Gp. A controlled trial of self-help treatment of recurrent headache conducted via the Internet. Journal of Consulting and Clinical Psychology. 2000:722-7.
79. ter Kuile MM[1], Spinhoven P, Linssen AC, van Houwelingen HC. Cognitive coping and appraisal processes in the treatment of chronic headaches. Pain. 1996 Feb;64(2):257-64.
80. Thorn BE, Pence LB, Ward LC, Kilgo G, Clements KL, Cross TH, et al. A Randomized Clinical Trial of Targeted Cognitive Behavioral Treatment to Reduce Catastrophizing in Chronic Headache Sufferers. Journal of Pain. 2007;8:938-49.
81. Wallasch TM[1], Kropp P. Multidisciplinary integrated headache care: a prospective 12-month follow-up observational study. J Headache Pain. 2012 Oct;13(7):521-9. doi: 10.1007/s10194012-0469-y. Epub 2012 Jul 12.
82. Winkler R[1], Underwood P, Fatovich B, James R, Gray D. A clinical trial of a self-care approach to the management of chronic headache in general practice. Soc Sci Med. 1989;29(2):213-9.
83. Zsombok T, Juhasz G, Budavari A, Vitrai J, Bagdy G. Effect of autogenic training on drug consumption in patients with primary headache: An 8-month follow-up study. Headache. 2003;43:251-7.
84. Carnes D, Homer Ke Fau - Miles CL, Miles Cl Fau - Pincus T, Pincus T Fau - Underwood M, Underwood M Fau - Rahman A, Rahman A Fau - Taylor SJC, et al. Effective delivery styles and content for self-management interventions for chronic musculoskeletal pain: a systematic literature review. (1536-5409 (Electronic)).
85. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, Bauman A, Hensley MJ, Walters EH: Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev 2003(1):CD001117.
86. Deakin T, McShane CE, Cade JE, Williams RD: Group based training for self-management strategies in people with type 2 diabetes mellitus. Cochrane Database Syst Rev 2005(2):CD003417.

87. Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, Heneghan CJ: Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev 2010(4):CD003839.
88. Fernandez-de-las-Penas C, Hernandez-Barrera V, Alonso-Blanco C, Palacios-Cena D, Carrasco-Garrido P, Jimenez-Sanchez S, Jimenez-Garcia R: Prevalence of neck and low back pain in community-dwelling adults in Spain: a population-based national study. Spine 2011, 36(3):E213-219.
89. Plesh O, Adams SH, Gansky SA: Self-reported comorbid pains in severe headaches or migraines in a US national sample. Headache 2012, 52(6):946-956.
90. Yoon MS, Manack A, Schramm S, Fritsche G, Obermann M, Diener HC, Moebus S, Katsarava Z: Chronic migraine and chronic tension-type headache are associated with concomitant low back pain: results of the German Headache Consortium study. Pain 2013, 154(3):484492.
91. Hagen K, Linde M, Steiner TJ, Zwart JA, Stovner LJ: The bidirectional relationship between headache and chronic musculoskeletal complaints: an 11-year follow-up in the Nord-Trondelag Health Study (HUNT). European journal of neurology: the official journal of the European Federation of Neurological Societies 2012, 19(11):1447-1454.
92. Aurora SK, Kulthia A, Barrodale PM: Mechanism of chronic migraine. Current pain and headache reports 2011, 15(1):57-63.
93. Obermann M, Nebel K, Schumann C, Holle D, Gizewski ER, Maschke M, Goadsby PJ, Diener HC, Katsarava Z: Gray matter changes related to chronic posttraumatic headache. Neurology 2009, 73(12):978-983.
94. Vlaeyen JW, Linton SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000, 85(3):317-332.
95. Norton PJ, Asmundson GJ: Anxiety sensitivity, fear, and avoidance behavior in headache pain. Pain 2004, 111(1-2):218-223.
96. Wieser T, Walliser U, Womastek I, Kress HG: Dysfunctional coping in headache: avoidance and endurance is not associated with chronic forms of headache. Eur J Pain 2012, 16(2):268277.
97. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. Journal of personality and social psychology 1986, 51(6):1173-1182.
98. Maizels M, Wolfe WJ: An expert system for headache diagnosis: the Computerized Headache Assessment tool (CHAT). Headache 2008, 48(1):72-78.
99. Lipton RB, Serrano D, Buse DC, Pavlovic JM, Blumenfeld AM, Dodick DW, Aurora SK, Becker WJ, Diener HC, Wang SJ, Vincent MB, Hindiyeh NA, Starling AJ, Gillard PJ, Varon SF, Reed ML. Improving the detection of chronic migraine: Development and validation of Identify Chronic Migraine (ID-CM). Cephalalgia. 2016 Mar;36(3):203-15.
100. Carnes D, Homer KE, Miles CL, Pincus T, Underwood M, Rahman A, et al. Effective delivery styles and content for self-management interventions for chronic musculoskeletal pain: a systematic literature review. The Clinical journal of pain. 2012;28(4):344-54.
101. Taylor SJC, Carnes D, Homer K, Pincus T, Kahan BC, Hounsome N, Eldridge S, Spencer A, Diaz-Ordaz K, Rahman A, Mars TS, Foell J, Griffiths CJ, Underwood MR. Improving the self-management of chronic pain: COping with persistent Pain, Effectiveness Research in Self-management (COPERS). Southampton (UK): NIHR Journals Library; 2016 Sep. Programme Grants for Applied Research.
102. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet (London, England). 2001;357(9263):1191-4.
103. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ (Clinical research ed). 2008;337:a1655.

104. Kosinski M[1], Bayliss MS, Bjorner JB, Ware JE Jr, Garber WH, Batenhorst A, Cady R, Dahlöf CG, Dowson A, Tepper S. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003 Dec;12(8):963-74.
105. McKenna SP, Doward LC, Davey KM. The Development and Psychometric Properties of the MSQOL: A Migraine-Specific Quality-of-Life Instrument. Clin Drug Investig. 1998;15(5):41323.
106. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. Journal of clinical epidemiology. 1998;51(11):1171-8.
107. Jenkinson C, Layte R: Development and testing of the UK SF12. JHealth Serv Res Policy 1997, 2(1):14-18.
108. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
109. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.
110. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. European journal of pain (London, England). 2007;11(2):153-63.
111. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns. 2007 May;66(2):192-201. Epub 2007 Feb 22.
112. Parsons S, Carnes D, Pincus T, Foster N, Breen A, Vogel S, Underwood M. Measuring troublesomeness of chronic pain by location. BMC Musculoskelet Disord. 2006 Apr 5;7:34.
113. Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. Lancet (London, England). 2010;375(9718):916-23.
114. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ (Clinical research ed). 2004;329(7479):1377.
115. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. BMJ 2006; 332(7538): 413-6.
116. Dignan MB, Carr PA. Program planning for health education and promotion. Philadelphia: Lea & Febiger; 1987.
117. Ellard D, Parsons S. Process evaluation: understanding how and why interventions work. In: Thorogood M, Coombes Y, eds. Evaluating health promotion Practice and methods. 3rd ed. Oxford: Oxford University Press; 2010: 87-104.
118. Geraets JJ, Goossens ME, van Haastregt JC, et al. Implications of process evaluation for clinical effectiveness and clinical practice in a trial on chronic shoulder complaints. Patient Educ Couns 2006; 61(1): 117-25.
119. Ellard D, Taylor S, Parsons S, Thorogood M. The OPERA trial: a protocol for the process evaluation of a randomised trial of an exercise intervention for older people in residential and nursing accommodation. Trials 2011; 12(1): 28.
120. Underwood M, Lamb S, Eldridge S, et al. Exercise for depression in care home residents. A randomised controlled trial with cost-effectiveness analysis (OPERA). Health Technol Assess 2013; 17(18).
121. Bryman A. Integrating quantitative and qualitative research: how is it done? Qualitative Research 2006; 6(1): 97-113.
122. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ 1995; 311(6996): 42-5.

123. Steckler A, Linnan L, editors. Process Evaluation for Public Health Interventions and Research. San Francisco: Jossey-Bass; 2002.
124. Mars T, Ellard D, Carnes D, Homer K, Underwood M, Taylor SJ. Fidelity in complex behaviour change interventions: a standardised approach to evaluate intervention integrity. BMJ Open 2013; 3(11): e003555.
125. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. Analysing qualitative data 1994.
126. Moerbeek M, Wong WK: Sample size formulae for trials comparing group and individual treatments in a multilevel model. Statistics in medicine 2008, 27(15):2850-2864.
127. Brookes ST, Whitley E, Peters TJ Mulheran PA, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: quantifying the risks of false- positives and false-negatives. HTA 2001;5(33).
128. Curtis L. In. Canterbury; 2012. NHS Business Services Authority. Prescription Cost Analysis (PCA) Data. NHS Business Services Authority, In.; 2013.
129. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

STATISTICAL ANALYSIS PLAN

Version: 1.1

Contents

SECTION 1 : ADMINISTRATIVE INFORMATION

SECTION 1: ADMINISTRATIVE INFORMATION

Title: *Chronic Headache and Self-management Study (CHESS)*

ISRCTN number: *79708100*

SAP Version: *Version 1.1 (Date: 16 July 2019)*

Protocol Version: *Version 3.4 (Date: 12 July 2018)*

SAP revisions: SAP Version 1.0 (Date: 6 August 2018) had the following minor revisions:

- Additional text added to analysis section to detail alternative distributions to consider if the headache days data are not normal
- Additional sensitivity analysis included in analysis section to exclude participants from the main analysis who reported less than 15 days of headache over the past 4 weeks at baseline

Roles and responsibility:

- Dr Dipesh Mistry, Warwick Clinical Trials Unit (WCTU) – Trial Statistician (Author of SAP)
- Dr Siew Wan Hee, Warwick Medical School (WMS) – Statistician (Co-applicant)
- Professor Sandra Eldridge, Barts and The London School of Medicine and Dentistry – Senior Statistician (Co-applicant)
- Professor Martin Underwood, Warwick Clinical Trials Unit (WCTU) – Principal Investigator

Signatures of:

	Name	**Date**	**Signature**
Author of SAP	Dipesh Mistry		
Co-applicant	Siew Wan Hee		
Senior statistician	Sandra Eldridge		
Principal investigator	Martin Underwood		

SECTION 2 : INTRODUCTION

SECTION 2: INTRODUCTION

Background and rationale

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

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

Objectives

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

SECTION 3 : STUDY METHODS

SECTION 3: STUDY METHODS

Trial design

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

Randomisation

The randomisation allocation ratio is 1:1.07 due to the method used to compute the sample size with clustering in one arm. Randomisation will be stratified by geographical locality (Midlands and Greater London) and headache type (six possible headache types; chronic tension type headache, probable chronic migraine and definite chronic migraine with or without medication overuse headache) using minimisation. Randomisation will take place using an online application specifically developed for the CHESS Study by the Warwick CTU programming team. (See section 2.6.3 of the protocol).

Sample size

A detailed description of the sample size calculation can be found in section 5.8 of the protocol. In brief, a sample size of 689 (333 in the relaxation arm and 356 in the self-management programme) will provide 90% power to detect a between group difference in those with migraine of 2 (SD: 6.9) in the HIT-6 score measured at 12 months at the two-sided 5% significance level. The sample size also accounted for 20% loss to follow-up and clustering in the self-management arm using an intra-class correlation coefficient (ICC) of 0.01 assuming an average group size of 10.

Framework

A superiority hypothesis testing framework will be used to compare the self-management arm to the relaxation arm.

Statistical interim analyses and stopping guidance

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There are no planned interim analyses or stopping guidelines for this study. However, in consultation with the Data Monitoring Committee (DMC) we would review the sample size around halfway through recruitment to ensure we have sufficient participants with probable or definite chronic migraine. If the proportion of participants with chronic tension type headache is $\leq$ 15% then we will recruit more participants with probable or definite chronic migraine such that we could perform the primary clinical analysis on this subpopulation.

Timing of final analysis

Once all of the data has been collected from participants, entered onto the database, fully validated and cleaned, the database will then be locked. The final analyses on all outcomes will then be conducted at each of the follow-up time points.

Timing of outcome assessments

Primary and secondary outcomes will be collected at baseline, 4, 8 and 12 months follow-up.

SECTION 4 : STATISTICAL PRINCIPLES

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SECTION 4: STATISTICAL PRINCIPLES

Confidence intervals and P values

All statistical tests will be two-sided at the 5% significance level. The estimate, 95% confidence interval (95% CI) and P value will be reported for each test undertaken.

Adherence and protocol deviations

We will look at two levels of adherence in this study; minimal adherence and full adherence. Minimal adherence with the intervention is defined as the participant attending day 1 of the intervention plus the one-to-one session. Full adherence is defined as the participant attending both days, plus individualised contact with the nurse. Both levels of adherence will inform the complier averaged causal effect (CACE) analysis.

Analysis populations

All analyses will be available case analyses based on 'Intention-to-treat' (ITT) principles. Participants will be analysed according to the treatment they were randomised to, irrespective of the treatment they actually received. All participants will be included in the analysis, regardless of whether they adhered to the protocol. The main summary tables and analyses will be based on the intention-to-treat population.

SECTION 5 : TRIAL POPULATION

SECTION 5: TRIAL POPULATION

Screening data

A detailed summary of the screening data will be presented as frequencies and percentages to describe the representativeness of the trial sample. The screening summary will start at the GP practice population search level (i.e. how many practices were approached, the number records searched, the number of mail outs etc.) right the way through to final consent and randomisation. This will also include a summary of how many participants were self-referrals and how many were approached via the GP practice.

Eligibility

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

Inclusion criteria

- Able and willing to comply with the study procedures and provision of written informed consent.
- Aged ≥18 years.
- Living with chronic headache; defined as headache on 15 or more days per month for at least three months.
- Result of nurse classification interview confirms headache type to be definite or probable chronic migraine, or chronic tension type headache, with or without medication overuse headache.
- Fluent in written and spoken English.

Exclusion criteria

- Unable to attend the group sessions.
- No access to a telephone.
- Has an underlying serious psychological disorder with ongoing symptoms which preclude or significantly interfere with participation in the group intervention.
- Previous entry or randomisation in the present trial.

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

The eligibility will be summarised using frequencies and percentages to describe how many people were:

- Eligible and randomised
- Eligible and not randomised
- Ineligible and randomised (in error)
- Ineligible and not randomised; summarising the main reasons for exclusion

In addition to the above, a summary of the different headache types identified from the nurse classification interviews will also be presented (definite or probable chronic migraine, or chronic tension type headache, with or without medication overuse).

Recruitment

The CONSORT diagram will illustrate the flow of participants throughout the trial. This will include:

- Number screened
- Of those screened, how many ineligible or declined
- Number randomised
- How many withdrew, died and were lost to follow-up at each follow-up time-point
- How many included in the final analyses at the primary endpoint listing reasons why participants were excluded

Withdrawal/follow-up

All withdrawals will be summarised by group using frequencies and percentages.

Level of withdrawal - will be summarised by treatment group i.e. how many withdrew from intervention alone but remained on follow-up and/or how many withdrew completely.

Timing of withdrawal - withdrawal timings in this trial will be summarised by treatment group as follows:

- Withdrawals after randomisation but before first group session (intervention arm only);
- Withdrawals during group sessions (intervention arm only);
- Withdrawals from follow-up - (i) withdrawal prior to 4-month follow-up (ii) withdrawal after 4-month follow-up but before 8-month follow-up (iii) withdrawal after 8-month follow-up but before 12-month follow-up

Withdrawal decision - the withdrawal decision i.e. decision made by participant or CHESS study team, will be summarised by treatment group

Withdrawal reason - participants have the option to provide a reason for withdrawal if they withdraw. Withdrawal reasons will be summarised.

Follow-up rates - follow-up rates are based on case report form (CRF) completion at follow-up time points. Once all follow-up data has been collected, the follow-up rate will be summarised as follows:

$$\% \text{ Follow-up rate (at time T)} = \frac{\text{Number of participants assessed at time T}}{\text{Total no.that should have been assessed at time T}} \times 100$$

Follow-up rates will be computed at the 4-, 8- and 12-month follow-up time-points. At each time point, a participant is defined as being lost to follow-up if they do not return their CRF within 3 months of their follow-up due date.

Baseline patient characteristics

The demographic characteristics and pre-randomisation clinical outcome measures of all randomised participants will be summarised by treatment allocation. The table below lists the demographic and clinical measures that will be collected.

Type of Data	Outcome measures
Demographic:	- Age - Gender

	- Racial and Ethnic group - Age at leaving full time education - Current work status
Clinical measures:	
General Health	- Fatigue - Sleep quality - Bodily pain - Troublesomeness grid
Headache Specific	- Headache Specific Information (HIT-6)[1] - Chronic Headache Quality of Life Questionnaire, version1.0 (CHQLQ) [2] - Headache frequency, severity
Health-related Quality of Life	- Short Form 12-item Health Survey (SF12 (v2)) [3] - EuroQoL (EQ5D-5L) [4] - Chronic Headache Quality of Life Questionnaire, version1.0 (CHQLQ) [2]
Mood	Hospital Anxiety and Depression Scale (HADS) [5]
Confidence	Pain Self-Efficacy Questionnaire (PSEQ) [6]
Social Activity	Social Integration Subscale (heiQ) [7]
Health economic measures:	
Medication	- Medication purchased in last four weeks over the counter - Cost
Healthcare Use	- Inpatient care - Admission details - NHS Day Care treatment - Community health and social care - Side effects from headache medication - Private treatment - Additional cost information

For continuous data, the number of participants (n), mean, standard deviation (SD), median and interquartile range (IQR) will be used to summarise the outcome measures by treatment allocation. The number (%) of participants will be used to summarise categorical outcome measures.

SECTION 6 : ANALYSIS

SECTION 6: ANALYSIS

Outcome definitions

The table below lists and describes the primary and secondary outcomes. This includes details of specification of outcomes, timings and the derivation of the outcome (if required).

Outcome	Time point	Derivation of outcome
Primary outcome		
HIT-6 score[1]	1, 2, 3, 4	HIT-6 consists of 6 questions, each with 5 responses (never to always) which are scored 6, 8, 10, 11, and 13 points respectively. The HIT-6 is computed by simply summing the scores across the 6 questions. The score ranges from 36-78; the higher the score the greater the severity of headache.
Secondary outcomes		
Chronic Headache Quality of Life Questionnaire, version1.0 (CHQLQ)	1, 2, 3, 4	Measures chronic headache quality of life on scale of 0-100 over 3 domains (role restrictive, role preventive and emotional function). A higher score indicates better quality of life.
SF-12 V2 [3]	1, 2, 3, 4	SF-12 score computed using the algorithm/software provided by the authors. The algorithm produces mental and physical component scores ranging from 0-100 where a higher score reflects better mental and physical functioning, respectively.
EQ-5D-5L [4]	1, 2, 3, 4	EQ-5D-5L score will be computed in Stata using the eq5d package. The EQ-5D-5L score ranges from 0-1 where a higher score reflects better quality of life.
Hospital Anxiety and Depression Scale (HADS) [5]	1, 2, 3, 4	The HADS consists of 14 questions each with 4 responses with an assigned score. Seven questions measure anxiety and the other seven measure depression. The scores are simply summed up to give an anxiety and depression score both ranging from 0-21 where a higher score reflects more severe anxiety and depression.
Pain Self-Efficacy Questionnaire (PSEQ) [6]	1, 2, 3, 4	PSEQ consists of 10 questions, each with 6 responses (Not at all confident to Completely confident) which are scored from 0-6 respectively. The PSEQ is computed by simply summing the scores across the 10 questions. The score ranges from 060 where higher scores reflect stronger self-efficacy beliefs.
Social Integration Subscale of the Health Education Impact Questionnaire (heiQ) [7]	1, 2, 3, 4	The Social Integration subscale of heiQ measures the impact of social engagement and support through interaction with others presented with the same illness. If >50% questions present then values can be assigned for scoring otherwise the score is missing. Score ranges from 1-4 where higher scores indicate higher level of social interaction.

Headache days (Collected via smartphone app, paper diary and follow-up questionnaire)	App/diary – Collected once a week for the first 6 months and then once a month for the following 6 months. Follow-up questionnaire - collected at 1, 2, 3, 4.	App/diary collects data on: - On how many days of the last 7 days have you had a headache - On those days, on average how long did they last - On those days, on average how severe were they Follow-up questionnaire collects data on: - On how many days of the last 4 weeks have you had a headache
Safety reporting		
Adverse Events and Serious Adverse Events	Throughout the trial	

1 Baseline
2 4 month after randomisation
3 8 months after randomisation
4 12 months after randomisation

Analysis methods

Participant characteristics and outcomes will be summarised as mean and standard deviation (SD) for continuous data or frequency and percentage for categorical data, summarised by treatment arm. The median and interquartile range (IQR) will be presented if data are non-normal.

The primary analysis approach will be intention to treat. To account for the trial design with clustering in the intervention arm, linear mixed effects models with partial clustering will be used to estimate treatment effects for both primary and secondary outcomes. This will be done using the *mixed* command in Stata. Analyses will be adjusted for age, gender, the baseline value of the dependent variable and baseline stratification factors (type of headache and geographical locality). The adjusted treatment effect estimates (mean difference) will be presented along with their associated 95% confidence interval (CI). The primary clinical analysis will assess the overall difference between the self-management therapy (intervention) and the relaxation therapy (control) groups in the population with either probable or definite chronic migraine (if the proportion of participants with chronic tension type headache is $\leq$15%). If the proportion of chronic tension type headache is >15%

then the primary analysis will be according to the whole population of chronic headache (chronic migraine and tension type headache).

The values of the variable "number of headache days in the 4 weeks" collected at baseline and each follow-up time point is in the range 0 to 28. As such a normal distribution may not be a suitable distribution to explain its frequency. We will therefore plot the frequency of headache days and explore whether other distributions, e.g. negative binomial and beta-binomial, may be able to better explain the data frequency. The plots will be examined visually before a distribution is assumed for the variable for further analysis. This will be done at each time point separately. If more than one distribution is considered to be sufficient for the data then they will be used for further analyses and all the results will be presented. We may also explore the possibility of transforming the number of headache day's data into proportion (or rate) or categorising the data into ordinal outcomes. The latter approach would decrease the precision and sensitivity of the outcome but may be better than assuming it follows an incorrect distribution.

The possibility of carrying out a complier averaged causal effect (CACE) analysis for the primary outcome will be explored. Pre-specified subgroup analyses will also be conducted using formal statistical tests for interaction to examine whether baseline anxiety, depression and severity are moderators of treatment effect.[8]

Missing data

The levels and patterns of non-responders at each follow-up time point (including the weekly/monthly headache days collected via the smartphone app) will be monitored regularly. This is to ensure that strategies could be identified and implemented to minimise non-responders.

The levels and patterns of missingness in the primary outcome will be assessed to determine the type of missingness (e.g. MAR, NMAR). If required, as an additional sensitivity analysis, imputation techniques relevant to the type of missing data mechanism

will be used to impute data and estimate the treatment effect to see how it compares to the main ITT analysis.

Additional analyses

In addition to the primary analyses, the overall result for those with all headache types will also be assessed. NICE was specifically interested in data on specific headache types; rejecting data that reported data on a mixed population of people with chronic headaches. Therefore in addition to the primary analyses, the results (mean difference and 95% CI) for each of the three headache types separately, and the results for those with or without medication overuse separately will also be presented to facilitate future meta-analyses and inform future condition specific guidelines.

Data on total headache days was collected from participants over the entire study period. Participants had a choice of reporting this outcome either using a smartphone app or diary records (not both). This data was also collected in the baseline and follow-up questionnaires. We will compare the total headache days between the two groups using an area under the curve (AUC) approach. If participants have reported headache day's data using both the app/diary and the follow-up form at the same time point, then we will use the app/diary as the primary data source.

We expect there will be missing data. Therefore we will apply the following algorithm in order to obtain a complete set of the headache day's outcome for each participant thus allowing us to undertake the AUC analysis. Just to note, the unit of measurement of headache days for the app/diary data (headache days over the past 7 days) is different to the follow-up questionnaire (headache days over the past 4 weeks). Therefore when imputing data using data from the questionnaire, the average headache days per week (7 days) will be calculated and used to ensure the unit of measurement is consistent.

- Create a blank observation for each expected observation.
- If there is a valid text message response for the expected observation, then the blank value is replaced with the headache days reported via text message.

- **If the participant did not register with the text messaging service and headache days is reported in the paper diary, then the blank value is replaced with this headache days reported in the paper diary.**
- **If the participant did not provide headache days data via either the text messaging service or the diary, but they reported it on the follow-up form, then the blank value is replaced with the headache days reported on the follow-up form.**
- **If the participant has completed only one data source (either text message or paper diaries) and observation X is missing in the middle of the data set, then the headache days for observation X is calculated as:**

$$\frac{(Obs\ X-1) + (Obs\ X+1)}{2} \quad \textbf{(1)}$$

- **If two or more adjacent observations for headache days is missing, then a monotonic assumption is made for the missing values between the most recent valid observation and the next available valid observation. For example if two consecutive observations are missing, observation X and observation X + 1, then the headache days reported at observation X − 1 and observation X + 2 are used to calculate the imputed values for observations X and day X + 1 as follows:**

$$Obs\ X = Obs\ X-1 + \frac{(Obs\ X+2) - (Obs\ X-1)}{Number\ of\ missing\ obs + 1} \quad (2)$$

$$Obs\ X+1 = Obs\ X + \frac{(Obs\ X+2) - (Obs\ X-1)}{Number\ of\ missing\ obs + 1} \quad (3)$$

- **If the participant has provided headache days data via both app/diary and the follow-up data, then the app/diary data is used.**
- **If the participant has complete both data sources but the app/diary score is missing, then the follow-up headache day's data is used.**
- **If the first observation is missing then the first valid observation for this participant is backfilled.**
- **If last expected observation is missing, then the headache days reported at 12 months follow-up will be used. If the 12 month observation is missing then the last observation will be carried forward.**

Around 30 participants will be included in the process evaluation interviews conducted from pre-randomisation to follow-up. It is possible that discussing their expectations before and during the study may influence the treatment effectiveness. A sensitivity analysis will therefore be performed that excludes these participants from the main analysis.

At the eligibility check, participants are eligible if they have chronic headache defined as 15 or more days of headache per month for at least three months. However on the baseline form, participants are asked to report the number of headache days over the last 4 weeks for which many report having less than 15 days of headache. A sensitivity analysis will therefore be performed that excludes these participants from the main analysis.

Harms

The frequency and percentage (%) of serious adverse events (SAE) and adverse events (AE) in the trial will be compared between the two treatments using the chi-squared test provided the expected values in the cross-tabulation are greater than five, otherwise Fisher's exact test will be used. Odds ratios and 95% confidence intervals will be reported. Adjusted analyses will not be performed for any harm data. The event type, severity assessment, expectedness and relatedness to intervention will also be summarised by treatment arm.

Statistical software

Statistical analyses will be conducted using the statistical software package Stata 15.0.

SECTION 7 : TEMPLATE TABLES AND FIGURES

SECTION 7: TEMPLATE TABLES AND FIGURES

The template tables and figures have been presented in a separate document that consists of the following sections:

SECTION 1 - Screening through to randomisation

SECTION 2 - Participant baseline and demographic data

SECTION 3 - Participant follow-up

SECTION 4 - Intervention data

SECTION 5 - Study outcome data

SECTION 6 - Adverse events and serious adverse events

REFERENCES

[1] Kosinski, M., et al., *A six-item short-form survey for measuring headache impact: the HIT-6.* Qual Life Res, 2003. **12**(8): p. 963-74.

[2] McKenna, S.P., L.C. Doward, and K.M. Davey, *The Development and Psychometric Properties of the MSQOL: A Migraine-Specific Quality-of-Life Instrument.* Clin Drug Investig, 1998. **15**(5): p. 413-23.

[3] Jenkinson, C. and R. Layte, *Development and Testing of the UK SF-12.* Journal of Health Services Research, 1997. **2**(1): p. 14-18.

[4] Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.

[5] Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.

[6] Nicholas, M.K., *The pain self-efficacy questionnaire: Taking pain into account.* Eur J Pain, 2007. **11**(2): p. 153-63.

[7] Osborne, R.H., G.R. Elsworth, and K. Whitfield, *The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions.* Patient Educ Couns, 2007. **66**(2): p. 192201.

[8] Brookes, S.T., et al., *Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.* Health Technol Assess, 2001. **5**(33): p. 1-56.

Health Economics Analysis Plan

HEALTH ECONOMICS ANALYSIS PLAN

SECTION 1: ADMINISTRATIVE INFORMATION

Title: Chronic Headache and Self-management Study (CHESS)
ISRCTN number: *79708100*
HEAP Version: Version 2.0 (Date: 27.Nov.2019
Protocol Version: Version 3.7 (Date: 19.09.2019
HEAP revisions: None
Roles and responsibility:
Signatures of:

(signed off on Q Pulse at dates below)

	Name	Date	Signature
Author of HEAP	Felix Achana	27/11/2019	
Co-applicant	Stavros Petrou	27/11/2019	
Co-applicant	Hema Mistry	22/01/2020	
Chief Investigator	Martin Underwood	24/01/2020	

SECTION 2: INTRODUCTION

Objective

The Chronic Headache Education and Self-management Study (CHESS) is a multicomponent programme of interlocking studies funded by an NIHR programme grant to develop an education and self-management support intervention for people living with chronic headache (here in referred to as the CHESS intervention) and assess its clinical and cost-effectiveness in a randomised controlled trial. This analysis plan relates to the economic evaluation of the CHESS intervention using data from the two-arm multi-centre randomised controlled trial component of the CHESS programme. The within-trial economic evaluation will aim to estimate the cost-effectiveness of the CHESS intervention compared with best supportive care over the 12-month trial period of follow-up. The purpose of the health economics analysis plan is to outline an explicit framework of methods that will be used to analyse the health economic data in a robust manner. The document has been written based on information contained in the trial protocol version 3.7 dated on 19.Sep.2019.

Background rationale

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

management education and appropriate use of prophylaxis and management of medication overuse headache in a chronic headache population.

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

Objectives

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

SECTION THREE: METHODS

General principles for economic evaluation

The within-trial economic analysis will be conducted under the intention to treat (ITT) principle. This requires that study participants are analysed according to their treatment assignment regardless of actual treatment received (1). The perspective of the base case analysis will be that of the UK National Health Service and Personal Social Services (NHS/PSS), the recommended perspective for technology appraisals in the National Institute for Health and Care Excellence (NICE) reference case (2). Secondary analyses will consider costs from a wider societal perspective (3). A 12-month time horizon will be adopted for the within-trial analysis to mirror the trial follow-up period and therefore costs and outcomes will not be discounted due to this shorter time horizon. However, we will develop a decision analytic model to extrapolate trial results beyond the trial follow-up and assess the longterm cost-effectiveness of the CHESS intervention. Costs and outcomes in the decision model will be discounted at 3.5% beyond the first year post randomisation in accordance

with the NICE reference case (2). Findings will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of health economic evaluations (4).

Resource use and costs

Health and social care resource use will be collected for each trial participant over the 12-month period of follow-up. As outlined in the study protocol, the CHESS intervention consists of i) a structured education and self-management sessions delivered to groups of 10-12 patients over two days, ii) one-to-one consultation with the group facilitator (usually a registered nurse) for each participant and iii) a follow-on telephone call within the first 8 weeks of participating in the group session. Each interventional group will be facilitated by a trained registered nurse (grade 5 and above) and one allied health professional. Resource use and costs associated with delivery of the intervention will be estimated based on: (i) a detailed record of each group activity including the number of patients attending each group, duration of sessions, number of staff facilitators and their respective grades and set-up costs such as administrative support, educational material/leaflets and the room/facilities where the group activities takes place, (ii) number and length of one-to-one consultations with the clinical nurse and (iii) number and length of telephone follow-up consultations and the clinical grade of the staff conducting the consultation. Participants in the control group will be provided with a relaxation CD, the unit cost of which will be calculated based on the procurement costs for use of the CD in the trial.

In addition to the resource use associated with delivery of the interventions, resource utilisation data covering the 4-month period prior to randomisation (to establish baseline estimates) and the 12-month post-randomisation period will be collected for each trial participant through two principal means: (i) the trial case report forms including relevant primary/community care service use and hospital inpatient admissions and outpatient attendances and (ii) the computerised electronic record systems of participating general practice (GP) surgeries. Primary care, hospital inpatient and outpatient resource utilisation will be extracted from these sources for each trial participant. Primary care utilisation will be extracted from the electronic general practice records, which include details of consultations i.e. the number and type of consultations for example with a GP, practice

nurse or other community based health and social care professional or service and prescriptions. Secondary care utilisation data to be extracted from the GP electronic health records will include details of hospital day case and inpatient admissions (referral method and type of admission, type of ward, length of stay and details of diagnosis and procedures undertaken) and details of outpatient attendances (for example, headache clinic/neurology clinics, physiotherapy clinics, accident and emergency, medical tests, scans and investigations). Economic questionnaires completed by study participants at 4, 8 and 12 month assessment will provide additional secondary sources of NHS and Personal social service utilisation (community health and social care encounters and utilisation of hospital-based services). Costs based on resource use extracted from the GP records will act as the primary source of cost data for the economic evaluation. Costs estimated from resource use collected through the patient reported questionnaires will act as secondary data sources and will only be used where no equivalent cost information is available from the GP records. Private healthcare utilisation (including over the counter medication use), out-of-pocket expenses and travel costs borne by participants and their relatives, time-off work due to illness, lost income and use of community social care services such as meals on wheels (although use of these would most likely be minimal for the CHESS trial population). These will be measured using the economic questionnaires completed by study participants at 4, 8 and 12 month assessment. Private healthcare costs will be categorised into costs borne by other sector of the economy, e.g. use of community social care services, and cost borne by individuals.

Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A per diem cost for each level of hospital care, delineated by level of intensity, will be calculated using national tariffs. The unit costs of community health and social services will largely be derived from latest Unit Costs of Health and Social Care 2018 report published by the Personal Social Services Research Unit (PSSRU)(5), supplemented by information obtained from published literature and online sources. The primary analysis will concentrate on direct intervention and broader healthcare/PSS costs, whilst wider impact (societal) costs will be included within one of the sensitivity analyses.

Outcomes

The primary outcome of the within-trial economic evaluation will be the quality-adjusted life year (QALY) as recommended in the NICE reference case (2). This will allow incremental cost-effectiveness ratios for CHESS intervention compared with best usual care to be generated in the form of incremental cost per QALY gained. The QALY is a measure that combines quantity and quality of life lived into a single metric, with one QALY notionally equating to one year of full health. QALY estimates are generated from combining length and health-related quality of life outcomes using area-under-the-curve approaches (6). This requires survival and health-related quality of life data from or on behalf of trial participants for the period covering the trial time horizon. Health-related quality of life collected for trial participants (see details below) will be converted into health-state utilities indexed at 0 and 1 where 0 represents death and 1 represents full health.

Participants will be asked to complete the EuroQoL EQ-5D-5L (7) and SF-12 (8) measures using postal questionnaire at baseline and during follow-up at the 4, 8 and 12 months post-randomisation assessment points. Responses to the EQ-5D and SF-12 will be converted into multi-attribute utility scores using established algorithms (9, 10) from which QALYs can be generated. The EQ-5D is a generic preference based 5-dimensional multi-attribute instrument for measuring health-related quality of life. Currently, there are two versions of the questionnaire: a 3-level version (EQ-5D-3L) first introduced in 1990 by the EuroQoL Group (11) and a newer 5-level version (EQ-5D-5L) introduced in 2009 (12). Patients in the CHESS trial will complete the 5L version of the questionnaire. The 5L responses can be converted into health utilities using a recently published value set for England (13). However, since publication of the EQ-5D-5L value set, NICE has released a position statement (14) advising against the use of the new tariff (13) until the outcome of ongoing research exploring the impact of adopting the EQ-5D-5L valuation set in the NICE reference case becomes available. The position statement further recommends that during this interim period, EQ-5D-5L responses should be mapped or cross-walked onto the EQ-5D-3L using the Hout et al. (15) algorithm and the health utilities then derived from EQ-5D-3L utility scores using the UK value set for the EQ-5D-3L (16). Therefore, we initially plan to use the utility values derived from cross-walking the EQ-5D-5L responses onto the EQ-5D-3L

using the Hout et al. method to generate QALYs for the base case analysis. Sensitivity analyses will s will be conducted using health utility values generated from the SF-12 using the algorithm of Brazier et al (17).

SECTION FOUR: Mapping sub-study

A separate sub-study will be conducted as part of the CHESS programme of research to develop methods for mapping or cross-walking two headache-specific questionnaires (the 6-item Headache Impact Test (HIT-6) and the Chronic Headache Quality of Life Questionnaire (CHQLQ v1) onto generic health related quality of life questionnaires (the EQ-5D-5L and the SF-12 v2). A cross-sectional sample (sample size: 400-500) of people living with chronic headaches will be recruited from among patients attending headache clinics within NHS hospital outpatient departments for the mapping study. The headache-specific questionnaires are more likely to be responsive to improvement or worsening in headache-related symptoms than generic health-related quality of life measures such as the EQ-5D-5L and SF-12. Utilities based on the EQ-5D-5L or the SF-6D (via SF-12) can then be derived from the mapping algorithms. We will use utilities generated from the HIT-6 and the CHQLQ via the mapping functions as an alternative source of health utility in the base-case analysis where data from the EQ-5D-5L and the SF-12 v2 are missing. We will also use them stand alone sensitivity analyses to explore the robustness of the cost-effectiveness results to different approaches to measuring health-related quality of life impact of intervention.

SECTION FIVE: DATA

Data quality and cleaning

All data relevant to the health economics analysis will be examined for data quality. Questionnaires will be checked for completeness on return to the trial office. Any questionable data will be queried with trial staff and inappropriate or unclear responses will be handled in accordance with pre-specified data entry guidance. Unresolved issues after referral to the data entry instructions will be discussed with the trial health economists and clarification sought from the clinical team if necessary. Agreed line of actions for addressing data quality issues will be documented in the data entry guidance documentation.

Missing data

Any missing items present after the data cleaning stage will be addressed within the health economic analysis strategy as missing data. Missing data is a common occurrence within trial-based economic evaluations and it is necessary to address it in a standardised principled manner. Within the health economic literature, trial-based economic evaluations have been subject to particular criticism for failing to use appropriate methods to address missing data (18). Descriptive analyses of missing data will be carried out (missing data patterns using graphical tools, association between missing data and baseline variables, association between missing data and outcomes). The results of the descriptive analysis will be discussed by the trial team to infer possible reasons for missing data and inform the assumption about the missing data mechanism. In line with best practice recommendations for analysis of within-trial economic data (19), multiple imputation by chain equations implemented through the MICE package (20) in statistical package R version 3.13 (21) will be used to handle missing data for each assessment point (baseline, 4-, 8- and 12-month follow-up). Multiple imputation (MI) generates a series of datasets with each dataset replacing missing values with sampled values. MI replaces each missing observation with a set of plausible imputed values, taken from the predictive distribution of the missing data given the observed data (22). Such methods can handle data assumed missing at random (MAR) and can be modified to handle data assumed missing not at random (MNAR) (23). Appropriateness of the MAR assumption will be assessed by comparing the characteristics of patients with and without missing data at each follow-up time point. Imputated data will be generated separately by treatment group as recommended by Faria et al (24) using the predictive mean matching method which has the advantage of preserving non-linear relationships and correlations between variables within the data. Estimates obtained will be pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule in order to capture within and between variances for imputed samples. We will fit models under a missing not at random (NMAR) assumption by systematically varying values of imputed costs and utilities from 0 to ±100% within the imputation models to assess the robustness of our base-case results to the missing at random assumption.

SECTION SIX: ANALYSIS

Summary of resource use and costs

Patient-level costs will be generated for each resource variable by multiplying the quantity reported with the respective unit cost, weighted by length of stay or duration of contact where appropriate. Summary statistics (means, standard errors and completion rates) will be generated by treatment allocation and assessment point. Between treatment-group differences in mean resource use and mean costs at each assessment point will be compared using the two-sample t-test. Statistical significance was assessed at the 5% significance level. A non-parametric bootstrap routine with bias correction for standard errors and confidence intervals will be implemented, generating 1,000 replications of the data. Estimates of standard errors surrounding mean resource use (or cost) estimates and 95% confidence intervals surrounding between-group differences in mean resource use (or costs) will be obtained from the bootstrap samples.

Cost-effectiveness analysis

Cost-effectiveness results for the base case analysis will be obtained by formulating a system of seemingly unrelated mixed-effects regressions for individual-level costs and effects, accounting for the patient-level correlations between the two and adjusting for pre-specified baseline patient characteristics. The covariates to be included in the regressions will be those selected a priori for the adjusted statistical analysis, namely age, gender and the baseline stratification factors (type of headache and geographical locality). The group sessions to which patients in the intervention as clustering variable in the intervention group and the control group will act as a separate cluster on its own. Additionally, we will control for imbalance in baseline costs and EQ-5D values between the two trial arms by including a covariate for baseline costs in the cost model and baseline health related quality of life in the QALY model, a practice that is now standard for trial-based economic evaluations (25). Estimates of the incremental costs and QALYs associated with the CHESS intervention compared with best usual care will be generated from the regressions and presented as incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs). This accommodates sampling (or stochastic) uncertainty and

varying levels of willingness to pay for an additional QALY such as £15,000 per QALY threshold recently estimated by Claxton et al. (26) and the £20,000 to £30,000 per QALY threshold used by NICE in its technology appraisal process.(27) Heterogeneity in the trial population will be explored by formulating a net-benefit value for each patient from the observed costs and effects, and then constructing a regression model with a treatment variable and covariates such as age, gender, medication overuse and headache type where data allows us to do so. Treatment by covariate interaction terms will be included for each covariate one at a time. The magnitude and significance of the coefficients on the interaction between the covariates and the treatment variable should provide an estimate of the cost-effectiveness of the intervention by sub-group.

Additionally, due to known limitations of within-trial economic evaluations(28), we will also construct a Cohort Markov model to model beyond the parameters of the proposed within-trial cost-effectiveness of the intervention in the relevant patient population. We will inform the model with data from the trial as well as information identified from our systematic search of the literature. Long term estimates of costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. All analyses will be conducted using the statistical package R (21).

Sensitivity analyses

The following sensitivity analyses will be conducted to investigate sensitivity of the base case results to:

- Utilities generated from via the SF-12/SF-6D tariff for UK (17)
- The new EQ-5D-5L tariff for England (29)
- Costs calculated from a societal perspective
- Complete case analysis as the base case cost-effectiveness analysis uses imputed attributable costs and QALYs.
- EQ-5D-5L utilities derived HIT-6 via mapping coefficients

- EQ-5D-5L utilities derived CHQLQ via mapping coefficients
- SF-6D utilities derived HIT-6 via mapping coefficients
- SF-6D utilities derived CHQLQ via mapping coefficients

Subgroup analyses

Estimates of incremental cost-effectiveness will be calculated for the following subgroup of patients.

- Medication overuse
    - Yes
    - No
- Location (Midlands versus Greater London)
- Gender (Female versus Male)
- Age group (<40years versus ≥40 years)

SECTION SEVEN: TEMPLATE TABLES AND FIGURES

Results Tables

Table 1: Completion rates for health economic outcomes

	Completion rates	
Assessment point and resource category	CHESS intervention (n=xxx)	Best usual care (n=xxx)
Baseline		
EQ-5D-5L index	xxx%	xxx%
EQ-5D-5L VAS	xxx%	xxx%
SF-12 (SF-6D) utility score	xxx%	xxx%
Hospital inpatient (admitted care)	xxx%	xxx%
Day case attendance	xxx%	xxx%
Outpatient attendance	xxx%	xxx%

Consultations (primary care) – does this need to be split by type ie GP, nurse	xxx%	xxx%
Tests and investigations (primary care)	xxx%	xxx%
Prescribed medication (primary care)		
Over the counter medication	xxx%	xxx%
Private healthcare expenditure	xxx%	xxx%
Additional costs	xxx%	xxx%
Lost income due to headache related illness	xxx%	xxx%
Time off work due to headache related illness	xxx%	xxx%
4 month assessment point		
8 month assessment point		
12 month assessment point		

Table 2: Health and social care resource utilisation during follow-up

		CHESS intervention (n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
Assessment point	Category	% missing	Number of visits, mean (se)	Total duration in days / minutes, mean (se)	% missing	Number of visits, mean (se)	Total duration in days/minutes, mean (se)	Total duration, mean difference (bootstrap 95% CI)[1]	P-value
Baseline	Hospital inpatient								
	Day case								
	Admitted care (overnight stay)								
	Hospital outpatient								
	Headache clinic								
	Physiotherapist								
	Occupational therapist								
	Radiology: MRI scan								
	Radiology: CT scan								
	Radiology: X-ray								
	Radiology: Ultrasound								
	Blood tests[2]								
	Accident and emergency								

	Other outpatient								
	Primary care								
	GP, surgery visit								
	GP, home visit								
	GP, telephone contact								
	Practice nurse								
	District nurse								
	Community physiotherapist								
	Occupational therapist								
	counsellor								
	Psychology/psychotherapy								
	Social worker								
	Any other contact								
4 month assessment point									
8 month assessment point									

12 month assessment point									

[1]mean
difference and 95% bias corrected bootstrap confidence intervals

Table 3: Health and social care costs incurred during trial follow-up

		CHESS intervention (n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
Assessment point	Category	% missing	% zero costs	Mean costs (se)	% missing	% zero costs	Mean costs (se)	Mean difference, (bootstrap 95% CI)[1]	P-value
Baseline	Hospital inpatient								
	Day case								
	Admitted care (overnight stay)								
	Total inpatient costs								
	Hospital outpatient								
	Headache clinic								
	Physiotherapist								
	Occupational therapist								
	Radiology: MRI scan								
	Radiology: CT scan								

	Radiology: X-ray								
	Radiology: Ultrasound								
	Accident and emergency								
	Other outpatient								
	Total outpatient costs								
	Primary care								
	GP, surgery visit								
	GP, home visit								
	GP, telephone contact								
	Practice nurse								
	District nurse								
	Community physiotherapist								
	Occupational therapist								
	counsellor								
	Psychology/psychotherapy								
	Social worker								
	Any other contact								
	Total primary care costs								

[1]mean difference and 95% bias corrected bootstrap confidence intervals

Table 4: Private health care resource use during follow-up

		CHESS intervention(n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
Assessment point	Category	% missing	Number of visits, mean (se)	Total duration in days ! minutes, mean (se)	% missing	Number of visits, mean (se)	Total duration in days ! minutes, mean (se)	Total duration, mean difference (bootstrap 95% CI)[1]	P-value
Baseline	Over the counter medication								
	Physiotherapist								
	Occupational therapist								
	Counsellor								

	Psychologist								
	Radiology: MRI scan								
	Radiology: CT scan								
	Radiology: X-ray								
	Radiology: Ultrasound								
	Consultant service								
	Osteopath								
	Chiropractor								
	Acupuncturist								
	Homeopath								
	Other								
4 month assessment point									
8 month assessment point									
12 month assessment point									

[1]mean difference and 95% bias corrected bootstrap confidence intervals

Table 5: Private healthcare costs incurred during follow-up

		CHESS intervention (n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
Assessment point	Category	% missing	% zero costs	Mean costs (se)	% missing	% zero costs	Mean costs (se)	Mean cost difference, (bootstrap 95% CI)[1]	Pvalue
Baseline	Over the counter medication								
	Physiotherapist								
	Occupational therapist								
	Counsellor								
	Psychologist								
	Radiology: MRI scan								
	Radiology: CT scan								
	Radiology: X-ray								
	Radiology: Ultrasound								
	Consultant service								
	Osteopath								
	Chiropractor								
	Acupuncturist								
	Homeopath								

	Other								
	Total baseline costs								
4 month assessment point									
8 month assessment point									
12 month assessment point									

[1]mean
difference and 95% bias corrected bootstrap confidence intervals

Table 6: Additional costs incurred during trial follow-up

		CHESS intervention (n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
Assessment point	Category	% missing	Number of visits, mean (se)	Total number of days, mean (se)	% missing	Number of visits, mean (se)	Total number of days, mean (se)	Mean difference, (bootstrap 95% CI)[1]	P-value
3 months post randomisation	Travel costs (e.g. bus fares)								
	Child care costs								
	Income lost								

	Cost of help with housework								
	Cost of laundry services								
	Other additional costs								
	Total additional costs								
4 month assessment point									
8 month assessment point									
12 month assessment point									

[1]mean difference and 95% bias corrected bootstrap confidence intervals for total number of days or number of contacts/visits when number of days is not relevant

Table 7: Sources of unit costs information

Category	Currency code	Unit cost	Source
Inpatients (per day of inpatient stay)			
Day case			
Admitted care			
Accident and emergency			
Out patients (per contact)			
General surgery			
ENT			
Accident and Emergency			
Pain clinic			
General Medicine			
Diabetes			
Cardiology			
Dermatology			
Breast clinic			
Neurology			
Rheumatology			
Dentist			
Eye Clinic			
Gynaecology			
Midwife			
Osteopath			
Physiotherapy			
Chiropractor			
Podiatrist			
Mental health			
Blood test			
Occupational health			
MRI Scan			
CT Scan			
X-Ray scan			
Primary and social care (cost per contact)			
Acupuncture			
Chiropractor			
Physiotherapy			

Osteopathy			

Massage			
Pharmacist			
Psychology			
Counsellor			
District nurse/ health visitor / midwife			
Practice nurse			
GP home visit			
GP surgery			
GP telephone			
Health care assistant			
Private costs			
Physiotherapy			
Psychology			

Table 8: Total economic costs

Costing perspective and list of included cost categories	CHESS intervention (n=xxxx)			Best usual care (n=xxxx)			CHESS intervention versus best usual care	
	% missing	% zero costs	Mean (SE), £	% missing	% zero costs	Mean (SE), £	Mean difference (bootstrap 95% CI), £	P-value
NHS/PSS perspective								
Intervention costs								
Follow-up costs								
Total NHS/PSS costs								
Societal perspective								
Intervention costs								
Follow-up costs (NHS/PSS)								
Follow-up costs (non-NHS/PSS)								
Total societal costs								

[1]Confidence intervals obtained by bootstrap bias corrected percentile method

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Table 9: Summary of EQ5D-5L responses and scores on the visual analogue (VAS) scale

	EQ-5D dimension/ response	CHESS intervention (n=xxxx)	Best usual care (n=xxxx)	p-value[1]
Baseline	*Mobility* No problems Slight problems Moderate problems Severe problems Unable to walk Missing			
	Self-care No problems Slight problems Moderate problems Severe problems Unable to wash/dress Missing			
	Usual activities No problems Slight problems Moderate problems Severe problems Unable to do usual activities Missing			
	Pain and discomfort No problems Slight problems Moderate problems Severe problems Extreme pain and discomfort Missing			
	Anxiety and depression No problems Slight problems Moderate problems Severe problems Extremely anxious/depressed Missing			
	Visual analogue score Mean score (SE)			

	Missing			
4 months assessment point	*Mobility* No problems Slight problems Moderate problems Severe problems Unable to walk Missing			
	Self-care No problems Slight problems Moderate problems Severe problems Unable to wash/dress Missing			
	Usual activities No problems Slight problems Moderate problems Severe problems Unable to do usual activities Missing			
	Pain and discomfort No problems Slight problems Moderate problems Severe problems Extreme pain and discomfort Missing			
	Anxiety and depression No problems Slight problems Moderate problems Severe problems Extremely anxious/depressed Missing			
	Visual analogue score Mean score (SE) Missing			
8 months assessment point	*Mobility* No problems Slight problems Moderate problems			

	Severe problems Unable to walk Missing			
	Self-care No problems Slight problems Moderate problems Severe problems Unable to wash/dress Missing			
	Usual activities No problems Slight problems Moderate problems Severe problems Unable to do usual activities Missing			
	Pain and discomfort No problems Slight problems Moderate problems Severe problems Extreme pain and discomfort Missing			
	Anxiety and depression No problems Slight problems Moderate problems Severe problems Extremely anxious/depressed Missing			
	Mobility No problems Slight problems Moderate problems Severe problems Unable to walk Missing			
	Visual analogue score Mean score (SE) Missing			
12 months assessment point	*Self-care* No problems Slight problems			

	Moderate problems Severe problems Unable to wash/dress Missing			
	Usual activities No problems Slight problems Moderate problems Severe problems Unable to do usual activities Missing			
	Pain and discomfort No problems Slight problems Moderate problems Severe problems Extreme pain and discomfort Missing			
	Anxiety and depression No problems Slight problems Moderate problems Severe problems Extremely anxious/depressed Missing			
	Visual analogue score Mean score (SE) Missing			

[1]P-values were generated from chi-squared tests for differences in sub-optimal levels of function for each dimension where responses indicating no functional impairment were categorised as optimal and responses indicating any functional impairment were categorised as sub-optimal.

Table 10: SF-12 v2 responses

Assessment point	Response	CHESS intervention (n=xxxx)	Best usual care (N=xxxx)	P-value[1]
Baseline	*General health* Excellent Very good Good Fair Poor Missing			
	Moderate activities Yes, limited a lot			

Yes, limited a little No, not limited at all Missing			
Climbing stairs Yes, limited a lot Yes, limited a little No, not limited at all Missing			
Accomplished less physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
Limited physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
Did less Work emotional All of the time Most of the time Some of the time A little of the time None of the time Missing			
Accomplished less emotionally All of the time Most of the time Some of the time A little of the time None of the time Missing			
Pain Not at all A little bit Moderately Quite a bit Extremely Missing			
Calm All the time Most of the time A good bit of the time Some of the time A little bit of the time			

	None of the time Missing			
	Energy All of the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Feeling down hearted All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Social activities All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
4 months post randomisation	*General health* Excellent Very good Good Fair Poor Missing			
	Moderate activities Yes, limited a lot Yes, limited a little No, not limited at all Missing			
	Climbing stairs Yes, limited a lot Yes, limited a little No, not limited at all Missing			
	Accomplished less physically All of the time Most of the time Some of the time A little of the time None of the time Missing			

Limited physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
Did less Work emotional All of the time Most of the time Some of the time A little of the time None of the time Missing			
Accomplished less emotionally All of the time Most of the time Some of the time A little of the time None of the time Missing			
Pain Not at all A little bit Moderately Quite a bit Extremely Missing			
Calm All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
Energy All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
Feeling down hearted All the time Most of the time A good bit of the time Some of the time			

	A little bit of the time None of the time Missing			
	Social activities All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
8 month post-randomisation	*General health* Excellent Very good Good Fair Poor Missing			
	Moderate activities Yes, limited a lot Yes, limited a little No, not limited at all Missing			
	Climbing stairs Yes, limited a lot Yes, limited a little No, not limited at all Missing			
	Accomplished less physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
	Limited physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
	Did less Work emotional All of the time Most of the time Some of the time A little of the time None of the time Missing			

	Accomplished less emotionally All of the time Most of the time Some of the time A little of the time None of the time Missing			
	Pain Not at all A little bit Moderately Quite a bit Extremely Missing			
	Calm All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Energy All of the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Feeling down hearted All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Social activities All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
12 months post randomisation	*General health* Excellent			

Very good Good Fair Poor Missing			
Moderate activities Yes, limited a lot Yes, limited a little No, not limited at all Missing			
Climbing stairs Yes, limited a lot Yes, limited a little No, not limited at all Missing			
Accomplished less physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
Limited physically All of the time Most of the time Some of the time A little of the time None of the time Missing			
Did less Work emotional All of the time Most of the time Some of the time A little of the time None of the time Missing			
Accomplished less emotionally All of the time Most of the time Some of the time A little of the time None of the time Missing			
Pain Not at all A little bit Moderately Quite a bit Extremely			

	Missing			
	Calm All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Energy All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Feeling down hearted All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			
	Social activities All the time Most of the time A good bit of the time Some of the time A little bit of the time None of the time Missing			

Table 11: Summary of health-related quality of life (utility) scores generated from EQ-5D-5L and SF-12 v2 instruments

	CHESS intervention			Best usual care			CHESS intervention versus best usual care
Outcomes	N	% missing	Mean (SE)	N	% missing	Mean (SE)	Mean difference (95% CI) P-value
EQ-5D-5L to 3L cross walk[1]							
Baseline	xxxx			xxxx			
4 months	xxxx			xxxx			
8 months	xxxx			xxxx			
12 months	xxxx			xxxx			
EQ-5D-5L (new UK tariff)[2]							
Baseline	xxxx			xxxx			
4 months	xxxx			xxxx			
8 months	xxxx			xxxx			
12 months	xxxx			xxxx			
SF-12 (SF-6D UK tariff)							
Baseline	xxxx			xxxx			
4 months	xxxx			xxxx			
8 months	xxxx			xxxx			
12 months	xxxx			xxxx			
EQ-5D-5L VAS							
Baseline	xxxx			xxxx			
4 months	xxxx			xxxx			
8 months	xxxx			xxxx			
12 months	xxxx			xxxx			

[1]The EQ-5D-5L cross-walk utility values were derived using the interim 5L to 3L cross-walk tariffs for the UK (15)
[2]New EQ-5D-5L value set for England (13)

Table 12: Unadjusted estimates of Quality-Adjusted Life Years (QALYs) accrued over 12 months of follow-up

	CHESS intervention			Best usual care plus relaxation			CHESS intervention versus best usual care	
Outcome measure	N	% missing	Mean (SE)	N	% missing	Mean (SE)	Mean difference (95% CI)	P-value
EQ-5D-5L cross-walk tariff	xxxx			xxxx				
EQ-5D-5L (New 5L tariff for England)	xxxx			xxxx				
SF-12 (SF-6D tariff)	xxxx			xxxx				

Table 13: Cost-effectiveness of the CHESS intervention compared with best usual care based on the within-trial economic analysis

	Cost-effectiveness outcomes				Probability CHESS intervention is cost-effective at cost-effectiveness threshold of		
Description	Mean incremental costs (95% CI), £	Mean incremental QALYs (95%	ICER[4]		£13,000 per QALY	£20,000 per QALY	£30,000 per QALY
Base case analysis[1]							
Sensitivity analyses Unadjusted analysis Complete case analysis Restricted to trial participants who did not participate in process evaluation interviews SF-12/SF-6D EQ-5D utilities derived HIT-6 via mapping coefficients EQ-5D utilities derived CHQLQ via mapping coefficients SF-6D utilities derived HIT-6 via mapping coefficients SF-6D utilities derived CHQLQ via mapping coefficients							
Sub-group analyses Headache type Chronic tension type headache Probable chronic migraine Definitive chronic migraine							
Headache type with medication overuse Chronic tension type headache Probable chronic migraine							

Definitive chronic migraine							
Headache type without medication overuse Chronic tension type headache Probable chronic migraine without Definitive chronic migraine without							
Geographical location Midlands Greater London							
Gender Female Male							
Age group <40years ≥40 years							

ICER = Incremental cost-effectiveness ratio; CI = confidence interval

1Adjusted for treatment allocation, age, gender, baseline stratification factors (type of headache and geographical locality), baseline health-related quality of life (QALY model) and baseline costs (cost model)

REFERENCES

1. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A. Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. Value in Health. 2005;8:521-33.

2. NICE. Guide to the methods of technology appraisal. NICE [Internet]. 2013 12 15. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.

3. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA. 2016;316(10):1093-103.

4. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ : British Medical Journal. 2013;346.

5. Curtis L. Unit costs of health and social care. Canterbury, UK: University of Kent; 2011.

6. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. 2nd ed. Gray A, Briggs A, editors. Oxford: Oxford University Press; 2015.

7. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.

8. Ware JE. How to Score Version 2 of the SF-12v2® Health Survey (With a Supplement Documenting SF-12® Health Survey) Lincoln, RI.: QualityMetric Inc; 2002.

9. Dolan P, Roberts J. Modelling valuations for Eq-5d health states: an alternative model using differences in valuations. Med Care. 2002;40(5):442-6.

10. Brazier J, Czoski-Murray C, Roberts J, Brown M, Symonds T, Kelleher C. Estimation of a preference-based index from a condition-specific measure: the King's Health Questionnaire. Medical decision making : an international journal of the Society for Medical Decision Making. 2008;28(1):113-26.

11. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

12. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality in Life Research. 2011;20(10):1727-36.

13. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2017:n/a-n/a.

14. National Istitute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set. Available from

https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf. Accessed on 28 September 2017. 2017.

15. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value in Health. 2012;15(5):708-15.

16. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Brit Med J. 1998;316(7133):736 - 41.

17. Brazier JE, Roberts J. The Estimation of a Preference-Based Measure of Health From the SF-12. Medical Care. 2004;42(9):851-9.

18. Gomes M, Grieve R, Nixon R, Carpenter J, Thompson SG. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. Medical Decision Making. 2012;32(2):350-61.

19. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-Effectiveness Analysis Alongside Clinical Trials II 2014;An ISPOR Good Research Practices Task Force Report. Value in Health.18(2):161-72.

20. Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate Imputation by Chained Equations. Journal of Statistical Software, 45, 1-67. . 2011.

21. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. 2017.

22. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:2393.

23. Faria R, Gomes M, Epstein D. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. PharmacoEconomics. 2014;32:1157-70.

24. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. PharmacoEconomics. 2014;32(12):1157-70.

25. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005;14(5):487-96.

26. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health technology assessment (Winchester, England). 2015;19(14):1-503, v-vi.

27. National Istitute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Avaialable from http://publications.nice.org.uk/pmg9. 2013.

28. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006;15(7):677-87.

29. Devlin N, Shah K, Feng F, Mulhern B, van Hout B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Available from https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england. 2016.

eAppendix 1 Health Economics Analysis Full Report

Introduction

The following are results from analyses according to the Health Economics Analysis Plan for "CHESS: a supportive self-management programme for people living with chronic headaches: a randomised controlled trial and economic evaluation".

Overview

A prospective within-trial economic evaluation was conducted to estimate the cost-effectiveness of the CHESS intervention compared with usual care alone for people living with chronic headaches. Costs are expressed in British pounds sterling valued at 2019 prices and health outcomes are expressed in terms of quality-adjusted life-years (QALYs). The base-case analysis used the intention-to-treat trial data covering the 12-month period from randomisation and was conducted from the perspective of the UK National Health Service and Personal Social Services (PSS) (NICE, 2013) Costs and outcomes were not discounted due to the one-year time horizon. Sensitivity analyses explored likely impact of alternative data inputs (e.g. adopting a broader societal perspective) and assumptions on cost-effectiveness outcomes. Subgroup analyses were conducted to estimate heterogeneity in cost-effectiveness results. The methods adhered to a pre-specified health economics analysis plan approved by the CHESS Steering Committee. Findings are reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (Husereau et al., 2013).

Methods

Measurement and valuation of resource use

The estimation of economic costs required estimates of resource inputs associated with the intervention and broader utilisation of hospital and community-based health and social care services. Resource inputs were then weighted by values reflecting the opportunity costs, or 'prices', for each respective input (unit cost).

Intervention costing

We did a micro-costing exercise to estimate the resource use associated with delivery of the CHESS intervention. Staff were asked to prospectively provide the number of hours it took them to deliver the group intervention, plus the one-to-one sessions, the follow-up telephone calls, including any administration time, as well as intervention-related training activities. We obtained hourly costs of staff time for delivery of the intervention from the Unit Costs of Health and Social Care for 2019 (Curtis and Burns, 2019); see Table . We estimated cost of venue hire based on the average costs for venues for which there was a charge. We have allowed for staff travel costs based on a car rate of 45pence/mile (https://www.gov.uk/government/publications/rates-and-allowances-travel-mileage-and-fuel-allowances/travel-mileage-and-fuel-rates-and-allowances). The cost of CDs and DVDs was based on preparation cost for the discs; i.e. we did not include cost of developing the content. We allowed for depreciation on equipment (phones, laptops, projectors) over 5-10 years. Other equipment costs were included as the total cost.

Hospital and community-based health and social care service use

Utilisation of hospital and community-based health and social care services covering the 12 month period from randomisation were collected for trial participants through two principal means:

- Data extracted from primary care electronic record systems held at GP surgeries. This provided a detailed profile of utilisation of primary care (consultations, prescriptions, tests and investigations) and

hospital-based services (emergency department attendances, inpatient admissions including length of stay, hospital day-case attendances and outpatient services).

- Economic questionnaires completed by trial participants at baseline, 4, 8 and 12 months' post-randomisation assessment points. These provided participant self-reports of primary and secondary care health and social care service use, private medical expenses (including over the counter medications), additional costs borne by participants (childcare costs, travel costs to attend headache related medical appointments) and productivity related costs (time-off work and income lost by participants and their partners as a result of headache-related illness).

Costs based on resource use extracted from the GP records acted as the primary source of cost data for the within-trial economic evaluation. Costs estimated from resource use collected through the patient reported questionnaires acted as a secondary source of information on utilisation of health and social care services. The latter data were used in the economic evaluation for trial participants for whom data from the electronic GP records were unavailable. Private healthcare utilisation (including over the counter medication use), out-of-pocket expenses and travel costs borne by participants and their relatives, time-off work due to illness, lost income and use of community social care services) were only available from the participant reported data.

Unit costs expressed in British pounds sterling for the 2019 price year were applied to each resource item to value total resource use in each arm of the trial. These are summarised in Table 1. The unit costs of community health and social services were derived from latest Unit Costs of Health and Social Care 2019 compendium published by the Personal Social Services Research Unit (PSSRU) (Curtis and Burns, 2019), the prescription cost analysis 2019 Tables (NHS Digital, 2019), national reference costs 2019 tables, and the online version of the British National Formulary (BNF) 2019 version (Joint Formulary Committee, 2019). These sources of unit cost data were supplemented by information obtained from published literature and online sources. The primary analysis concentrated on direct intervention and broader healthcare/PSS costs, whilst wider impact (societal) costs were considered as part of the sensitivity analyses.

Table 1: Unit costs of health and social care services (2019 prices).

Service	Unit	unit cost (in £)	Source
Primary care			
General practitioner	Contact (10 minutes)	39	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Pharmacist	Contact (1 hour)	45	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Physiotherapist	Contact (1 hour)	45	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Hypnotherapist	Contact (1 hour)	45	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Practice nurse/band 6 nurse	Contact (1 hour)	46	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Occupational therapist	Contact (1 hour)	45	PSSRU Unit Costs 2019 (Curtis and Burns , 2019)
Admitted care			
Acute medical admission	care episode	589	2019 reference costs (NES, 1 day) (NHS Digital (b))
Lumber puncture	care episode	2259	2019 reference costs (AA31, NEL, 9 days) (NHS Digital (b))
Greater occipital nerve block injections	care episode	753	2019 reference costs (AB16Z, 9 days) (NHS Digital (b))
Emergency department	visit	116	2019 reference costs, VB09Z (NHS Digital (b))
Hospital outpatients			
Acupuncture	contact	35	British Acupuncture Council estimates £35 - £50 per hour (British Acupuncture Council, 2019)
City of London Med Centre	contact	175	Harley Street - 30 minutes, online (https://walkin-clinic.co.uk/pricing)
Ear nose and throat (ENT)	contact	107	2019 reference costs (NHS Digital (b))
Harley Street Med Centre	contact	175	Harley Street - 30 minutes (https://walkin-clinic.co.uk/pricing)
Integrated Medicine	contact	167	2019 reference costs (NHS Digital (b))
Ophthalmology	contact	98	2019 reference costs (NHS Digital (b))
Orthopaedics	contact	120	2019 reference costs (NHS Digital (b))

Rheumatology	contact	147	2019 reference costs (NHS Digital (b))
Stroke	contact	197	2019 reference costs (NHS Digital (b))
Urology	contact	108	2019 reference costs (NHS Digital (b))
Botox injection	contact	349	TA260 (2012 prices, updated to 2019 prices) (NICE, 2012)
Outpatients (pain management / neurology)	contact	177	2019 reference costs (NHS Digital (b))

Outcomes

The primary health outcome in this within-trial economic evaluation is the quality-adjusted life year (QALY) in line with the NICE reference case (NICE, 2013). The QALY is a measure of health benefit that combines quantity and health-related quality of life lived into a single metric. One QALY notionally equates to one year of full health. QALY estimates were generated from combining length and health-related quality of life outcomes using area-under-the-curve approaches (Glick et al., 2014) Information on survival was estimated over the 12 months' duration of study follow-up. Health-related quality of life outcomes were collected for trial participants (see details below) and converted into health utilities indexed at 0 and 1 where 0 represents death and 1 represents full health.

Participants were asked to complete the EuroQoL EQ-5D-5L (Herdman et al., 2011) and SF-12 (Ware, 2002) measures using postal questionnaire at baseline and during follow-up at the 4, 8- and 12-months post-randomisation assessment points. Responses to the EQ-5D-5L and SF-12 measures were converted into multi-attribute utility scores using established algorithms (Brazier et al., 2002) from which were generated. The EQ-5D is a generic preference based 5-dimensional multi-attribute instrument for measuring health-related quality of life. Currently, there are two versions of the questionnaire: a 3-level version (EQ-5D-3L) first introduced in 1990 by the EuroQoL Group (EuroQol Group, 1990) and a newer 5-level version (EQ-5D-5L) introduced in 2009 (Herman et al., 2011) Patients in the CHESS trial completed the 5L version of the questionnaire. The 5L responses were converted into health utilities based on the UK tariff for the EQ-5D-3L descriptive system (Kind et al., 1998) using the van Hout and Hernandaez-Alarva crosswalk algorithms in line with current NICE recommendations (van Hout et al., 2012, Hernandez-Alava and Pudney, 2018). The base-case analysis used EQ-5D-5L QALYs generated from the van Hout crosswalk method. Sensitivity analyses were conducted using EQ-5D-5L QALYs based on utilities generated from Hernandez-Alava method (Hernandez-Alava and Pudney, 2018); and SF-6D QALYs generated from the SF-12 using the algorithm of Brazier and colleagues (Brazier et al., 2002).

Statistical Methods

Summary of resource use and costs

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

Summary of health-related quality of life data

Responses to each health dimension of the EQ-5D-5L and SF-12 are presented by level of function. Comparisons of responses are conducted on the basis of optimal level of function (for example “no problem” on the EQ-5D-5L) versus sub-optimal level of function (indicating any functional impairment). Between-group differences in optimal versus sub-optimal level of function for each health dimension were compared for each health-related quality of life measure using chi-squared tests. Summary statistics (means, standard errors and

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

Missing data

Multiple imputation by chain equations implemented through the R package MICE (Van Buuren and Groothuis-Oudshoorn, 2011) was used to predict values for any missing items, assuming data were missing at random. Missing costs and health utility values were imputed at the level of resource category and health-related quality of life assessment, stratified by intervention arm in accordance with good practice recommendations (Faria et al., 2014). Imputation was achieved using predictive mean matching, which has the advantage of preserving non-linear relationships and correlations between variables within the data. Fifty imputed datasets were generated and used to inform the base-case and subsequent sensitivity and subgroup analyses. Parameter estimates were pooled across the 50 imputed datasets using Rubin's rules to account for between and within-imputation components of variance terms associated with parameter estimates.

Base-case cost-effectiveness

The base-case cost-effectiveness analysis uses the intention-to-treat data to estimate the cost-effectiveness of the CHESS intervention compared with usual care from the perspective of the UK NHS and PSS. Economic costs and QALYs were calculated for each patient over a 12-month post-randomisation time period. Total costs were calculated by summing costs associated with the delivery of the intervention (we assigned £0.40 to the usual care arm representing the cost of a relaxation CD) and costs of broader hospital and community-based health and social care services.

Bivariate generalised linear mixed-effects regressions assuming a Gamma distributed error structure and logarithmic link function were fitted to imputed data in R using methods we have recently developed for cost-effectiveness analyses of cluster randomised and multicentre trial data (Achana et al., in press). The models account for the within-cluster and between-cluster correlation between skewed costs and effects data measured from the same individuals. We controlled for intervention arm, age, gender, headache type, baseline costs (in the cost equation) and baseline utilities (in the QALY equation).

The incremental cost-effectiveness ratio (ICER) was calculated for the CHESS intervention compared with usual care by dividing the between-group difference in adjusted mean total costs by the between-group difference in adjusted mean QALYs. Cost-effectiveness was assessed by comparing the ICER to cost-effectiveness thresholds between £15,000 and £30,000 per QALY gained in line with NICE guidance (NICE, 2013) and the recent empirical threshold of £13,000 per QALY estimate suggested by Claxton and colleagues (Claxton et al., 2015). The incremental net (monetary) benefit of the intervention compared with usual care was calculated for cost-effectiveness thresholds at £15,000, £20,000 and £30,000 per QALY gained. Net monetary benefit values reflect the opportunity cost of (or the benefits forgone) from adopting a new treatment when resources could be put to use elsewhere. A positive net monetary benefit would suggest that, on average, the CHESS intervention provides a net gain compared to usual care for the NHS and PSS and can be considered cost-effective at the given cost-effectiveness threshold.

Uncertainty around the mean cost-effectiveness estimates was characterised through a Monte Carlo method (Glick et al, 2014) This involved simulating 2,000 replicates of the ICER from a joint distribution of the incremental costs and QALYs and plotting the simulated ICERs on the cost-effectiveness plane. Cost-effectiveness acceptability curves were also plotted to give graphical display of the probability that the CHESS intervention is cost-effective across a wide range of cost-effectiveness thresholds.

Sensitivity analyses

The following sensitivity analyses were conducted to investigate sensitivity of the base-case results to:

- QALYs generated from EQ-5D-5L utilities using the alternative Hernandez-Alava and Putney crosswalk function (Hernandez-Alava and Pudney, 2018).
- Utilities generated via the SF-6D UK tariff based on SF-12 responses (Brazier et al., 2002).
- Total costs estimated from a societal perspective
- Unadjusted analysis of the multiple imputation data
- Adjusted complete case analysis.

Subgroup analyses

Estimates of incremental cost-effectiveness were also calculated for the following pre-specified subgroups of patients: i) medication overuse (yes/no), ii) Location (London versus Midlands), iii) gender (male versus female) and iv) age group (<40 years versus ≥40 years).

Results

Study population

Seven hundred and thirty-six participants were randomised into the CHESS (380 to the CHESS intervention and 356 to the usual care). Of these, 9 study participants with a tension-type headache were excluded leaving a total of 727 participants (376 in the intervention group and 351 in the usual care) for analysis. Resource use data were collected via the trial case report forms for all study participants (CRF data) and via general practice record (GP data) reporting primary and secondary care utilisation for 586 (data from GP records was available for 80.6% of the 727 participants).

Costs of the intervention

Table 2 displays intervention cost estimates from the micro-costing exercise stratified by intervention group and resource input. The intervention was delivered to 42 groups – 30 of these groups were in the Midlands and the remainder were in London. The number of participants in the groups ranged from 3 to 16 and the overall mean number of participants per group was 9.

Staff time - The average times for delivering day 1, day 2, the 1-2-1 sessions and the telephone follow-up sessions for the intervention by a nurse were 7.0, 7.0, 8.0 and 2.7 hours, respectively. The average times for delivering day 1 or day 2 by an AHP were 6.8 and 6.7 hours, respectively. The total staffing costs ranged from £1,694 (COV002) to £2,772 (TOW001)

Venue hire - The intervention was delivered for 18 groups in community centres; for 15 groups in GP practices; and for 9 groups in healthcare/medical or walk-in centres. Only 17 groups provided the cost of venue hire and for all of these 17 groups the intervention was delivered in the community centres. The average cost of hiring the venue for the 17 groups that provided a cost was £310.62 (ranging from £170 to £600).

Travel – We assumed that the nurses would travel 30 miles and incur a cost of £13.50 and the AHPs would travel 20 miles and incur a cost of £9.00.

Equipment and disposables - The average cost per participant for the equipment and disposables was £3.38.

Total costs

Table 2 shows the estimates of the total costs of delivering the CHESS intervention for each group. As noted earlier, the cost components are aggregated into four headings: staff costs, venue hire, travel costs, and equipment and disposables. The total costs varied between £2,209 (COV001) to £3,152 (TOW001).

Table 2: Costs associated with delivery of intervention.

Area	Group	No of participants allocated to group	Staffing	Venue hire	Equipment and disposables	Travel	Total costs	Average cost per participant
Midlands	COV001	6	£1,855.41	£310.62	£20.29	£22.50	£2,208.82	£368.14
Midlands	KEN001	6	£2,400.41	£346.50	£20.29	£22.50	£2,789.70	£464.95
Midlands	WAR001	10	£2,132.49	£310.62	£33.81	£22.50	£2,499.42	£249.94
Midlands	WAR002	7	£2,031.24	£310.62	£23.67	£22.50	£2,388.03	£341.15
Midlands	BIR001	4	£1,944.41	£310.62	£13.52	£22.50	£2,291.06	£572.76
Midlands	STR001	9	£2,217.91	£310.62	£30.43	£22.50	£2,581.46	£286.83
Midlands	WAR003	9	£2,061.41	£310.62	£30.43	£22.50	£2,424.96	£269.44
Midlands	TUT001	11	£2,031.42	£238.00	£37.19	£22.50	£2,329.11	£211.74
Midlands	ABI001	11	£2,047.25	£310.62	£37.19	£22.50	£2,417.56	£219.78
Midlands	BIR002	8	£1,939.42	£420.00	£27.05	£22.50	£2,408.97	£301.12
Midlands	COV002	10	£1,694.41	£310.62	£33.81	£22.50	£2,061.34	£206.13
Midlands	TUT002	6	£2,047.25	£238.00	£20.29	£22.50	£2,328.03	£388.01
Midlands	WIT001	7	£2,047.25	£310.62	£23.67	£22.50	£2,404.04	£343.43
Midlands	WOR001	8	£1,893.42	£310.62	£27.05	£22.50	£2,253.59	£281.70
Midlands	BIR003	7	£1,986.24	£280.00	£23.67	£22.50	£2,312.41	£330.34
Midlands	NUN001	13	£2,301.24	£297.50	£43.96	£22.50	£2,665.19	£205.01
Midlands	WNT001	13	£2,047.25	£310.62	£43.96	£22.50	£2,424.33	£186.49
Midlands	WOR002	8	£1,899.41	£400.00	£27.05	£22.50	£2,348.96	£293.62
Midlands	COV003	7	£1,986.24	£310.62	£23.67	£22.50	£2,343.03	£334.72
Midlands	ABI002	11	£2,047.25	£245.00	£37.19	£22.50	£2,351.94	£213.81
Midlands	LIC001	14	£1,941.24	£310.62	£47.34	£22.50	£2,321.70	£165.84
Midlands	BED001	3	£1,941.24	£324.00	£10.14	£22.50	£2,297.88	£765.96
Midlands	NOT001	8	£1,986.24	£210.00	£27.05	£22.50	£2,245.79	£280.72
Midlands	MIL001	9	£2,047.25	£310.62	£30.43	£22.50	£2,410.80	£267.87
Midlands	LEI001	9	£1,992.41	£252.00	£30.43	£22.50	£2,297.34	£255.26
Midlands	LIC002	13	£2,031.24	£310.62	£43.96	£22.50	£2,408.32	£185.26
Midlands	WOR003	16	£2,243.41	£169.60	£54.10	£22.50	£2,489.61	£155.60
Midlands	SOL001	9	£1,975.01	£420.00	£30.43	£22.50	£2,447.94	£271.99
Midlands	HER001	6	£1,986.24	£210.00	£20.29	£22.50	£2,239.02	£373.17
Midlands	NOT002	8	£1,986.24	£210.00	£27.05	£22.50	£2,245.79	£280.72
London	BRO001	7	£2,165.77	£310.62	£23.67	£22.50	£2,522.56	£360.37
London	WAN001	8	£2,136.78	£310.62	£27.05	£22.50	£2,496.95	£312.12
London	CAM001	10	£2,219.94	£600.00	£33.81	£22.50	£2,876.25	£287.62
London	SOU001	7	£2,136.78	£310.62	£23.67	£22.50	£2,493.57	£356.22
London	NEW001	6	£2,079.94	£310.62	£20.29	£22.50	£2,433.35	£405.56
London	CAM002	11	£2,136.78	£420.00	£37.19	£22.50	£2,616.47	£237.86
London	SOU002	14	£2,136.78	£310.62	£47.34	£22.50	£2,517.24	£179.80
London	LAM001	14	£2,136.78	£310.62	£47.34	£22.50	£2,517.24	£179.80
London	SOU003	13	£2,136.78	£310.62	£43.96	£22.50	£2,513.86	£193.37
London	TOW001	14	£2,771.94	£310.62	£47.34	£22.50	£3,152.40	£225.17
London	HOU001	10	£2,255.77	£310.62	£33.81	£22.50	£2,622.70	£262.27
London	TOW002	6	£2,385.45	£310.62	£20.29	£22.50	£2,738.86	£456.48

Summary of resource use and costs collected via GP records and the trial case report forms

Table summarise NHS and PSS resource use values by intervention group, resource category and trial period for complete cases reported by study participants. Resource values are presented for subcategories of resource use, including hospital emergency department attendances, hospital inpatient and outpatient care, primary care (residential care, community health and social care) and prescribed medications. Health and social care service use data extracted from GP records are summarised in Table stratified by intervention group. Broader societal resource inputs and costs including privately purchased medications, travel costs, childcare, lost income, housework help and laundry service costs and presented in Table . No notable differences were observed between the intervention versus usual care groups across all categories of resource use extracted from the CRF data (Table) and the GP records data (Table). In terms of non-NHS and PSS resource use, encompassing expenditures incurred by patients, family members and lost income due to ill-health as a result of headache related illnesses for the intervention and usual care groups (Table), no significant differences were observed across all the assessment time periods.

Costs estimated from resource use data collected via CRFs and GP records

Health and social care costs based on the participant reported CRF data and disaggregated at the level of resource use variable, intervention group and assessment point are presented in Table 11. The equivalent cost summaries covering the 12 months' post-randomisation period based on the GP data are presented in Table 2. Non-NHS/PSS costs based on participant self-reports of broader societal resource inputs and costs such as privately purchased medications, travel, childcare, lost income, housework help and laundry service costs are presented in Table . No notable differences were observed between the intervention and usual care groups across all categories of economic costs based on data extracted from the CRF data and the GP records.

Total NHS/PSS and total societal costs over 12 months of follow-up

Total NHS/PSS cost estimates are based on resource use data extracted from GP records for 586 (81%) of the 727 study participants for whom we were able to extract data from GP records. We were unable to extract data from GP records for the remaining 141 (19%) of the 727 study participants and so, for these participants, NHS/PSS costs were estimated from the participant self-reports of resource use collected using the trial case-report forms. Non-NHS/PSS components of societal costs including productivity related costs (lost income and time-off work) and additional cost of illness borne by families were estimated from the CRF data for all study participants. Table presents the total NHS/PSS and total societal cost estimates covering the 12 month period from randomisation for the whole trial population. Over the trial-follow-up period, total costs were on average higher for the intervention group than the usual care group. The unadjusted mean cost difference was £263 (bootstrap 95% CI £204 to £322, p-value <0.001) from an NHS/PSS perspective and £345 (bootstrap 95% CI -£344 to £1,357, p-value = 0.405) from a societal perspective. The difference in costs between the two groups was driven by the higher cost of the group intervention which costs on average £266.55 (bootstrap 95% CI £257 to £277, p-value <0.001).

Table 3: Total NHS/PSS and total societal costs estimates from combining CRF and GP resource use data 2019 prices.

	Number with complete cases		Mean (standard error) costs, £			
Cost category	CHESS intervention	Usual care	CHESS intervention	Usual care	Mean cost difference (95% CI)	P-value
Intervention	376	351	266.95 (4.79)	0.40 (0)	266.55 (257.46, 276.62)	<0.001
Primary care	356	312	268.25 (14.34)	285.48 (16.45)	-17.22 (-62.14, 24.55)	0.4105
Secondary care	358	318	71.82 (11.81)	52.83 (10.24)	18.99 (-11.25, 48.70)	0.216
Medications	376	351	7.21 (1.34)	12.06 (3.18)	-4.85 (-14.66, 0.20)	0.1495
Total NHS/PSS costs	356	312	614.88 (20.77)	351.85 (20.42)	263.03 (204.01, 321.51)	<0.001
Private medical expenses	356	312	16.60 (7.52)	14.34 (6.07)	2.26 (-15.30, 22.93)	0.81
Additional costs	280	250	91.96 (27.21)	47.89 (13.98)	44.07 (-6.59, 118.66)	0.149
Productivity costs	262	241	1164.14 (312.75)	1268.63 (316.25)	-104.49 (-927.51, 813.71)	0.821
Total Non-NHS/PSS costs	242	212	1226.42 (343.6)	1126.32 (256.39)	100.10 (-570.47, 1198.51)	0.815
Total societal costs	242	212	1779.90 (340.65)	1435.25 (260.52)	344.64 (-344.27, 1356.53)	0.405

Health-related quality-of-life outcomes

The distribution of the responses to the EQ-5D-5L and SF-12 HRQoL questionnaires by trial group and trial period are presented in Table and Table , respectively. The comparisons of responses were conducted on the basis of optimal level of function (for example "no problem" on the EQ-5D-5L) versus sub-optimal level of function (indicating any functional impairment). The only statistically significant differences in levels of function in HRQoL was observed in the anxiety and depression dimension of the EQ-5D-5L at the 12-month assessment point with lower levels of anxiety and depression in the CHESS intervention arm (p=0.016). There were no statistically significant differences in levels of function in HRQoL for participant reported dimensions of the EQ-5D-5L or SF-12 measures between the intervention and usual care groups for all other assessment points.

Table presents unadjusted health utility scores generated from the EQ-5D-5L using the van Hout crosswalk and Hernandez-Alava and Putney crosswalk algorithms and from the SF-6D (derived from SF-12) based on complete case analyses. On average, the intervention generated higher mean utility values than usual care at baseline and at the 4-, 8- and 12-months post-randomisation assessment points. The difference in mean utility generated from the EQ-5D-5L via the van Hout crosswalk was 0.052 (bootstrap 95% CI 0.005 to 0.096, p-value = 0.028) at 4 months and 0.051 (bootstrap 95% CI 0.007 to 0.093, p-value = 0.024) at the 8-month assessment point (with higher utility scores observed in the CHESS intervention arm). Overall, the difference in mean utility was statistically significant at 4- and 8-months' assessment points using the van Hout crosswalk to estimate EQ-5D-5L utilities. At 4 months using the Hernandez-Alava crosswalk to estimate EQ-5D-5L utilities and at baseline, 8 months and 12 months assessment points using the SF-6D algorithm to estimate utilities from the SF-12 version 2, differences in mean utility values were statistically significant.

Table 4 Unadjusted health-related quality of life (utility) weights collected for trial participants.

Assessment point and utility measure	Intervention		Usual care		Mean difference (95% CI)	P-value
	N	Mean (SE)	N	Mean (SE)		
EQ-5D-5L, Van Hout crosswalk						
Baseline	372	0.637 (0.013)	346	0.624 (0.013)	0.014 (-0.023, 0.053)	0.488
4 months	274	0.682 (0.016)	276	0.630 (0.017)	0.052 (0.005, 0.096)	0.028
8 months	280	0.697 (0.014)	262	0.646 (0.017)	0.051 (0.007, 0.093)	0.024
12 months	301	0.694 (0.014)	283	0.663 (0.016)	0.031 (-0.01, 0.073)	0.168
EQ-5D-5L, Hernandez-Alava crosswalk						
Baseline	366	0.628 (0.013)	342	0.617 (0.013)	0.01 (-0.024, 0.048)	0.590
4 months	270	0.669 (0.016)	272	0.625 (0.016)	0.044 (-0.002, 0.089)	0.058
8 months	274	0.685 (0.014)	258	0.642 (0.016)	0.043 (0.002, 0.084)	0.036
12 months	295	0.684 (0.014)	278	0.658 (0.015)	0.026 (-0.014, 0.066)	0.218
SF-6D						
Baseline	357	0.614 (0.006)	340	0.596 (0.006)	0.018 (0.001, 0.036)	0.044
4 months	243	0.653 (0.008)	238	0.637 (0.009)	0.016 (-0.007, 0.042)	0.206
8 months	247	0.660 (0.008)	221	0.635 (0.009)	0.025 (0.002, 0.049)	0.044
12 months	260	0.672 (0.008)	230	0.638 (0.009)	0.035 (0.01, 0.059)	0.006

N = participants with complete data, SE = Standard error

Table presents unadjusted QALY estimates over the 12-month assessment period stratified by utility instrument, assessment period and intervention group based on complete case analysis. On average, the CHESS intervention generated higher mean QALYs than usual care at each assessment point. Over the 12-months of follow-up, mean QALYs were on average 0.047 (bootstrap 95% CI 0.004 to 0.088, p-value = 0.028) higher using the van Hout EQ-5D-5L crosswalk measure, 0.041 (bootstrap 95% CI -0.001 to 0.082, p-value =0.058) higher using the Hernandez-Alava and Putney EQ-5D-5L crosswalk measure and 0.031 (bootstrap 95% CI 0.008 to 0.055, p-value = 0.012) higher using the SF-6D algorithm based on the SF-12 instrument.

Table 5: Unadjusted QALY estimates derived from EQ-5D-5L and SF-12 data.

Assessment point and utility measure	Intervention		Usual care		Mean difference (95% CI	P-value
	N	Mean (SE)	N	Mean (SE)		
EQ5D-5L, van Hout crosswalk						
0-4 months	272	0.224 (0.005)	272	0.210 (0.005)	0.013 (0, 0.028)	0.062
4-8 months	241	0.230 (0.005)	238	0.217 (0.005)	0.013 (-0.001, 0.027)	0.072
8-12 months	258	0.233 (0.005)	248	0.218 (0.005)	0.015 (0.002, 0.029)	0.038
0-12 months	225	0.697 (0.015)	224	0.650 (0.016)	0.047 (0.004, 0.088)	0.028
EQ5D-5L, Hernandez-Alava crosswalk						
0-4 months	269	0.220 (0.005)	268	0.208 (0.005)	0.012 (-0.001, 0.025)	0.098
4-8 months	237	0.226 (0.005)	234	0.214 (0.005)	0.012 (-0.003, 0.026)	0.122
8-12 months	252	0.229 (0.004)	244	0.217 (0.005)	0.012 (0, 0.026)	0.072
0-12 months	222	0.685 (0.014)	220	0.644 (0.015)	0.041 (-0.001, 0.082)	0.058
SF-6D						
0-4 months	237	0.215 (0.003)	235	0.208 (0.002)	0.007 (0.001, 0.014)	0.050
4-8 months	215	0.221 (0.003)	192	0.212 (0.003)	0.008 (0, 0.017)	0.060
8-12 months	223	0.223 (0.002)	195	0.213 (0.003)	0.010 (0.002, 0.018)	0.024
0-12 months	197	0.664 (0.008)	170	0.634 (0.009)	0.031 (0.008, 0.055)	0.012

N = participants with complete data, SE = Standard error

Cost-effectiveness results

Base-case analysis

The base-case cost-effectiveness results are presented in Table 6: Within-trial cost-effectiveness estimates (base-case and sensitivity analyses) in 2019 prices. The results suggest the CHESS intervention generated incremental adjusted costs of £268 (95% CI £176 to £377) and incremental adjusted QALYs of 0.031 (95% CI -0.005 to 0.063) over 12-months of follow-up from an NHS/PSS perspective compared with usual care. The base-case ICER was £8,617 per QALY gained. The incremental net monetary benefit was £354 (95% CI -£375 to £1,084) with probability that the intervention is cost-effective approaching 0.83 if the cost-effectiveness threshold is £20,000 per QALY gained and 0.90 at £30,000 per QALY (Figure 1 The graph on the left-hand side is the cost-effectiveness plane displaying 1000 base-case ICERs simulated from the joint distribution of incremental costs and incremental QALYs. The graph on the right-hand side represent cost-effectiveness acceptability.

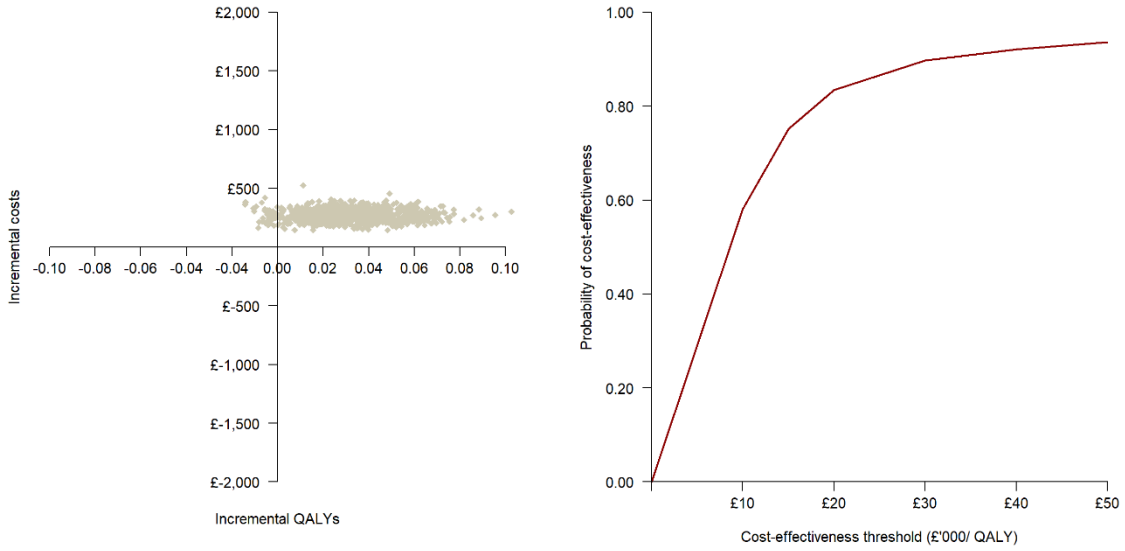

Figure 1 The graph on the left-hand side is the cost-effectiveness plane displaying 1000 base-case ICERs simulated from the joint distribution of incremental costs and incremental QALYs. The graph on the right-hand side represent cost-effectiveness acceptability.

Sensitivity analyses

The base-case analysis used multiple imputation to account for missing data and incorporates costs from the perspective of the NHS and PSS and QALYs derived from EQ-5D-5L using the van Hout crosswalk algorithm. Results from sensitivity analyses were carried out to assess the robustness of cost-effectiveness to departures from the base-case assumptions (Table). The ICERs ranged from £765 per QALY gained based on societal costs to £32,083 per QALY gained using QALYs derived from SF-6D utilities. In the sensitivity analysis that adopted a societal perspective, the incremental net monetary benefit and probability of cost-effectiveness were £626 (95% CI -£602 to £1,854) and 0.843 at £20,000 per QALY gained, respectively. For the analyses based on SF-6D utilities, the net monetary benefit was negative at £20,000 per QALY, suggesting that the intervention would be generating on average a net loss of £101 (95% CI -£463 to £666) for the NHS and PSS at this cost-effectiveness threshold. The probability that the intervention would be cost-effectiveness was 0.36 using the SF-6D algorithm based on the SF-12 instrument.

Subgroup analyses

The results of subgroup analyses by age group, gender, medication overuse and recruiting location (London versus Midlands) are presented in Table . The results suggest at the £20,000 per QALY cost-effectiveness threshold, the intervention is most likely to be cost-effective among over 40-year olds with probability of cost-effectiveness of 0.89, among females with probability 0.85, among those experiencing medication overuse headaches with probability 0.84, and among participants from the West Midlands with probability 0.81.

Table 6: Within-trial cost-effectiveness estimates (base-case and sensitivity analyses) in 2019 prices.

	Incremental estimates (95% CI)			Incremental net monetary benefit (95% CI)			Probability of cost-effectiveness		
Analysis	**Costs (£)**	**QALYs**	**ICER**	**£15K/QALY**	**£20K/QALY**	**£30K/QALY**	**£15K/QALY**	**£20K/QALY**	**£30K/QALY**
Base-case (van Hout EQ-5D-5L)	268 (176, 377)	0.031 (-0.005, 0.063)	8617	199 (-352, 750)	354 (-375, 1084)	666 (-423, 1755)	0.752	0.834	0.897
EQ-5D-5L, Hernandez-Alava	269 (170, 388)	0.028 (-0.001, 0.055)	9535	154 (-297, 606)	296 (-297, 889)	578 (-299, 1456)	0.752	0.835	0.902
SF-6D utility	269 (162, 399)	0.008 (-0.02, 0.035)	32083	-143 (-570, 283)	-101 (-666, 463)	-17 (-861, 826)	0.247	0.361	0.475
Societal costs	25 (-702, 1231)	0.033 (-0.001, 0.063)	765	463 (-681, 1608)	626 (-602, 1854)	952 (-490, 2393)	0.784	0.843	0.894
Intervention (16 participants)	157 (81, 245)	0.032 (-0.002, 0.062)	4965	317 (-181, 814)	474 (-185, 1133)	790 (-192, 1772)	0.887	0.916	0.939
Intervention (3 participants)	834 (689, 1000)	0.032 (-0.005, 0.065)	26167	-356 (-956, 244)	-197 (-976, 583)	122 (-1022, 1266)	0.118	0.303	0.586
Unadjusted analysis	229 (82, 432)	0.033 (-0.112, 0.127)	6895	270 (-1789, 2329)	436 (-2281, 3153)	768 (-3264, 4801)	0.621	0.658	0.688
Adjusted complete case analysis	321 (202, 465)	0.017 (-0.01, 0.042)	18968	-67 (-508, 374)	17 (-556, 591)	187 (-656, 1029)	0.392	0.519	0.665

£15K/QALY = £15,000 per QALY cost-effectiveness threshold
£20K/QALY = £20,000 per QALY cost-effectiveness threshold
£30K/QALY = £20,000 per QALY cost-effectiveness threshold

Table 7: Subgroup analyses results.

	Incremental estimates (95% CI)			Incremental net monetary benefit (95% CI)			Probability of cost-effectiveness		
Subgroup	**Costs (£)**	**QALYs**	**ICER**	**£15K/QALY**	**£20K/QALY**	**£30K/QALY**	**£15K/QALY**	**£20K/QALY**	**£30K/QALY**
Age group									
Under 40-year olds	371 (192, 615)	0.017 (-0.047, 0.07)	22173	-120 (-1056, 816)	-36 (-1272, 1199)	131 (-1708, 1970)	0.399	0.477	0.548
40 or more-years	226 (106, 375)	0.047 (-0.011, 0.097)	4790	481 (-436, 1398)	717 (-503, 1936)	1188 (-639, 3014)	0.868	0.891	0.920
Gender									
Male	484 (211, 909)	0.017 (-0.074, 0.088)	28261	-227 (-1543, 1089)	-142 (-1871, 1588)	30 (-2535, 2595)	0.369	0.416	0.492
Female	230 (118, 368)	0.046 (-0.018, 0.102)	4969	465 (-582, 1512)	697 (-695, 2088)	1160 (-922, 3242)	0.816	0.851	0.882

Medication over use									
No	303 (166, 479)	0.028 (-0.025, 0.072)	10991	111 (-700, 921)	248 (-823, 1320)	524 (-1072, 2120)	0.579	0.654	0.725
Yes	238 (103, 413)	0.042 (-0.021, 0.095)	5692	390 (-634, 1414)	599 (-759, 1957)	1018 (-1010, 3047)	0.802	0.843	0.879
Region									
London	270 (140, 438)	0.024 (-0.021, 0.064)	11089	95 (-609, 799)	217 (-713, 1147)	461 (-923, 1845)	0.605	0.685	0.756
West Midlands	253 (0, 652)	0.059 (-0.05, 0.143)	4310	628 (-1254, 2509)	921 (-1568, 3411)	1509 (-2201, 5219)	0.780	0.814	0.836

£15K/QALY = £15,000 per QALY cost-effectiveness threshold
£20K/QALY = £20,000 per QALY cost-effectiveness threshold
£30K/QALY = £20,000 per QALY cost-effectiveness threshold

Table 8: Summary of NHS/PSS resource use reported by trial participants

	Intervention		Usual care			
Resource variable and assessment point	**N complete cases**	**Mean (SE)**	**N complete cases**	**Mean (SE)**	**Mean difference (bootstrap 95% CI)**	**P-value**
Primary care (baseline)						
GP surgery, contacts	325	0.85 (0.1)	303	0.74 (0.11)	0.11 (-0.21, 0.38)	0.446
GP home visit, contacts	334	0.01 (0.01)	306	0.03 (0.01)	-0.01 (-0.05, 0.02)	0.355
Practice nurse, contacts	334	0.05 (0.02)	306	0.05 (0.02)	0.01 (-0.06, 0.05)	0.8395
Occupational therapist, contacts	334	0.04 (0.02)	306	0.03 (0.01)	0.01 (-0.03, 0.1)	0.6555
Counsellor, contacts	334	0.09 (0.05)	306	0.02 (0.01)	0.07 (0.01, 0.26)	0.123
Other Primary care, contacts	327	0.13 (0.04)	300	0.06 (0.02)	0.07 (-0.01, 0.16)	0.1045
Secondary care (baseline)						
Emergency department, contacts	333	0.21 (0.07)	304	0.2 (0.05)	0.02 (-0.13, 0.19)	0.837
Inpatient care, days	331	0.02 (0.01)	303	0.07 (0.06)	-0.05 (-0.32, 0.02)	0.5695
Outpatients, contacts	333	0.14 (0.02)	305	0.13 (0.02)	0.02 (-0.05, 0.08)	0.6095
MRI, contacts	330	0.04 (0.01)	306	0.07 (0.02)	-0.03 (-0.07, 0.01)	0.2045
CT, contacts	331	0.03 (0.01)	306	0.05 (0.01)	-0.02 (-0.06, 0.01)	0.1905
Medications (baseline)						
Medications, tablets	376	11.22 (2.39)	351	23.25 (4.21)	-12.02 (-23.07, -3.8)	0.014
Primary care (4 months)						
GP surgery, contacts	365	0.32 (0.05)	346	0.29 (0.06)	0.03 (-0.16, 0.16)	0.725
GP home visit, contacts	369	0.01 (0)	346	0.01 (0.01)	-0.01 (-0.04, 0.01)	0.565
Practice nurse, contacts	369	0.02 (0.01)	347	0.02 (0.01)	0 (-0.04, 0.04)	0.949
Occupational Therapist, contacts	368	0.01 (0.01)	346	0.01 (0.01)	0 (-0.03, 0.01)	0.926
Counsellor, contacts	369	0.02 (0.01)	348	0.01 (0.01)	0.01 (-0.03, 0.05)	0.681
Other Primary care, contacts	366	0.04 (0.02)	344	0.08 (0.03)	-0.04 (-0.13, 0.03)	0.277
Secondary care (4 months)						
Emergency department, contacts	366	0.09 (0.04)	346	0.12 (0.05)	-0.03 (-0.15, 0.09)	0.594
Inpatient care, days	368	0 (0)	347	0.01 (0)	-0.01 (-0.02, 0)	0.2295
Outpatients, contacts	366	0.05 (0.01)	347	0.07 (0.02)	-0.02 (-0.06, 0.02)	0.364
MRI, contacts	369	0.02 (0.01)	348	0.01 (0.01)	0 (-0.01, 0.02)	0.576
CT, contacts	369	0.01 (0.01)	347	0.01 (0.01)	0 (-0.02, 0.01)	0.9205
Medications (4 months)						
Medications, tablets	376	5.88 (1.81)	351	7.7 (2.04)	-1.82 (-7.14, 3.65)	0.508
Primary care (8 months)						
GP surgery, contacts	372	0.24 (0.04)	348	0.27 (0.05)	-0.04 (-0.17, 0.09)	0.576
GP home visit, contacts	375	0.03 (0.02)	351	0.02 (0.01)	0.01 (-0.02, 0.05)	0.5825
Practice nurse, contacts	375	0.03 (0.01)	351	0.02 (0.01)	0.01 (-0.05, 0.03)	0.712
Occupational Therapist, contacts	374	0.04 (0.03)	351	0.01 (0.01)	0.03 (-0.01, 0.17)	0.4375

Counsellor, contacts	374	0.02 (0.02)	351	0 (0)	0.01 (-0.01, 0.08)	0.453
Other Primary care, contacts	373	0.04 (0.01)	348	0.05 (0.02)	-0.01 (-0.06, 0.04)	0.723
Secondary care (8 months)						
Emergency department, contacts	372	0.09 (0.03)	348	0.15 (0.08)	-0.07 (-0.39, 0.04)	0.427
Inpatient care, days	373	0.01 (0)	350	0 (0)	0 (-0.01, 0.01)	0.694
Outpatients, contacts	374	0.06 (0.02)	349	0.04 (0.01)	0.02 (-0.01, 0.07)	0.223
MRI, contacts	375	0.02 (0.01)	351	0.03 (0.01)	0 (-0.03, 0.02)	0.7025
CT, contacts	375	0.01 (0.01)	351	0.01 (0.01)	0 (-0.02, 0.02)	0.9045
Medications (8 months)						
Medications, tablets	376	7.41 (2.62)	351	4.98 (1.58)	2.42 (-2.97, 9.69)	0.4195
Primary care (12 months)						
GP surgery, contacts	250	0.27 (0.05)	223	0.31 (0.06)	-0.04 (-0.19, 0.1)	0.6195
GP home visit, contacts	253	0.02 (0.01)	226	0 (0)	0.01 (0, 0.06)	0.3805
Practice nurse, contacts	253	0.05 (0.02)	224	0.02 (0.01)	0.03 (0, 0.1)	0.2045
Occupational Therapist, contacts	253	0.02 (0.01)	226	0.01 (0.01)	0.01 (-0.02, 0.05)	0.609
Counsellor, contacts	252	0.02 (0.01)	225	0.01 (0.01)	0.01 (-0.02, 0.04)	0.6065
Other Primary care, contacts	253	0.01 (0.01)	226	0.08 (0.03)	-0.08 (-0.15, -0.03)	0.0105
Secondary care (12 months)						
Emergency department, contacts	252	0.06 (0.02)	225	0.06 (0.02)	0.01 (-0.05, 0.06)	0.8445
Inpatient care, days	254	0 (0)	226	0.04 (0.04)	-0.04 (-0.21, 0)	0.546
Outpatients, contacts	252	0.09 (0.03)	226	0.09 (0.02)	-0.01 (-0.07, 0.06)	0.8735
MRI, contacts	253	0.02 (0.01)	223	0.01 (0.01)	0 (-0.02, 0.02)	0.833
CT, contacts	253	0 (0)	225	0.02 (0.01)	-0.01 (-0.04, 0)	0.1385
Medications (12 months)						
Medications, tablets	376	3.55 (1.17)	351	4.47 (1.33)	-0.92 (-4.43, 2.49)	0.581

Table 9: Summary of NHS resource use extracted from GP records

	Intervention		**Usual care**			
Resource variable and assessment point	**N complete cases**	**Mean (SE)**	**N complete cases**	**Mean (SE)**	**Mean difference (bootstrap 95% CI)**	**P-value**
Primary care						
GP surgery	315	3.74 (0.21)	271	4.06 (0.24)	-0.32 (-0.99, 0.27)	0.3175
GP home visit	315	0.04 (0.02)	271	0.06 (0.05)	-0.01 (-0.25, 0.05)	0.842
GP telephone consultation	315	1.36 (0.14)	271	1.38 (0.15)	-0.02 (-0.43, 0.38)	0.9325
Practice nurse	315	1.85 (0.13)	271	1.94 (0.17)	-0.09 (-0.55, 0.3)	0.6735
Practice nurse home visit	315	0.02 (0.02)	271	0.01 (0.01)	0 (-0.02, 0.06)	0.839
Practice nurse telephone consultation	315	0.14 (0.04)	271	0.12 (0.03)	0.02 (-0.07, 0.12)	0.621
Other primary care consultations	315	0 (0)	271	0.01 (0.01)	-0.01 (-0.03, 0)	0.2285

Secondary care						
Emergency department	315	0.03 (0.01)	271	0.03 (0.01)	-0.01 (-0.05, 0.02)	0.6445
Inpatient care	315	0.03 (0.02)	271	0.03 (0.03)	0 (-0.13, 0.05)	0.976
Outpatients (pain management / neurology)	315	0.28 (0.04)	271	0.23 (0.04)	0.04 (-0.07, 0.16)	0.4575
Other outpatients	315	0.02 (0.01)	271	0.03 (0.01)	-0.01 (-0.04, 0.02)	0.626
Medications						
Medications	315	13.04 (0.02)	271	13.03 (0.01)	0.02 (-0.02, 0.07)	0.4785

Table 10: Summary of Non-NHS/PSS resource use reported by trial participants

	Intervention		**Usual care**			
Resource variable and assessment point	**N complete cases**	**Mean (SE)**	**N complete cases**	**Mean (SE)**	**Mean difference (bootstrap 95% CI)**	**P-value**
Productivity costs (baseline)						
In come lost, amount reported	317	97.15 (31.19)	302	272.07 (142.42)	-174.92 (-707.47, -0.82)	0.209
Time off work, days	316	3.77 (0.77)	302	3.82 (0.85)	-0.05 (-2.23, 2.27)	0.956
Additional costs to you (baseline)						
Travel costs to you, amount reported	323	2.16 (1.05)	304	3.57 (1.24)	-1.41 (-4.62, 1.78)	0.3985
Childcare costs to you, amount reported	328	2.03 (1.9)	307	0.08 (0.08)	1.95 (0.01, 12.79)	0.269
Other additional costs to you, amount reported	376	14.37 (5.06)	351	6.75 (2.59)	7.62 (-1.42, 22.85)	0.179
Additional costs to partner (baseline)						
Travel costs to partner, amount reported	323	1.68 (1.55)	304	0.78 (0.29)	0.9 (-0.83, 8.54)	0.615
Childcare costs to partner, amount reported	328	0 (0)	307	0.2 (0.2)	-0.2 (-1.06, 0)	0.4875
Other additional costs to partner, amount reported	376	5.66 (2.74)	351	5.76 (5.43)	-0.1 (-22.95, 7.52)	0.986
Productivity costs (4 months)						
In come lost, amount reported	361	66.05 (29.39)	339	64.06 (27.36)	1.99 (-78.74, 82.71)	0.967
Time off work, days	360	1.43 (0.41)	338	1.1 (0.38)	0.33 (-0.74, 1.48)	0.552
Additional costs to you (4 months)						
Travel costs to you, amount reported	365	7.12 (5.72)	345	3.39 (1.89)	3.72 (-3.52, 28.25)	0.572
Childcare costs to you, amount reported	366	2.76 (2.2)	346	0.7 (0.44)	2.06 (-0.54, 15.99)	0.376
Other additional costs to you, amount reported	376	21.12 (16.25)	351	4.72 (1.58)	16.4 (-1.08, 94.09)	0.3195
Additional costs to partner (4 months)						
Travel costs to partner, amount reported	365	0.43 (0.25)	345	0.35 (0.18)	0.08 (-0.42, 0.87)	0.8035
Childcare costs to partner, amount reported	366	0.07 (0.07)	346	0.38 (0.3)	-0.31 (-1.74, 0.06)	0.3235
Other additional costs to partner, amount reported	376	0.22 (0.15)	351	0.51 (0.5)	-0.29 (-2.34, 0.31)	0.5925
Productivity costs (8 months)						
In come lost, amount reported	364	58.31 (27.57)	343	115 (80.53)	-56.69 (-378.68, 51.44)	0.532
Time off work, days	364	1.18 (0.3)	343	1.18 (0.35)	0 (-0.91, 0.87)	1
Additional costs to you (8 months)						

Travel costs to you, amount reported	370	1.47 (0.63)	347	1.42 (0.61)	0.04 (-1.59, 1.98)	0.961
Childcare costs to you, amount reported	373	0 (0)	349	0.4 (0.38)	-0.4 (-2.31, 0)	0.1955
Other additional costs to you, amount reported	376	9.59 (3.24)	351	3 (1.5)	6.59 (0.91, 15.45)	0.065
Additional costs to partner (8 months)						
Travel costs to partner, amount reported	370	0.47 (0.19)	347	0.61 (0.3)	-0.14 (-1.07, 0.41)	0.678
Childcare costs to partner, amount reported	373	0.54 (0.53)	349	0.4 (0.41)	0.14 (-0.83, 2.05)	0.7
Other additional costs to partner, amount reported	376	0.88 (0.82)	351	0.14 (0.14)	0.74 (-0.18, 4.62)	0.4415
Productivity costs (12 months)						
In come lost, amount reported	330	68.73 (42.09)	295	167.04 (133.51)	-98.31 (-641.45, 69.19)	0.4865
Time off work, days	329	2.14 (0.7)	295	1.67 (0.53)	0.48 (-1.09, 2.45)	0.5905
Additional costs to you (12 months)						
Travel costs to you, amount reported	338	2.29 (1.22)	298	2.47 (1.3)	-0.18 (-3.77, 3.23)	0.9145
Childcare costs to you, amount reported	339	0.19 (0.15)	301	2.04 (1.47)	-1.85 (-9.02, -0.12)	0.1815
Other additional costs to you, amount reported	376	8.62 (3.94)	351	5.91 (2.9)	2.71 (-5.86, 13.39)	0.5925
Additional costs to partner (12 months)						
Travel costs to partner, amount reported	338	0.5 (0.43)	298	2.3 (1.97)	-1.8 (-10.37, 0.56)	0.4115
Childcare costs to partner, amount reported	339	0 (0)	301	0.5 (0.5)	-0.5 (-3.02, 0)	0.181
Other additional costs to partner, amount reported	376	1.06 (1.09)	351	0 (0)	1.06 (0, 6.56)	0.5055

Table 11: Summary of NHS/PSS costs based on resource use data reported by trial participants (CRF data)

Cost category and assessment point	Mean (SE) costs intervention	Mean (SE) costs usual care arm	Mean difference (bootstrap 95% CI)	P-value
Primary care (baseline)				
GP surgery, contacts	33.12 (3.76)	28.7 (4.31)	4.42 (-8.32, 14.85)	0.442
GP home visit, contacts	0.47 (0.36)	1.02 (0.5)	-0.55 (-1.88, 0.55)	0.337
Practice nurse, contacts	2.14 (0.68)	1.92 (0.89)	0.22 (-2.63, 1.94)	0.8415
Occupational Therapist, contacts	1.75 (1.13)	1.18 (0.64)	0.58 (-1.21, 4.71)	0.644
Counsellor, contacts	3.91 (2.23)	0.74 (0.33)	3.17 (0.51, 11.48)	0.12
Other Primary care, contacts	9.78 (2.8)	5.44 (1.9)	4.34 (-1.62, 11.88)	0.198
Total primary care costs	51.34 (5.61)	38.82 (5.25)	12.52 (-3.22, 27.52)	0.1075
Secondary care (baseline)				
Emergency department, contacts	24.64 (7.57)	22.81 (5.96)	1.83 (-15.36, 22.05)	0.845
Inpatient care, days	0.02 (0.01)	0.07 (0.06)	-0.05 (-0.29, 0.02)	0.585
Outpatients, contacts	25.57 (4.06)	22.68 (3.92)	2.89 (-7.66, 14.44)	0.603
MRI, contacts	5.78 (1.52)	9.35 (2.33)	-3.57 (-9.68, 1.63)	0.2165
CT, contacts	2.26 (0.74)	4.08 (1.16)	-1.82 (-4.95, 0.64)	0.19
Total secondary care costs	58.02 (9.42)	58.43 (9.42)	-0.41 (-25.1, 26.03)	0.9795
Medications (baseline)				
Medications, tablets	3.85 (1.09)	3.79 (1.11)	0.07 (-3.2, 2.82)	0.965
Primary care (4 months)				
GP surgery, contacts	12.61 (2.12)	11.5 (2.36)	1.11 (-6.35, 6.64)	0.7325

GP home visit, contacts	0.32 (0.18)	0.56 (0.41)	-0.25 (-1.55, 0.4)	0.5935
Practice nurse, contacts	0.8 (0.57)	0.85 (0.52)	-0.05 (-1.64, 1.53)	0.956
Occupational Therapist, contacts	0.49 (0.24)	0.52 (0.41)	-0.03 (-1.38, 0.62)	0.928
Counsellor, contacts	0.98 (0.65)	0.65 (0.52)	0.33 (-1.14, 2.27)	0.689
Other Primary care, contacts	1.97 (0.99)	11.23 (5.04)	-9.25 (-26.85, -2.19)	0.054
Total primary care costs	17.33 (2.65)	25.26 (7.08)	-7.93 (-31.64, 2.62)	0.289
Secondary care (4 months)				
Emergency department, contacts	10.74 (4.32)	14.36 (5.33)	-3.63 (-17.97, 9.27)	0.592
Inpatient care, days	0 (0)	0.01 (0)	-0.01 (-0.02, 0)	0.096
Outpatients, contacts	9.69 (2.34)	13.29 (3.1)	-3.6 (-11.79, 3.35)	0.347
MRI, contacts	2.21 (0.9)	1.57 (0.77)	0.65 (-1.57, 2.9)	0.602
CT, contacts	0.9 (0.45)	0.96 (0.59)	-0.06 (-1.83, 1.11)	0.9245
Total secondary care costs	23.83 (5.96)	30.41 (7.46)	-6.58 (-27.19, 10.51)	0.472
Medications (4 months)				
Medications, tablets	1.11 (0.39)	1.49 (0.57)	-0.38 (-2.1, 0.77)	0.582
Primary care (8 months)				
GP surgery, contacts	9.23 (1.41)	10.65 (2.06)	-1.42 (-6.56, 3.04)	0.567
GP home visit, contacts	1.04 (0.59)	0.67 (0.38)	0.37 (-0.82, 2.03)	0.6085
Practice nurse, contacts	1.12 (0.42)	0.84 (0.64)	0.28 (-1.79, 1.37)	0.7115
Occupational Therapist, contacts	1.68 (1.45)	0.38 (0.29)	1.3 (-0.38, 8.36)	0.4575
Counsellor, contacts	0.72 (0.72)	0.13 (0.13)	0.59 (-0.25, 3.73)	0.5865
Other Primary care, contacts	2.49 (1)	4.56 (1.94)	-2.07 (-8.21, 1.1)	0.335
Total primary care costs	16.36 (2.85)	16.72 (3.25)	-0.35 (-8.88, 8.02)	0.9275
Secondary care (8 months)				
Emergency department, contacts	9.94 (3.43)	17.6 (8.83)	-7.66 (-39.4, 4.86)	0.4165
Inpatient care, days	0.01 (0)	0 (0)	0 (-0.01, 0.01)	0.6885
Outpatients, contacts	10.91 (2.83)	6.61 (1.88)	4.3 (-1.93, 11.18)	0.203
MRI, contacts	2.91 (1.12)	3.49 (1.12)	-0.59 (-3.6, 2.62)	0.7085
CT, contacts	1.11 (0.5)	1.19 (0.53)	-0.08 (-1.51, 1.32)	0.9005
Total secondary care costs	24.62 (5.06)	28.45 (9.84)	-3.83 (-35.18, 12.56)	0.7305
Medications (8 months)				
Medications, tablets	1.7 (0.55)	1.68 (0.65)	0.03 (-1.84, 1.54)	0.9755
Intervention (12 months)				
Intervention, costs	266.95 (4.77)	0.4 (0)	266.55 (258.09, 276.6)	0
Primary care (12 months)				
GP surgery, contacts	10.61 (1.93)	12.07 (2.3)	-1.46 (-7.25, 4.35)	0.6285
GP home visit, contacts	0.62 (0.49)	0.17 (0.17)	0.44 (-0.19, 2.3)	0.4465
Practice nurse, contacts	1.99 (0.89)	0.75 (0.37)	1.24 (-0.13, 3.93)	0.2
Occupational Therapist, contacts	0.71 (0.54)	0.4 (0.4)	0.31 (-0.81, 1.93)	0.669
Counsellor, contacts	0.71 (0.55)	0.4 (0.41)	0.31 (-0.76, 2.19)	0.607
Other Primary care, contacts	0.62 (0.47)	12.2 (6.91)	-11.57 (-44.26, -3.53)	0.068
Total primary care costs	15.32 (3.07)	26.28 (7.7)	-10.96 (-35.54, 0.62)	0.1885
Secondary care (12 months)				
Emergency department, contacts	7.34 (2.3)	6.68 (2.39)	0.66 (-6.2, 6.64)	0.835
Inpatient care, days	0 (0)	0.04 (0.04)	-0.04 (-0.19, 0)	0.5465

Outpatients, contacts	15.48 (4.4)	16.48 (3.88)	-1 (-11.86, 10.52)	0.8665
MRI, contacts	2.15 (1.06)	1.83 (1.04)	0.32 (-2.72, 3.19)	0.824
CT, contacts	0.33 (0.33)	1.48 (0.74)	-1.15 (-3.4, 0)	0.1385
Total secondary care costs	24.1 (5.66)	26.36 (5.68)	-2.26 (-17.59, 15.19)	0.78
Medications (12 months)				
Medications, tablets	0.55 (0.17)	5.11 (2.86)	-4.56 (-17.49, -1.27)	0.0775

Table 12: NHS/PSS costs based on resource used extracted from GP records over 12 months of follow-up

Cost category and assessment point	Mean (SE) costs intervention	Mean (SE) costs usual care arm	Mean difference (bootstrap 95% CI)	P-value
Primary care				
GP surgery	145.72 (8.01)	158.16 (9.36)	-12.43 (-38.11, 11.32)	0.315
GP home visit	1.73 (0.64)	2.16 (1.98)	-0.43 (-9.3, 2.08)	0.829
GP telephone consultation	52.99 (5.4)	53.68 (6.04)	-0.69 (-16.73, 14.92)	0.931
Practice nurse	77.87 (5.7)	81.68 (7.36)	-3.81 (-25.12, 12.34)	0.666
Practice nurse home visit	0.73 (0.73)	0.51 (0.49)	0.22 (-1.01, 2.95)	0.7065
Practice nurse telephone consultation	6 (1.6)	5.11 (1.13)	0.89 (-2.59, 5.3)	0.658
Other primary care consultations	0 (0)	0.33 (0.24)	-0.33 (-1.13, 0)	0.2355
Total primary care costs	285.04 (14.04)	301.63 (16.59)	-16.58 (-59.29, 26.43)	0.454
Secondary care				
Emergency department	2.94 (1.03)	3.84 (1.65)	-0.9 (-5.55, 2.6)	0.6515
Inpatient care	18.26 (9.28)	8.34 (8.46)	9.92 (-17.07, 34.42)	0.4145
Outpatients (pain management / neurology)	51.07 (8.28)	41.15 (7.3)	9.93 (-11.2, 32.37)	0.365
Other outpatients	2.41 (1.08)	4.03 (1.55)	-1.63 (-5.92, 1.52)	0.3915
Total secondary care costs	74.68 (13.16)	57.35 (11.48)	17.32 (-17.84, 50.49)	0.3235
Medications				
Medications	132.35 (16.97)	143.62 (18.76)	-11.27 (-60.36, 39.5)	0.669

Table 13: Summary of private medical and non-medical expenses and additional costs to families in lost productivity

Cost category and assessment point	Mean (SE) costs intervention	Mean (SE) costs usual care arm	Mean difference (bootstrap 95% CI)	P-value
Primary care (baseline)				
GP surgery, contacts	0 (0)	0.13 (0.13)	-0.13 (-0.67, 0)	0.171
Occupational Therapist, contacts	0 (0)	0.59 (0.29)	-0.59 (-1.47, -0.15)	0.047
Counsellor, contacts	0.94 (0.4)	1.18 (0.66)	-0.23 (-2.35, 0.9)	0.7485
Other Primary care, contacts	7.09 (2.39)	10.57 (3.79)	-3.48 (-13.91, 4.02)	0.4355
Total primary care costs	8.29 (2.51)	12.59 (3.93)	-4.3 (-15.24, 3.62)	0.3615
Secondary care (baseline)				
Emergency department, contacts	30.19 (8.16)	33.07 (7.4)	-2.88 (-23.09, 19.98)	0.7985

Outpatients, contacts	3.73 (1.91)	4.65 (1.62)	-0.92 (-5.18, 5.01)	0.7045
MRI, contacts	0.83 (0.58)	0.89 (0.62)	-0.06 (-1.85, 1.6)	0.8855
CT, contacts	0.25 (0.27)	0.54 (0.38)	-0.29 (-1.41, 0.46)	0.424
Total secondary care costs	35.28 (8.68)	38.93 (7.98)	-3.65 (-25.03, 22.03)	0.7675
Productivity costs (baseline)				
In come lost, amount reported	97.15 (30.9)	272.07 (144.33)	-174.92 (-817.48, 6.45)	0.221
Time off work, days	421.42 (85.63)	427.27 (97.44)	-5.85 (-274.8, 241.21)	0.9655
Total productivity related costs	518.88 (109.65)	699.35 (211.25)	-180.47 (-839.72, 168.02)	0.4525
Additional costs to you (baseline)				
Travel costs to you, amount reported	2.16 (1.02)	3.57 (1.25)	-1.41 (-4.65, 1.84)	0.366
Childcare costs to you, amount reported	2.03 (1.8)	0.08 (0.08)	1.95 (0, 10.31)	0.1975
Other additional costs to you, amount reported	14.37 (5.42)	6.75 (2.55)	7.62 (-1.83, 23.89)	0.1965
Total additional costs, study participants	18.97 (6.32)	10.68 (3.45)	8.29 (-3.21, 26.91)	0.245
Additional costs to partner (baseline)				
Travel costs to partner, amount reported	1.68 (1.55)	0.78 (0.29)	0.9 (-0.84, 7.4)	0.627
Childcare costs to partner, amount reported	0 (0)	0.2 (0.19)	-0.2 (-1.11, 0)	0.175
Other additional costs to partner, amount reported	5.66 (2.78)	5.76 (5.43)	-0.1 (-17.93, 8.13)	0.9845
Total additional costs, partner	8.27 (3.54)	7.65 (6.42)	0.62 (-23.59, 10.37)	0.9355
Primary care (4 months)				
Occupational Therapist, contacts	0.24 (0.25)	0.13 (0.13)	0.11 (-0.26, 1.02)	0.812
Counsellor, contacts	0 (0)	2.97 (2.21)	-2.97 (-12.5, -0.26)	0.1505
Other Primary care, contacts	4.06 (2.06)	2.22 (1.11)	1.83 (-2.09, 7.68)	0.431
Total primary care costs	4.35 (2.1)	4.63 (2.41)	-0.28 (-6.96, 5.55)	0.932
Secondary care (4 months)				
Emergency department, contacts	26.52 (8.9)	15.7 (6.15)	10.83 (-7, 36.22)	0.316
Outpatients, contacts	5.33 (2.25)	1.53 (0.86)	3.8 (0.37, 10.4)	0.1035
MRI, contacts	1.11 (0.82)	0 (0)	1.11 (0, 4.3)	0.1025
Total secondary care costs	33.15 (9.57)	17.29 (6.57)	15.87 (-6.08, 39.71)	0.163
Productivity costs (4 months)				
In come lost, amount reported	66.05 (29.54)	64.06 (27.1)	1.99 (-78.66, 84.15)	0.9565
Time off work, days	159.51 (46.67)	122.63 (40.33)	36.88 (-71.38, 172)	0.5335
Total productivity related costs	225.74 (73.37)	186.61 (67.07)	39.14 (-153.7, 242.41)	0.6835
Additional costs to you (4 months)				
Travel costs to you, amount reported	7.12 (5.45)	3.39 (1.86)	3.72 (-3.3, 26.58)	0.5505
Childcare costs to you, amount reported	2.76 (2.23)	0.7 (0.43)	2.06 (-0.5, 13.2)	0.3895
Other additional costs to you, amount reported	21.12 (16.53)	4.72 (1.57)	16.4 (-1.42, 118.45)	0.331
Total additional costs, study participants	31.73 (18.51)	8.9 (2.96)	22.83 (0.15, 101.42)	0.202
Additional costs to partner (4 months)				
Travel costs to partner, amount reported	0.43 (0.25)	0.35 (0.18)	0.08 (-0.42, 0.81)	0.802
Childcare costs to partner, amount reported	0.07 (0.07)	0.38 (0.31)	-0.31 (-1.55, 0.06)	0.334
Other additional costs to partner, amount reported	0.22 (0.16)	0.51 (0.49)	-0.29 (-2.91, 0.3)	0.5835
Total additional costs, partner	0.73 (0.36)	1.25 (0.71)	-0.52 (-2.76, 0.67)	0.511
Primary care (8 months)				
GP surgery, contacts	0.21 (0.21)	0.45 (0.35)	-0.24 (-1.36, 0.35)	0.5725
Occupational Therapist, contacts	0.24 (0.17)	0.13 (0.13)	0.11 (-0.28, 0.51)	0.616

Counsellor, contacts	0.48 (0.47)	0.9 (0.57)	-0.42 (-2.1, 0.89)	0.547
Other Primary care, contacts	16.02 (12.06)	6.85 (4.39)	9.16 (-6.23, 53.53)	0.489
Total primary care costs	17.04 (12.04)	8.41 (4.38)	8.63 (-6.57, 59.31)	0.513
Secondary care (8 months)				
Emergency department, contacts	36.66 (11.34)	20.92 (8.63)	15.74 (-11.69, 44.96)	0.28
Outpatients, contacts	1.42 (1.05)	2.03 (1.44)	-0.61 (-5, 2.43)	0.7065
MRI, contacts	0.36 (0.37)	0.78 (0.78)	-0.41 (-3.35, 0.73)	0.521
Total secondary care costs	38.56 (11.55)	23.81 (10.04)	14.75 (-16.52, 45.31)	0.331
Productivity costs (8 months)				
In come lost, amount reported	58.31 (27.44)	115 (82.63)	-56.69 (-402.84, 47.35)	0.5345
Time off work, days	131.98 (33.92)	131.91 (36.95)	0.06 (-106.75, 91.69)	0.9985
Total productivity related costs	190.29 (59.93)	246.91 (112.05)	-56.62 (-467.36, 117.74)	0.6435
Additional costs to you (8 months)				
Travel costs to you, amount reported	1.47 (0.63)	1.42 (0.61)	0.04 (-1.65, 1.82)	0.9535
Childcare costs to you, amount reported	0 (0)	0.4 (0.4)	-0.4 (-2.44, 0)	0.18
Other additional costs to you, amount reported	9.59 (3.25)	3 (1.51)	6.59 (0.54, 15.69)	0.0675
Total additional costs, study participants	11.21 (3.56)	4.86 (1.71)	6.35 (-0.35, 16.09)	0.1095
Additional costs to partner (8 months)				
Travel costs to partner, amount reported	0.47 (0.19)	0.61 (0.3)	-0.14 (-1.03, 0.43)	0.6885
Childcare costs to partner, amount reported	0.54 (0.55)	0.4 (0.4)	0.14 (-0.83, 2)	0.843
Other additional costs to partner, amount reported	0.88 (0.83)	0.14 (0.14)	0.74 (-0.17, 4.23)	0.49
Total additional costs, partner	1.9 (1.05)	1.16 (0.56)	0.74 (-1.08, 3.84)	0.537
Primary care (12 months)				
GP surgery, contacts	0.16 (0.15)	0.35 (0.36)	-0.19 (-1.61, 0.31)	0.6365
Other Primary care, contacts	0.53 (0.53)	1.79 (1.25)	-1.26 (-5.78, 0.51)	0.3445
Total primary care costs	0.7 (0.59)	2.18 (1.35)	-1.48 (-6.74, 0.49)	0.299
Secondary care (12 months)				
Emergency department, contacts	29.81 (8.34)	13.35 (6.33)	16.45 (-3.54, 37.61)	0.117
Outpatients, contacts	0 (0)	2.35 (1.72)	-2.35 (-10.03, 0)	0.0945
Total secondary care costs	29.93 (8.6)	15.93 (6.62)	14 (-6.31, 35.1)	0.202
Productivity costs (12 months)				
In come lost, amount reported	68.73 (43.74)	167.04 (132.08)	-98.31 (-691.28, 67.12)	0.4965
Time off work, days	239.4 (78.03)	186.33 (57.95)	53.07 (-123.78, 263.2)	0.5875
Total productivity related costs	308.04 (109.7)	353.37 (183.39)	-45.33 (-724.11, 244.5)	0.8385
Additional costs to you (12 months)				
Travel costs to you, amount reported	2.29 (1.28)	2.47 (1.3)	-0.18 (-3.94, 3.42)	0.9035
Childcare costs to you, amount reported	0.19 (0.15)	2.04 (1.42)	-1.85 (-8.11, -0.16)	0.1735
Other additional costs to you, amount reported	8.62 (3.94)	5.91 (2.89)	2.71 (-5.44, 13.95)	0.565
Total additional costs, study participants	12.07 (4.6)	11.37 (4.47)	0.7 (-11.09, 13.94)	0.9105
Additional costs to partner (12 months)				
Travel costs to partner, amount reported	0.5 (0.45)	2.3 (1.96)	-1.8 (-10.57, 0.57)	0.416
Childcare costs to partner, amount reported	0 (0)	0.5 (0.51)	-0.5 (-2.72, 0)	0.5045
Other additional costs to partner, amount reported	1.06 (1.04)	0 (0)	1.06 (0, 6.38)	0.1885
Total additional costs, partner	1.68 (1.25)	2.8 (2.07)	-1.12 (-8.48, 2.37)	0.624

Total non-NHS/PSS costs, costs	776.08 (318.67)	693.28 (200.72)	82.81 (-508.52, 1148.29)	0.825

Table 14: Summary of EQ-5D-5L dimensions

EQ5D-5L dimensional responses	Intervention	Usual care	P-value
Mobility (baseline)			
No problems in walking	231 (61.4%)	214 (61%)	0.85
Slight problems in walking	77 (20.5%)	75 (21.4%)	
Moderate problems in walking	45 (12%)	35 (10%)	
Severe problems in walking	18 (4.8%)	23 (6.6%)	
Unable to walk	2 (0.5%)	4 (1.1%)	
Missing	3 (0.8%)	0 (0%)	
Self-care (baseline)			
No problems washing or dressing	316 (84%)	291 (82.9%)	0.697
Slight problems washing or dressing	29 (7.7%)	30 (8.5%)	
Moderate problems washing or dressing	22 (5.9%)	17 (4.8%)	
Severe problems washing or dressing	5 (1.3%)	9 (2.6%)	
Unable to wash or dress	1 (0.3%)	2 (0.6%)	
Missing	3 (0.8%)	2 (0.6%)	
Usual activities (baseline)			
No problems doing my usual activities	153 (40.7%)	151 (43%)	0.615
Slight problems doing my usual activities	116 (30.9%)	97 (27.6%)	
Moderate problems doing my usual activities	72 (19.1%)	70 (19.9%)	
Severe problems doing my usual activities	25 (6.6%)	27 (7.7%)	
Unable to do my usual activities	7 (1.9%)	5 (1.4%)	
Missing	3 (0.8%)	1 (0.3%)	
Pain and discomfort (baseline)			
No pain or discomfort	37 (9.8%)	32 (9.1%)	0.819
Slight pain or discomfort	133 (35.4%)	112 (31.9%)	
Moderate pain or discomfort	131 (34.8%)	136 (38.7%)	
Severe pain or discomfort	60 (16%)	53 (15.1%)	
Extreme pain or discomfort	12 (3.2%)	17 (4.8%)	
Missing	3 (0.8%)	1 (0.3%)	
Anxiety and depression (baseline)			
Not anxious or depressed	128 (34%)	107 (30.5%)	0.32
Slightly anxious or depressed	118 (31.4%)	122 (34.8%)	
Moderately anxious or depressed	80 (21.3%)	81 (23.1%)	
Severely anxious or depressed	31 (8.2%)	24 (6.8%)	
Extremely anxious or depressed	15 (4%)	15 (4.3%)	
Missing	4 (1.1%)	2 (0.6%)	
Mobility (4 months)			
No problems in walking	185 (49.2%)	171 (48.7%)	0.248
Slight problems in walking	54 (14.4%)	55 (15.7%)	
Moderate problems in walking	21 (5.6%)	25 (7.1%)	
Severe problems in walking	14 (3.7%)	19 (5.4%)	
Unable to walk	2 (0.5%)	6 (1.7%)	

Missing	100 (26.6%)	75 (21.4%)	
Self-care (4 months)			
No problems washing or dressing	232 (61.7%)	225 (64.1%)	0.499
Slight problems washing or dressing	24 (6.4%)	25 (7.1%)	
Moderate problems washing or dressing	12 (3.2%)	17 (4.8%)	
Severe problems washing or dressing	6 (1.6%)	8 (2.3%)	
Unable to wash or dress	2 (0.5%)	1 (0.3%)	
Missing	100 (26.6%)	75 (21.4%)	
Usual activities (4 months)			
No problems doing my usual activities	136 (36.2%)	120 (34.2%)	0.187
Slight problems doing my usual activities	86 (22.9%)	87 (24.8%)	
Moderate problems doing my usual activities	36 (9.6%)	35 (10%)	
Severe problems doing my usual activities	15 (4%)	26 (7.4%)	
Unable to do my usual activities	2 (0.5%)	8 (2.3%)	
Missing	101 (26.9%)	75 (21.4%)	
Pain and discomfort (4 months)			
No pain or discomfort	54 (14.4%)	39 (11.1%)	0.116
Slight pain or discomfort	105 (27.9%)	92 (26.2%)	
Moderate pain or discomfort	84 (22.3%)	98 (27.9%)	
Severe pain or discomfort	26 (6.9%)	37 (10.5%)	
Extreme pain or discomfort	8 (2.1%)	10 (2.8%)	
Missing	99 (26.3%)	75 (21.4%)	
Anxiety and depression (4 months)			
Not anxious or depressed	102 (27.1%)	81 (23.1%)	0.075
Slightly anxious or depressed	91 (24.2%)	105 (29.9%)	
Moderately anxious or depressed	55 (14.6%)	60 (17.1%)	
Severely anxious or depressed	15 (4%)	18 (5.1%)	
Extremely anxious or depressed	13 (3.5%)	11 (3.1%)	
Missing	100 (26.6%)	76 (21.7%)	
Mobility (8 months)			
No problems in walking	194 (51.6%)	164 (46.7%)	0.17
Slight problems in walking	50 (13.3%)	43 (12.3%)	
Moderate problems in walking	20 (5.3%)	36 (10.3%)	
Severe problems in walking	16 (4.3%)	14 (4%)	
Unable to walk	2 (0.5%)	4 (1.1%)	
Missing	94 (25%)	90 (25.6%)	
Self-care (8 months)			
No problems washing or dressing	246 (65.4%)	214 (61%)	0.092
Slight problems washing or dressing	17 (4.5%)	25 (7.1%)	
Moderate problems washing or dressing	11 (2.9%)	13 (3.7%)	
Severe problems washing or dressing	6 (1.6%)	6 (1.7%)	
Unable to wash or dress	1 (0.3%)	3 (0.9%)	
Missing	95 (25.3%)	90 (25.6%)	
Usual activities (8 months)			
No problems doing my usual activities	141 (37.5%)	138 (39.3%)	0.591
Slight problems doing my usual activities	90 (23.9%)	66 (18.8%)	
Moderate problems doing my usual activities	36 (9.6%)	34 (9.7%)	

Severe problems doing my usual activities	11 (2.9%)	18 (5.1%)	
Unable to do my usual activities	4 (1.1%)	6 (1.7%)	
Missing	94 (25%)	89 (25.4%)	
Pain and discomfort (8 months)			
No pain or discomfort	58 (15.4%)	44 (12.5%)	0.309
Slight pain or discomfort	113 (30.1%)	97 (27.6%)	
Moderate pain or discomfort	80 (21.3%)	80 (22.8%)	
Severe pain or discomfort	24 (6.4%)	32 (9.1%)	
Extreme pain or discomfort	7 (1.9%)	9 (2.6%)	
Missing	94 (25%)	89 (25.4%)	
Anxiety and depression (8 months)			
Not anxious or depressed	102 (27.1%)	84 (23.9%)	0.342
Slightly anxious or depressed	103 (27.4%)	96 (27.4%)	
Moderately anxious or depressed	50 (13.3%)	50 (14.2%)	
Severely anxious or depressed	19 (5.1%)	20 (5.7%)	
Extremely anxious or depressed	7 (1.9%)	12 (3.4%)	
Missing	95 (25.3%)	89 (25.4%)	
Mobility (12 months)			
No problems in walking	200 (53.2%)	179 (51%)	0.543
Slight problems in walking	58 (15.4%)	47 (13.4%)	
Moderate problems in walking	28 (7.4%)	38 (10.8%)	
Severe problems in walking	13 (3.5%)	13 (3.7%)	
Unable to walk	3 (0.8%)	5 (1.4%)	
Missing	74 (19.7%)	69 (19.7%)	
Self-care (12 months)			
No problems washing or dressing	249 (66.2%)	231 (65.8%)	0.952
Slight problems washing or dressing	28 (7.4%)	32 (9.1%)	
Moderate problems washing or dressing	17 (4.5%)	11 (3.1%)	
Severe problems washing or dressing	8 (2.1%)	7 (2%)	
Unable to wash or dress	0 (0%)	1 (0.3%)	
Missing	74 (19.7%)	69 (19.7%)	
Usual activities (12 months)			
No problems doing my usual activities	156 (41.5%)	145 (41.3%)	1
Slight problems doing my usual activities	89 (23.7%)	76 (21.7%)	
Moderate problems doing my usual activities	39 (10.4%)	43 (12.3%)	
Severe problems doing my usual activities	14 (3.7%)	11 (3.1%)	
Unable to do my usual activities	4 (1.1%)	7 (2%)	
Missing	74 (19.7%)	69 (19.7%)	
Pain and discomfort (12 months)			
No pain or discomfort	61 (16.2%)	48 (13.7%)	0.369
Slight pain or discomfort	122 (32.4%)	108 (30.8%)	
Moderate pain or discomfort	84 (22.3%)	90 (25.6%)	
Severe pain or discomfort	30 (8%)	33 (9.4%)	
Extreme pain or discomfort	5 (1.3%)	4 (1.1%)	
Missing	74 (19.7%)	68 (19.4%)	
Anxiety and depression (12 months)			
Not anxious or depressed	128 (34%)	92 (26.2%)	0.016

Slightly anxious or depressed	104 (27.7%)	94 (26.8%)	
Moderately anxious or depressed	43 (11.4%)	71 (20.2%)	
Severely anxious or depressed	18 (4.8%)	11 (3.1%)	
Extremely anxious or depressed	8 (2.1%)	15 (4.3%)	
Missing	75 (19.9%)	68 (19.4%)	

Table 15: SF-12 version 2 dimensions scores

Responses to SF-12 dimensions	Intervention	Usual care	P-value
In general, would you say your health is? (baseline)			
Excellent	13 (3.5%)	10 (2.8%)	0.769
Very good	71 (18.9%)	65 (18.5%)	
Good	156 (41.5%)	127 (36.2%)	
Fair	85 (22.6%)	97 (27.6%)	
Poor	38 (10.1%)	45 (12.8%)	
Missing	13 (3.5%)	7 (2%)	
Moderate activities, such as moving a table, pushing (baseline)			
Yes, limited a lot	49 (13%)	60 (17.1%)	0.357
Yes, limited a little	131 (34.8%)	123 (35%)	
No, not limited at all	184 (48.9%)	161 (45.9%)	
Climbing several flights of stairs (baseline)			
Yes, limited a lot	67 (17.8%)	82 (23.4%)	0.254
Yes, limited a little	118 (31.4%)	108 (30.8%)	
No, not limited at all	179 (47.6%)	153 (43.6%)	
Physical health, accomplished less than you would like (baseline)			
All of the time	41 (10.9%)	40 (11.4%)	1
Most of the time	65 (17.3%)	76 (21.7%)	
Some of the time	126 (33.5%)	110 (31.3%)	
A little of the time	82 (21.8%)	71 (20.2%)	
None of the time	50 (13.3%)	47 (13.4%)	
Missing	12 (3.2%)	7 (2%)	
Physical health, were limited in the kind of work or other activities (baseline)			
All of the time	38 (10.1%)	32 (9.1%)	0.349
Most of the time	54 (14.4%)	67 (19.1%)	
Some of the time	118 (31.4%)	97 (27.6%)	
A little of the time	75 (19.9%)	86 (24.5%)	
None of the time	74 (19.7%)	60 (17.1%)	
Missing	17 (4.5%)	9 (2.6%)	
Emotional problems, accomplished less than you would like (baseline)			
All of the time	30 (8%)	25 (7.1%)	0.092
Most of the time	73 (19.4%)	69 (19.7%)	
Some of the time	85 (22.6%)	100 (28.5%)	
A little of the time	80 (21.3%)	81 (23.1%)	
None of the time	95 (25.3%)	71 (20.2%)	
Missing	13 (3.5%)	5 (1.4%)	
Emotional problems, did work or other activities less carefully than usual (baseline)			
All of the time	23 (6.1%)	18 (5.1%)	0.233
Most of the time	52 (13.8%)	48 (13.7%)	
Some of the time	85 (22.6%)	97 (27.6%)	
A little of the time	89 (23.7%)	88 (25.1%)	

None of the time	114 (30.3%)	93 (26.5%)	
Missing	13 (3.5%)	7 (2%)	
How much did pain interfere with your normal? (baseline)			
Not at all	25 (6.6%)	23 (6.6%)	1
A little bit	103 (27.4%)	88 (25.1%)	
Moderately	97 (25.8%)	88 (25.1%)	
Quite a bit	101 (26.9%)	105 (29.9%)	
Extremely	38 (10.1%)	42 (12%)	
Missing	12 (3.2%)	5 (1.4%)	
Have you felt calm and peaceful? (baseline)			
All of the time	6 (1.6%)	1 (0.3%)	0.146
Most of the time	62 (16.5%)	63 (17.9%)	
Some of the time	117 (31.1%)	120 (34.2%)	
A little of the time	125 (33.2%)	116 (33%)	
None of the time	53 (14.1%)	45 (12.8%)	
Missing	13 (3.5%)	6 (1.7%)	
Did you have a lot of energy? (baseline)			
All of the time	1 (0.3%)	3 (0.9%)	0.579
Most of the time	35 (9.3%)	31 (8.8%)	
Some of the time	113 (30.1%)	111 (31.6%)	
A little of the time	135 (35.9%)	117 (33.3%)	
None of the time	80 (21.3%)	83 (23.6%)	
Missing	12 (3.2%)	6 (1.7%)	
Have you felt downhearted and low? (baseline)			
All of the time	18 (4.8%)	23 (6.6%)	0.702
Most of the time	85 (22.6%)	85 (24.2%)	
Some of the time	125 (33.2%)	109 (31.1%)	
A little of the time	95 (25.3%)	94 (26.8%)	
None of the time	40 (10.6%)	34 (9.7%)	
Missing	13 (3.5%)	6 (1.7%)	
Social activities (baseline)			
All of the time	24 (6.4%)	22 (6.3%)	1
Most of the time	74 (19.7%)	67 (19.1%)	
Some of the time	105 (27.9%)	113 (32.2%)	
A little of the time	94 (25%)	96 (27.4%)	
None of the time	66 (17.6%)	46 (13.1%)	
Missing	13 (3.5%)	7 (2%)	
In general, would you say your health is? (4 months)			
Excellent	10 (2.7%)	4 (1.1%)	0.193
Very good	60 (16%)	56 (16%)	
Good	96 (25.5%)	95 (27.1%)	
Fair	66 (17.6%)	64 (18.2%)	
Poor	15 (4%)	21 (6%)	
Missing	129 (34.3%)	111 (31.6%)	
Moderate activities, such as moving a table, pushing (4 months)			
Yes, limited a lot	30 (8%)	41 (11.7%)	0.574
Yes, limited a little	82 (21.8%)	74 (21.1%)	
No, not limited at all	136 (36.2%)	124 (35.3%)	
Climbing several flights of stairs (4 months)			
Yes, limited a lot	41 (10.9%)	41 (11.7%)	0.188
Yes, limited a little	71 (18.9%)	84 (23.9%)	
No, not limited at all	132 (35.1%)	114 (32.5%)	
Physical health, accomplished less than you would like (4 months)			

All of the time	21 (5.6%)	21 (6%)	0.963
Most of the time	25 (6.6%)	37 (10.5%)	
Some of the time	85 (22.6%)	63 (17.9%)	
A little of the time	67 (17.8%)	72 (20.5%)	
None of the time	50 (13.3%)	47 (13.4%)	
Missing	128 (34%)	111 (31.6%)	
Physical health, were limited in the kind of work or other activities (4 months)			
All of the time	23 (6.1%)	23 (6.6%)	0.644
Most of the time	23 (6.1%)	34 (9.7%)	
Some of the time	68 (18.1%)	51 (14.5%)	
A little of the time	66 (17.6%)	73 (20.8%)	
None of the time	66 (17.6%)	59 (16.8%)	
Missing	130 (34.6%)	111 (31.6%)	
E*motional problems, accomplished less than you would like (4 months)*			
All of the time	12 (3.2%)	15 (4.3%)	0.087
Most of the time	34 (9%)	41 (11.7%)	
Some of the time	56 (14.9%)	60 (17.1%)	
A little of the time	63 (16.8%)	63 (17.9%)	
None of the time	82 (21.8%)	62 (17.7%)	
Missing	129 (34.3%)	110 (31.3%)	
Emotional problems, did work or other activities less carefully than usual (4 months)			
All of the time	8 (2.1%)	11 (3.1%)	0.205
Most of the time	21 (5.6%)	31 (8.8%)	
Some of the time	57 (15.2%)	53 (15.1%)	
A little of the time	64 (17%)	65 (18.5%)	
None of the time	97 (25.8%)	80 (22.8%)	
Missing	129 (34.3%)	111 (31.6%)	
How much did pain interfere with your normal? (4 months)			
Not at all	35 (9.3%)	29 (8.3%)	0.596
A little bit	90 (23.9%)	91 (25.9%)	
Moderately	57 (15.2%)	52 (14.8%)	
Quite a bit	48 (12.8%)	50 (14.2%)	
Extremely	17 (4.5%)	17 (4.8%)	
Missing	129 (34.3%)	112 (31.9%)	
Have you felt calm and peaceful? How much did pain interfere with your normal? (4 months)			
All of the time	8 (2.1%)	1 (0.3%)	0.048
Most of the time	57 (15.2%)	56 (16%)	
Some of the time	88 (23.4%)	91 (25.9%)	
A little of the time	67 (17.8%)	68 (19.4%)	
None of the time	27 (7.2%)	25 (7.1%)	
Missing	129 (34.3%)	110 (31.3%)	
Did you have a lot of energy? (4 months)			
All of the time	4 (1.1%)	2 (0.6%)	0.704
Most of the time	33 (8.8%)	32 (9.1%)	
Some of the time	82 (21.8%)	83 (23.6%)	
A little of the time	85 (22.6%)	80 (22.8%)	
None of the time	43 (11.4%)	44 (12.5%)	
Missing	129 (34.3%)	110 (31.3%)	
Have you felt downhearted and low? (4 months)			
All of the time	9 (2.4%)	13 (3.7%)	0.24
Most of the time	44 (11.7%)	51 (14.5%)	
Some of the time	66 (17.6%)	69 (19.7%)	

A little of the time	81 (21.5%)	72 (20.5%)	
None of the time	48 (12.8%)	36 (10.3%)	
Missing	128 (34%)	110 (31.3%)	
Social activities (4 months)			
All of the time	15 (4%)	10 (2.8%)	0.455
Most of the time	32 (8.5%)	47 (13.4%)	
Some of the time	65 (17.3%)	73 (20.8%)	
A little of the time	65 (17.3%)	48 (13.7%)	
None of the time	71 (18.9%)	63 (17.9%)	
Missing	128 (34%)	110 (31.3%)	
In general, would you say your health is? (8 months)			
Excellent	10 (2.7%)	7 (2%)	0.792
Very good	65 (17.3%)	51 (14.5%)	
Good	99 (26.3%)	93 (26.5%)	
Fair	56 (14.9%)	51 (14.5%)	
Poor	19 (5.1%)	21 (6%)	
Missing	127 (33.8%)	128 (36.5%)	
Moderate activities, such as moving a table, pushing (8 months)			
Yes, limited a lot	31 (8.2%)	30 (8.5%)	0.843
Yes, limited a little	74 (19.7%)	67 (19.1%)	
No, not limited at all	144 (38.3%)	126 (35.9%)	
Climbing several flights of stairs (8 months)			
Yes, limited a lot	36 (9.6%)	30 (8.5%)	0.711
Yes, limited a little	73 (19.4%)	71 (20.2%)	
No, not limited at all	140 (37.2%)	119 (33.9%)	
Physical health, accomplished less than you would like (8 months)			
All of the time	14 (3.7%)	19 (5.4%)	0.552
Most of the time	29 (7.7%)	28 (8%)	
Some of the time	90 (23.9%)	62 (17.7%)	
A little of the time	60 (16%)	69 (19.7%)	
None of the time	56 (14.9%)	44 (12.5%)	
Missing	127 (33.8%)	129 (36.8%)	
Physical health, were limited in the kind of work or other activities (8 months)			
All of the time	14 (3.7%)	18 (5.1%)	0.794
Most of the time	25 (6.6%)	22 (6.3%)	
Some of the time	78 (20.7%)	57 (16.2%)	
A little of the time	67 (17.8%)	63 (17.9%)	
None of the time	65 (17.3%)	61 (17.4%)	
Missing	127 (33.8%)	130 (37%)	
Emotional problems, accomplished less than you would like (8 months)			
All of the time	11 (2.9%)	14 (4%)	0.538
Most of the time	30 (8%)	29 (8.3%)	
Some of the time	64 (17%)	64 (18.2%)	
A little of the time	70 (18.6%)	57 (16.2%)	
None of the time	73 (19.4%)	59 (16.8%)	
Missing	128 (34%)	128 (36.5%)	
Emotional problems, did work or other activities less carefully than usual (8 months)			
All of the time	7 (1.9%)	11 (3.1%)	0.775
Most of the time	24 (6.4%)	20 (5.7%)	
Some of the time	50 (13.3%)	56 (16%)	
A little of the time	78 (20.7%)	59 (16.8%)	
None of the time	88 (23.4%)	75 (21.4%)	

Missing	129 (34.3%)	130 (37%)	
How much did pain interfere with your normal? (8 months)			
Not at all	33 (8.8%)	37 (10.5%)	0.363
A little bit	104 (27.7%)	74 (21.1%)	
Moderately	61 (16.2%)	41 (11.7%)	
Quite a bit	45 (12%)	51 (14.5%)	
Extremely	6 (1.6%)	19 (5.4%)	
Missing	127 (33.8%)	129 (36.8%)	
Have you felt calm and peaceful? (8 months)			
All of the time	3 (0.8%)	4 (1.1%)	0.883
Most of the time	66 (17.6%)	59 (16.8%)	
Some of the time	90 (23.9%)	74 (21.1%)	
A little of the time	64 (17%)	59 (16.8%)	
None of the time	26 (6.9%)	27 (7.7%)	
Missing	127 (33.8%)	128 (36.5%)	
Did you have a lot of energy? (8 months)			
All of the time	0 (0%)	4 (1.1%)	0.105
Most of the time	45 (12%)	33 (9.4%)	
Some of the time	83 (22.1%)	71 (20.2%)	
A little of the time	76 (20.2%)	73 (20.8%)	
None of the time	45 (12%)	42 (12%)	
Missing	127 (33.8%)	128 (36.5%)	
Have you felt downhearted and low? (8 months)			
All of the time	9 (2.4%)	13 (3.7%)	0.297
Most of the time	35 (9.3%)	40 (11.4%)	
Some of the time	81 (21.5%)	67 (19.1%)	
A little of the time	82 (21.8%)	74 (21.1%)	
None of the time	42 (11.2%)	29 (8.3%)	
Missing	127 (33.8%)	128 (36.5%)	
Social activities (8 months)			
All of the time	12 (3.2%)	21 (6%)	0.078
Most of the time	23 (6.1%)	23 (6.6%)	
Some of the time	60 (16%)	58 (16.5%)	
A little of the time	80 (21.3%)	65 (18.5%)	
None of the time	73 (19.4%)	56 (16%)	
Missing	128 (34%)	128 (36.5%)	
In general, would you say your health is? (12 months)			
Excellent	8 (2.1%)	7 (2%)	1
Very good	52 (13.8%)	38 (10.8%)	
Good	111 (29.5%)	96 (27.4%)	
Fair	74 (19.7%)	64 (18.2%)	
Poor	18 (4.8%)	27 (7.7%)	
Missing	113 (30.1%)	119 (33.9%)	
Moderate activities, such as moving a table, pushing (12 months)			
Yes, limited a lot	27 (7.2%)	34 (9.7%)	0.666
Yes, limited a little	95 (25.3%)	69 (19.7%)	
No, not limited at all	139 (37%)	129 (36.8%)	
Climbing several flights of stairs (12 months)			
Yes, limited a lot	44 (11.7%)	38 (10.8%)	0.315
Yes, limited a little	72 (19.1%)	76 (21.7%)	
No, not limited at all	144 (38.3%)	116 (33%)	
Physical health, accomplished less than you would like (12 months)			
All of the time	7 (1.9%)	15 (4.3%)	0.928

Most of the time	53 (14.1%)	39 (11.1%)	
Some of the time	70 (18.6%)	61 (17.4%)	
A little of the time	76 (20.2%)	65 (18.5%)	
None of the time	57 (15.2%)	52 (14.8%)	
Missing	113 (30.1%)	119 (33.9%)	
Physical health, were limited in the kind of work or other activities (12 months)			
All of the time	8 (2.1%)	13 (3.7%)	0.902
Most of the time	41 (10.9%)	34 (9.7%)	
Some of the time	59 (15.7%)	56 (16%)	
A little of the time	77 (20.5%)	58 (16.5%)	
None of the time	77 (20.5%)	70 (19.9%)	
Missing	114 (30.3%)	120 (34.2%)	
Emotional problems, accomplished less than you would like (12 months)			
All of the time	10 (2.7%)	14 (4%)	0.09
Most of the time	29 (7.7%)	30 (8.5%)	
Some of the time	65 (17.3%)	54 (15.4%)	
A little of the time	66 (17.6%)	68 (19.4%)	
None of the time	93 (24.7%)	64 (18.2%)	
Missing	113 (30.1%)	121 (34.5%)	
Emotional problems, did work or other activities less carefully than usual (12 months)			
All of the time	7 (1.9%)	13 (3.7%)	0.97
Most of the time	25 (6.6%)	20 (5.7%)	
Some of the time	59 (15.7%)	56 (16%)	
A little of the time	76 (20.2%)	59 (16.8%)	
None of the time	96 (25.5%)	83 (23.6%)	
Missing	113 (30.1%)	120 (34.2%)	
How much did pain interfere with your normal? (12 months)			
Not at all	49 (13%)	34 (9.7%)	0.298
A little bit	102 (27.1%)	85 (24.2%)	
Moderately	61 (16.2%)	39 (11.1%)	
Quite a bit	41 (10.9%)	57 (16.2%)	
Extremely	10 (2.7%)	16 (4.6%)	
Missing	113 (30.1%)	120 (34.2%)	
Have you felt calm and peaceful? (12 months)			
All of the time	6 (1.6%)	7 (2%)	0.813
Most of the time	85 (22.6%)	62 (17.7%)	
Some of the time	90 (23.9%)	73 (20.8%)	
A little of the time	57 (15.2%)	70 (19.9%)	
None of the time	25 (6.6%)	19 (5.4%)	
Missing	113 (30.1%)	120 (34.2%)	
Did you have a lot of energy? (12 months)			
All of the time	5 (1.3%)	7 (2%)	0.603
Most of the time	49 (13%)	36 (10.3%)	
Some of the time	95 (25.3%)	73 (20.8%)	
A little of the time	79 (21%)	81 (23.1%)	
None of the time	35 (9.3%)	34 (9.7%)	
Missing	113 (30.1%)	120 (34.2%)	
Have you felt downhearted and low? (12 months)			
All of the time	14 (3.7%)	15 (4.3%)	0.94
Most of the time	34 (9%)	47 (13.4%)	
Some of the time	74 (19.7%)	59 (16.8%)	
A little of the time	96 (25.5%)	72 (20.5%)	
None of the time	45 (12%)	38 (10.8%)	

Missing	113 (30.1%)	120 (34.2%)	
Social activities (12 months)			
All of the time	10 (2.7%)	13 (3.7%)	0.455
Most of the time	30 (8%)	29 (8.3%)	
Some of the time	71 (18.9%)	66 (18.8%)	
A little of the time	79 (21%)	71 (20.2%)	
None of the time	73 (19.4%)	52 (14.8%)	
Missing	113 (30.1%)	120 (34.2%)	

References

Achana F, Oppong R, Gallacher D, Kim SW, Petrou S, Mason J, Crowther M. Multivariate generalised linear mixed-effects models for analysis of clinical trial-based cost-effectiveness data. *Medical Decision Making*, in press.

British Acupuncture Council. London: British Acupuncture Council, 2019. https://www.acupuncture.org.uk/public-content/public-ask-an-expert/ask-an-expert-about-acupuncture/ask-an-expert-about-acupuncture-nhs-private-healthcare/2679-how-much-does-acupuncture-cost-and-how-many-treatments.html

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics* 2002;21(2):271-92.

Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health technology assessment (Winchester, England). 2015;19(14):1-503, v-vi.

Curtis LA, Burns A. Unit Costs of Health and Social Care 2019. Unit Costs of Health and Social Care. Personal and Social Services Research Unit (PSSRU): Kent, UK, 2019. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. PharmacoEconomics. 2014;32(12):1157-70.

Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials: OUP Oxford; 2014.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20(10):1727-36.

Hernandez-Alava M, Pudney S. Eq5Dmap: A Command for Mapping between EQ-5D-3L and EQ-5D-5L. The Stata Journal, 2018. **https://journals.sagepub.com/doi/abs/10.1177/1536867X1801800207**

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health 2013;16(2):231-50.

Joint Formulary Committee. British National Formulary. (online). London: BMJ Group and Pharmaceutical Press, 2019. URL: www.evidence.nhs.uk/formulary/bnf/current

Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Brit Med J. 1998;316(7133):736-41.

National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. London, UK: NICE, 2013.

National Institute for Health and Care Excellence (NICE). Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. London, UK: NICE, 2012. https://www.nice.org.uk/guidance/ta260/resources/botulinum-toxin-typea-for-the-prevention-of-headaches-in-adults-with-chronic-migraine-pdf-82600545273541

NHS Digital. Prescription Cost Analysis - England, 2019. In: Health Do, editor. London: NHS Digital; 2019. https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data

NHS Digital (b). Reference Costs 2018-2019. In: Department of Health, editor. London: NHS Digital; 2019. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/reference-costs

Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate Imputation by Chained Equations. Journal of Statistical Software, 45, 1-67. 2011.

van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value in Health. 2012;15(5):708-15.

Ware JE. How to Score Version 2 of the SF-12v2® Health Survey (With a Supplement Documenting SF-12® Health Survey) Lincoln, RI.: QualityMetric Inc; 20