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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Randomized placebo-controlled trial of opioid analgesia for acute low back pain and neck pain: Appendices

Date: 7th February 2023

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Appendix 1: OPAL Investigators and Coordinators

Steering committee

Christine Lin (Chair, The University of Sydney and Sydney Local Health District), Laurent Billot (Member, The George Institute for Global Health), Ric Day (Member, The University of New South Wales), Bart Koes (Member, Erasmus Medical Centre, The Netherlands), Jane Latimer (Deputy Chair, The University of Sydney and Sydney Local Health District), Christopher Maher (Deputy Chair, The University of Sydney and Sydney Local Health District), Andrew McLachlan (Member, The University of Sydney)

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Appendix 2: Protocol changes between first (version 1·0) and final (version 6·0)

- Page 4 - Date of registration: changed from “not yet registered” to “27 July 2015 (ACTRN12615000775516)”
- Page 4 - Contact for public enquiries changed from Chief Investigator Christine Lin to OPAL study manager Hanan McLachlan
- Page 5 - Key exclusion criteria changed from “have taken a prescription opioid analgesic for the current episode” to “have taken greater than 15MME per day of an opioid analgesic for 5 or more consecutive days for the current episode” on the 7th of February 2018.
- Page 5 - Date of first enrolment: changed from “not yet started” to “29 February 2016”
- Page 5 - Recruitment: changed from “not yet started” to “Ongoing”
- Page 7 - Name and contact: changed from physical address in Kent St, Sydney, to The George’s PO Box
- Page 7 - Protocol synopsis (and throughout): removed references to opioids being recommended as “second line care”, and for those “slow to recover”
- Page 14 - Study setting (and throughout): removed reference to “GPs” and replaced with “medical practitioners” or “doctors”, and added “hospital, outpatient and specialist clinics” to allow for the conduct of the study in hospital and specialist clinics
- Page 14/15 - Eligibility criteria: removed “Current episode of pain is at least 2 weeks but no more than 12 weeks since onset” and replaced with “Current episode of pain

is no more than 12 weeks since onset and is considered appropriate for opioid analgesia by the study doctor" on the 5th of October 2016.

- Page 20 - Allocation: removed reference to stratifying randomisation by pain site (back or neck) and replaced with "in permuted blocks"
- Page 22 - Plans to promote participant retention and complete follow up: removed statement "No financial reimbursement to participants will be offered"· We offered patients a $50 gift card upon completing their final survey
- Page 22 - Data management: removed "backed up daily" and replaced with "backed up regularly"
- Page 22 - Data management: removed "Adverse events will be coded using the preferred term of MedDRA (Medical Dictionary for Regulatory Activities)"
- Page 23 - Primary analysis: Removed "longitudinal" and replaced with "repeated-measure linear mixed models"
- Page 23 - Primary analysis: removed "accounted for using generalised estimating equations" and replaced with "will be modelled using a repeated effect"
- Page 23 - Secondary analysis: added "Self-reported data will be used as the primary source of data and supported by data reported by the study doctors."
- Page 25 - Site monitoring: added "Regular visits to study doctors will be conducted to monitor and reinforce the participant screening, consent and treatment provision processes· Regular visits to study pharmacies will be conducted to monitor the dispensing, return and destruction of the study medication."
- Page 25 - Data monitoring: removed "It is anticipated that the DSMB will review data after one-third of participants have been recruited, and again after two-thirds of participants have been recruited."

- Page 25/26 - Harms: removed paragraph explaining details of reporting and example of Mundipharma process, and replaced with “Serious adverse events will be reported to the relevant bodies (e·g· ethics committee, regulatory body) within the required timeline.”
- Page 26 - Auditing: added “No formal auditing is planned. However if required by the Steering Committee or Sponsor, independent auditing of core study processes and documents will be arranged by The George Institute for Global Health.”

Appendix 3: List of outcomes collected and timepoints

Outcome	Measurement tool	Measurement occasions
Primary outcome		
Pain severity	Pain Severity Score of the Brief Pain Inventory	Baseline, weeks 2, 4, 6 and 12
Secondary outcomes		
Physical functioning (generic)	Pain Interference Score of the Brief Pain Inventory·	Baseline, weeks 2, 4, 6 and 12
Physical functioning (condition-specific)	Roland-Morris Disability Questionnaire (24 items, for participants reporting low back pain only) and Neck Disability Questionnaire (for participants reporting neck pain only)	Baseline and 6 weeks
Time to recovery (average daily pain of 0 or 1 of 10 for the past seven consecutive days)	Pain diary	Daily until recovery or up to 12 weeks
Quality of life (physical)	SF-12	Baseline, weeks 2, 4, 6 and 12

Quality of life (mental)	SF-12	Baseline, weeks 2, 4, 6 and 12
Participants' rating of global improvement	Global Perceived Effect scale	Baseline, weeks 2, 4, 6 and 12
Other outcomes		
Adverse events	Self-report and doctor report	Self-report at weeks 2, 4, 6 and 12 Doctor report after each follow-up visit
Work absenteeism	Self-report	Baseline, weeks 2, 4, 6 and 12
Use of treatment or health care services	Self-report	Baseline, weeks 2, 4, 6 and 12
Compliance to study medication	Self-reported adherence recorded in a medication diary compared against doctor prescription data, supported by returned medicine count	Medicine diary is recorded daily over 6 weeks Doctor prescription data at each visit Returned medicine count at end of treatment period (6 weeks)
Success of blinding	Participants are asked to estimate their allocation group as active opioid,	Week 6

	inactive placebo, or don't know	
Long-term outcomes		
Pain severity	Pain Severity Score of the Brief Pain Inventory	Weeks 26 and 52
Use of treatment or health care services	Self-report	Weeks 26 and 52 if still experiencing low back pain and/or neck pain (>1/10)
Risk of misuse	Current Opioid Misuse Measure	Weeks 12, 26 and 52

Appendix 4: Breakdown of participant flow in CONSORT diagram

Assessed for eligibility	1349
Recruited	346
Excluded	1003
• Not meeting inclusion criteria	711
- Ineligible - already taken opioids for this episode	130
- Ineligible - contraindication to opioids	40
- Ineligible - high COMMS score	7
- Ineligible - insufficient English	74
- Ineligible - multiple reasons	36
- Ineligible - other	34
- Ineligible - pain <2 weeks	10
- Ineligible - pain >12 weeks	223
- Ineligible - pain location	7
- Ineligible - pain mild	98
- Ineligible - pregnant or planning to conceive	10
- Ineligible - serious pathology suspected	31*
- Ineligible – had or planned surgery	5
- Ineligible - under 18	8
• Decline to participant	
- Eligible but not interested - not willing to commit	12
- Eligible but not interested - opioid concerns	55

- Eligible but not interested - other	12
- Eligible but not interested - placebo concerns	10
- Eligible but not interested - preferred other treatments	14
- Eligible but not interested - reason not stated	168
- Eligible but recovered prior to randomisation	4
- Eligible but insurance scheme (workers' compensation) prohibits opioids	13

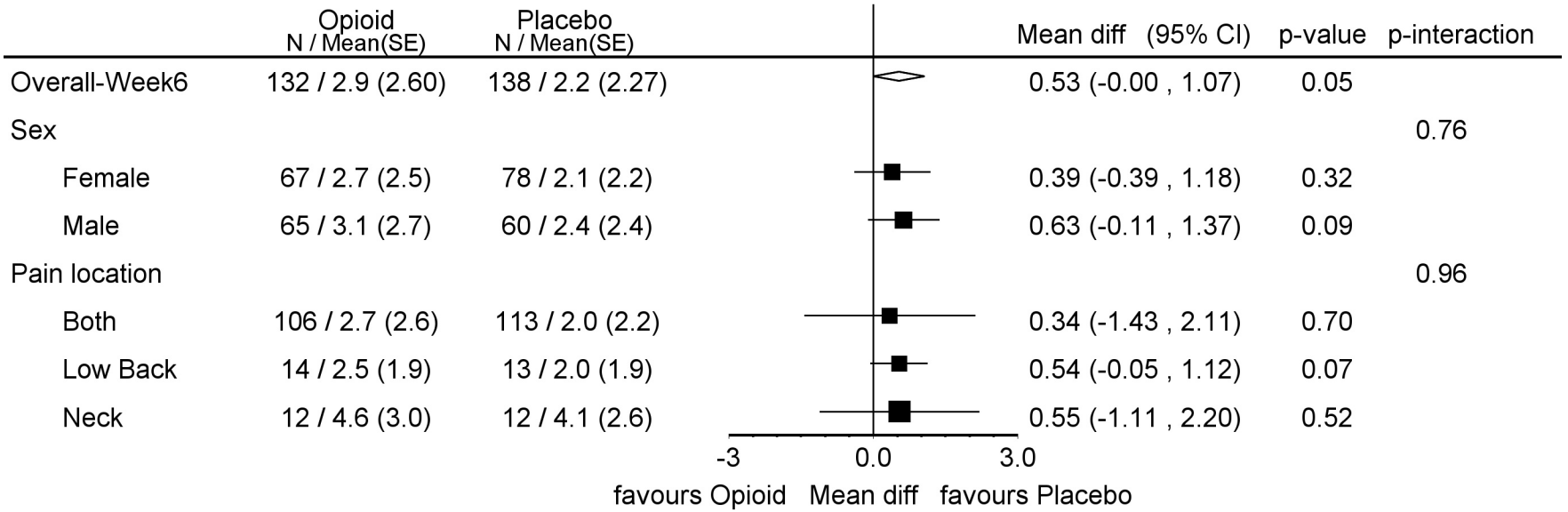
** Includes 1 participant who was considered a post randomisation exclusion as spinal metastases discovered within the first two weeks*

Appendix 5: Baseline characteristics comparison of study participants with and without pain scores at week 6

	Pain score data	No pain score data	Total	p-value
Gender				0·047
Female	125/270 (46·3%)	45/76 (59·2%)	170/346 (49·1%)	
Male	145/270 (53·7%)	31/76 (40·8%)	176/346 (50·9%)	
Age (years)				0·093
Mean (SD)	45·5 (15·80)	42·0 (15·58)	44·7 (15·80)	
Median (Q1; Q3)	45·0 (32·0; 55·0)	38·0 (30·0; 54·0)	43·0 (32·0; 55·0)	
min max	18 90	18 78	18 90	
n	267	74	341	
Pain duration (days)				0·051
Mean (SD)	16·2 (20·28)	27·4 (84·28)	18·6 (42·58)	
Median (Q1; Q3)	7·0 (3·0; 21·0)	7·0 (4·0; 28·0)	7·0 (3·0; 21·0)	
min max	1 89	1 700	1 700	
n	265	70	335	
Pain severity (BPI Pain severity)				0·44
Mean (SD)	5·6 (1·47)	5·8 (1·41)	5·7 (1·46)	
Median (Q1; Q3)	5·5 (4·5; 6·5)	5·8 (4·8; 7·0)	5·8 (4·8; 6·8)	
min max	2 10	3 9	2 10	
n	270	75	345	

Note:
** p-values obtained using chi-square test or t-test*
T:\Statistics\Projects\OPAL\Common\Programs\Final\Tables\t_supp_bl_comp_painscore·sas
Data cutoff: 20APR2022 - Last run: 29AUG2022 12:17 - Run by: Sana Shan

Appendix 6: Subgroup analysis



Appendix 7: Imputations and sensitivity analysis

Analysis of primary outcomes on imputed data

	Oxycodone/Naloxone mean(se)	Placebo mean(se)	Mean difference (95% CI)	P-value
Pain Intensity (BPI-PS)				
Week-2	3·88 (0·19)	3·59 (0·19)	0·29 (-0·25; 0·82)	
Week-4	3·13 (0·19)	2·77 (0·19)	0·36 (-0·17; 0·89)	
Week-6	2·82 (0·20)	2·31 (0·19)	0·51 (-0·03; 1·05)	0·062
Week-12	2·70 (0·20)	2·14 (0·19)	0·56 (0·01; 1·10)	0·046
Week-26	2·73 (0·20)	1·95 (0·20)	0·78 (0·23; 1·33)	
Week-52	2·42 (0·19)	1·81 (0·20)	0·61 (0·07; 1·16)	0·028

Missing data for Pain Score (using the BPI-PS subscale) at Week 2, 4, 6, 12 ,26 and 52 were imputed using a fully conditional specification with 100 imputations.

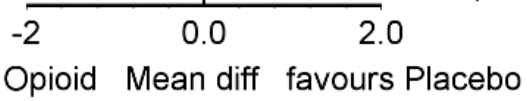
The following variables were included in the multiple imputation algorithm: Pain severity score at each visit, randomised treatment, age, sex, BMI, pain location, number of previous pain episodes, paid employment, employment classification, whether pain is compensable, household income, health service utilisation prior to enrolment, prior use of prescription opioid analgesic, BPI pain interference score at each visit, Roland Morris score at baseline and week 6, SF12 Physical and mental scores at each visit, and global perceived effect at each visit.

(see Statistical analysis plan for more details).[1]

1· Jones CMP, Lin CWC, Day RO, et al. OPAL: a randomised, placebo-controlled trial of opioid analgesia for the reduction of pain severity in people with acute spinal pain—a statistical analysis plan. Trials [Internet] 2022 [cited 2022 May 2];23(1):1–13. Available from: https://trialsjournal·biomedcentral·com/articles/10·1186/s13063-022-06028-y

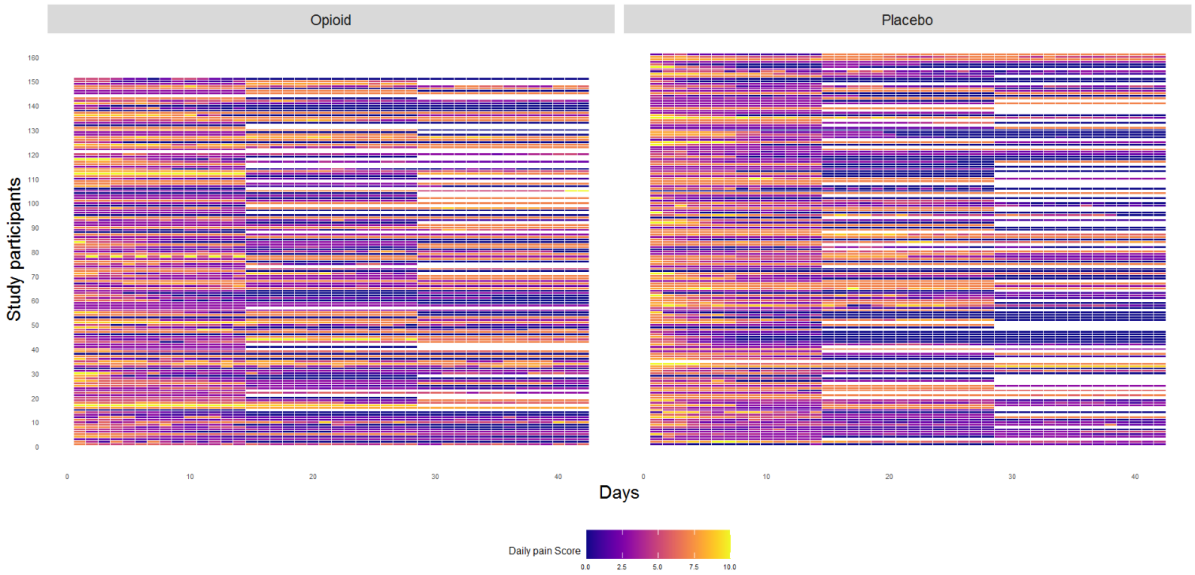
Tipping point analyses

	Opioid Mean(SE)	Placebo Mean(SE)	Mean diff (95% CI)	P value
MI + 3	3.54 (0.22)	2.89 (0.21)	0.65 (0.04 , 1.25)	0.036
MI + 2	3.30 (0.21)	2.70 (0.20)	0.60 (0.03 , 1.17)	0.039
MI + 1	3.06 (0.20)	2.51 (0.19)	0.56 (0.01 , 1.10)	0.046
Multiple Imputation (MI)	2.82 (0.20)	2.31 (0.19)	0.51 (-0.03 , 1.05)	0.06
MI - 1	2.64 (0.19)	2.16 (0.18)	0.48 (-0.04 , 0.99)	0.07
MI - 2	2.49 (0.18)	2.04 (0.18)	0.45 (-0.05 , 0.95)	0.08
MI - 3	2.38 (0.18)	1.96 (0.18)	0.43 (-0.06 , 0.91)	0.09

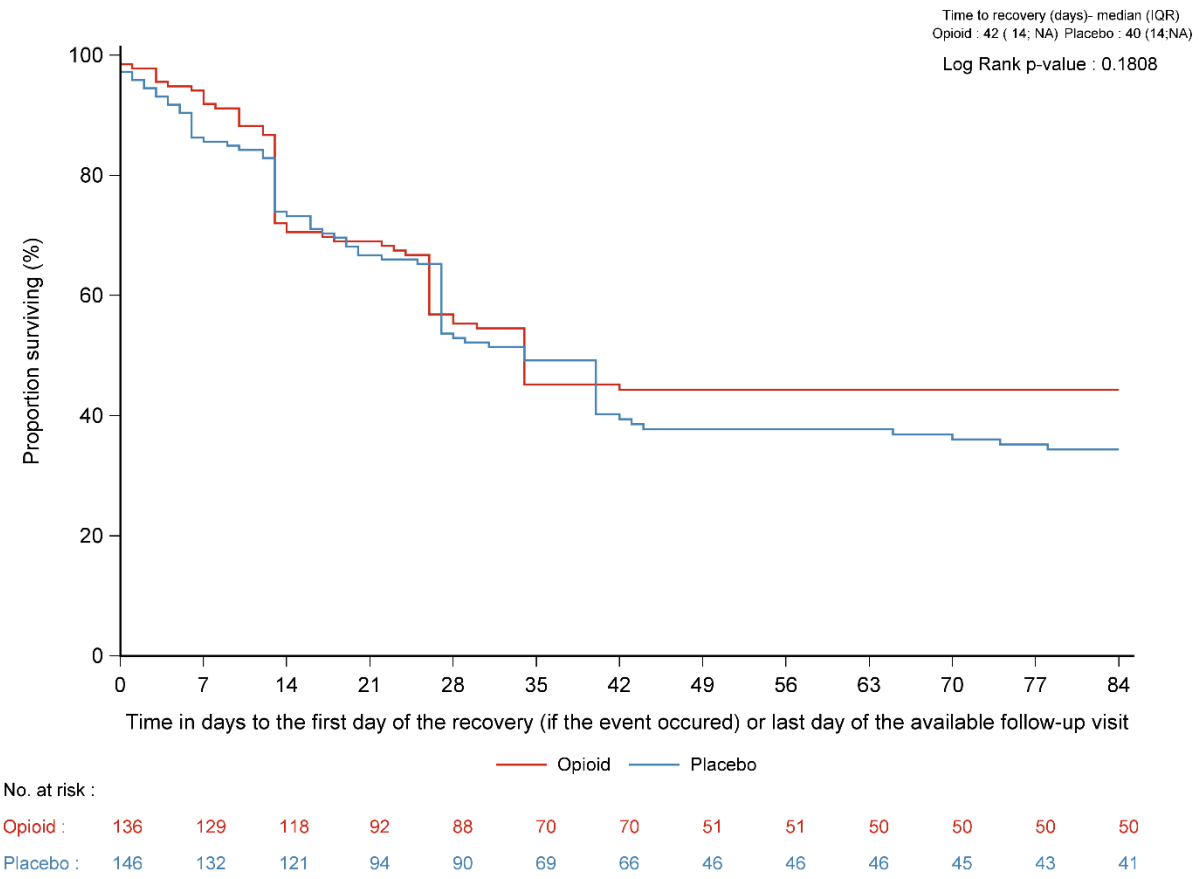


Sensitivity analysis of primary outcome at week 6 involving addition and subtraction of 1, 2 or 3 to the imputed pain scores in both opioid and placebo groups. The first 3 scenarios assume that a missing value is likely associated with worse pain, while last 3 scenarios assume less pain.

Appendix 8a: Time to recovery – heatmap of daily scores



Appendix 8b: Time to recovery – survival analysis



Opioid = Up to 20mg Oxycodone and 10mg Naloxone daily

Appendix 8c: Time to recovery

Recovered participants	**n/N (%)**	**n/N (%)**		**p-value**[1]
by Week-2	38 /136 (27·9%)	38 /146 (26·0%)		0·34
by Week-4	58 /136 (42·6%)	66 /146 (45·2%)		0·56
by Week-6	73 /136 (53·7%)	84 /146 (57·5%)		0·97
by Week-12	74 /136 (54·4%)	91 /146 (62·3%)		0·17
	Median (IQR)	**Median(IQR)**		**Log-rank p-value**
Time to recovery (days)	42 (14; NA)	40 (14; NA)		0·18

Note: for recovered participants, numerators(n) are cumulative and use all randomised patients with available recovery data as the denominator (N).

1. *P-values obtained using chi-square test*

Appendix 9: Secondary outcomes for those with ongoing pain at weeks 26 and 52

	Number of events, number (%) of participants with at least one event Opioid	Number of events, number (%) of participants with at least one event Placebo	Fisher exact test p-value
Use of health services in patients with ongoing pain	**N = 65**	**N = 54**	
Week 26 - overall	20, 16 (24·6%)	33, 23 (42·6%)	0·049
General practitioner	4, 4 (6·2%)	11, 11 (20·4%)	
Imaging	2, 2 (3·1%)	5, 3 (5·6%)	
Other healthcare	7, 6 (9·2%)	6, 6 (11·1%)	
Physiotherapy	7, 7 (10·8%)	11, 11 (20·4%)	
Specialist doctor	0, 0 (0·0%)	0, 0 (0·0%)	
	N = 66	**N = 50**	
Week 52 - overall	47, 30 (45·5%)	27, 19 (38·0%)	0·45
General practitioner	13, 13 (19·7%)	9, 9 (18·0%)	
Imaging	7, 5 (7·6%)	4, 4 (8·0%)	
Other healthcare	11, 9 (13·6%)	8, 7 (14·0%)	
Physiotherapy	11, 11 (16·7%)	4, 4 (8·0%)	

Specialist doctor	5, 3 (4·5%)	2, 2 (4·0%)	
Use of concomitant medications in patients with ongoing pain[**]	**N = 65**	**N = 54**	
Week 26 - overall	50, 33 (50·8%)	48, 29 (53·7%)	0·85
Simple analgesia	14, 14 (21·5%)	16, 16 (29·6%)	
NSAID	14, 13 (20·0%)	15, 14 (25·9%)	
Combination opioid	6, 6 (9·2%)	5, 5 (9·3%)	
Strong opioid	3, 3 (4·6%)	6, 5 (9·3%)	
Weak opioid	0, 0 (0·0%)	0, 0 (0·0%)	
Other	13, 10 (15·4%)	6, 6 (11·1%)	
	N = 66	**N = 50**	
Week 52 - overall	62, 37 (56·1%)	34, 24 (48·0%)	0·45
Simple analgesia	17, 16 (24·2%)	7, 7 (14·0%)	
NSAID	17, 16 (24·2%)	9, 9 (18·0%)	
Combination opioid	12, 11 (16·7%)	8, 8 (16·0%)	
Strong opioid	6, 6 (9·1%)	5, 4 (8·0%)	
Weak opioid	0, 0 (0·0%)	0, 0 (0·0%)	

Other	10, 8 (12·1%)	5, 5 (10·0%)	

Appendix 10: Detailed serious adverse events

SAE categories	ICD-10 Code	details	Opioid Nevt Npt(%) N = 174	Placebo Nevt Npt(%)\ N = 173	Total Nevt Npt(%) N = 347
Outside the treatment window	C50·9	Malignant neoplasm of breast, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Outside the treatment window	G35	Multiple Sclerosis	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
Outside the treatment window	M75·1	Rotator cuff syndrome	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Related	F99	Mental disorder, not otherwise specified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Unrelated	C79·5	Secondary malignant neoplasm of bone and bone marrow	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
Unrelated	J45·9	Asthma, unspecified	1 1 (0·6%)	0 0 (0·00%)	1 1 (0·3%)
Unrelated	K80	Cholelithiasis	1 1 (0·6%)	0 0 (0·00%)	1 1 (0·3%)
Unrelated	M51·9	Intervertebral disc disorder, unspecified	1 1 (0·6%)	2 2 (1·2%)	3 3 (0·9%)
Unrelated	M54·2	Cervicalgia	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Unrelated	M54·5	Low back pain	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)

SAE categories	ICD-10 Code	details	Opioid Nevt Npt(%) N = 174	Placebo Nevt Npt(%)\ N = 173	Total Nevt Npt(%) N = 347
Unrelated	S99·9	Unspecified injury of ankle and foot	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Unrelated	T81·9	Unspecified complication of procedure	0 0 (0·00%)	1 1 (0·6%)	1 1 (0·3%)

Nevt = number of events, Npt = number of patients reporting event

Appendix 11: Detailed adverse events

		Opioid Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
ICD Codes	**Details**	**N = 174**	**N = 173**	**N = 347**
A08·4	Viral intestinal infection, unspecified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
B34·0	Adenovirus infection, unspecified site	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
B99	Other and unspecified infectious diseases	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
F41·8	Other specified anxiety disorders	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
G43·9	Migraine	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
G56·0	Carpal tunnel syndrome	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
H04·1	Other disorders of lacrimal gland	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
H53·9	Visual disturbance, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
H57·9	Disorder of eye and adnexa, unspecified	2 1 (0·6%)	0 0 (0·0%)	2 1 (0·3%)
H66·9	Otitis media, unspecified	0 0 (0·0%)	3 1 (0·6%)	3 1 (0·3%)
J00	Acute nasopharyngitis [common cold]	3 3 (1·7%)	5 5 (2·9%)	8 8 (2·3%)
J02·9	Acute pharyngitis, unspecified	0 0 (0·0%)	4 1 (0·6%)	4 1 (0·3%)
J11	Influenza, virus not identified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
J22	Unspecified acute lower respiratory infection	2 1 (0·6%)	0 0 (0·0%)	2 1 (0·3%)

		Opioid Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
ICD Codes	**Details**	**N = 174**	**N = 173**	**N = 347**
J45·9	Asthma, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
K05·0	Acute gingivitis	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
K25·9	Gastric ulcer - unspecified as acute or chronic	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
K46	Unspecified abdominal hernia	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
K58	Irritable bowel syndrome	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
K59·0	Constipation	22 13 (7·5%)	8 6 (3·5%)	30 19 (5·5%)
K92·9	Disease of digestive system, unspecified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
L29·9	Pruritus, unspecified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
M13·9	Arthritis, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
M15·8	Other polyarthrosis	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
M25·5	Pain in joint	2 2 (1·2%)	1 1 (0·6%)	3 3 (0·9%)
M50·1	Cervical disc disorder with radiculopathy	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
M51·8	Other specified intervertebral disc disorders	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
M51·9	Intervertrebral disc disorder, unspecified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
M54·2	Cervicalgia	1 1 (0·6%)	1 1 (0·6%)	2 2 (0·6%)

		Opioid Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
ICD Codes	**Details**	**N = 174**	**N = 173**	**N = 347**
M54·5	Low back pain	1 1 (0·6%)	4 3 (1·7%)	5 4 (1·2%)
M54·6	Pain in thoracic spine	1 1 (0·6%)	3 1 (0·6%)	4 2 (0·6%)
M54·8	Other dorsalgia	3 2 (1·2%)	0 0 (0·0%)	3 2 (0·6%)
M54·9	Dorsalgia, unspecified	2 2 (1·2%)	4 3 (1·7%)	6 5 (1·4%)
M62·8	Other specified disorders of muscle	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
M75·5	Bursitis of shoulder	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
M79·6	Pain in limb	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
M84·1	Nonunion of fracture [pseudarthrosis	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
N39·9	Disorder of urinary system, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R00·2	Palpitations	3 2 (1·2%)	0 0 (0·0%)	3 2 (0·6%)
R00·8	Other and unspecified abnormalities of heart bea	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R04·0	Epistaxis	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R05	Cough	1 1 (0·6%)	1 1 (0·6%)	2 2 (0·6%)
R07·4	Chest pain, unspecified	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R10·4	Other and unspecified abdominal pain	4 3 (1·7%)	0 0 (0·0%)	4 3 (0·9%)

		Opioid Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
ICD Codes	**Details**	**N = 174**	**N = 173**	**N = 347**
R11	Nausea and vomiting	25 13 (7·5%)	8 6 (3·5%)	33 19 (5·5%)
R19·4	Change in bowel habit	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R20·8	Other disturbances of skin sensation	1 1 (0·6%)	1 1 (0·6%)	2 2 (0·6%)
R21	Rash and other nonspecific skin eruption	2 1 (0·6%)	1 1 (0·6%)	3 2 (0·6%)
R22·4	Localized swelling, mass and lump, lower limb	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R25·2	Cramp and spasm	3 1 (0·6%)	0 0 (0·0%)	3 1 (0·3%)
R31	Unspecified haematuria	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
R40·0	Somnolence	6 4 (2·3%)	1 1 (0·6%)	7 5 (1·4%)
R41·0	Disorientation, unspecified	2 1 (0·6%)	0 0 (0·0%)	2 1 (0·3%)
R42	Dizziness and giddiness	6 5 (2·9%)	3 1 (0·6%)	9 6 (1·7%)
R47·8	Other and unspecified speech disturbance	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
R51	Headache	1 1 (0·6%)	9 3 (1·7%)	10 4 (1·2%)
R52·9	Pain, unspecified	3 3 (1·7%)	1 1 (0·6%)	4 4 (1·2%)
R53	Malaise and fatigue	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
R68·8	Rigors	0 0 (0·0%)	2 1 (0·6%)	2 1 (0·3%)

		Opioid Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
ICD Codes	**Details**	**N = 174**	**N = 173**	**N = 347**
S32·0	Fracture of lumbar vertebra	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
S39·9	Unspecified injury of abdomen, lower back and pelvis	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
S99·9	Unspecified injury of the foot or ankle	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
T14·1	Open wound of unspecified body region	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
T81·4	Infection following a procedure, not elsewhere classified	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
Y83·8	Other surgical procedures	0 0 (0·0%)	3 2 (1·2%)	3 2 (0·6%)

Nevt = number of events, Npt = number of patients reporting event

Appendix 12: Compliance to study medication

	Oxycodone/Naloxone (N=174)	Placebo (N=172)
GP Prescription doses of study medication - either opioid or placebo (tablets per week)		
Week-1 n*	172	172
Number of tablets - Mean (95% CI)	14·0 (13·9, 14·0)	14·1 (13·9, 14·2)
Week-2 n*	109	107
Number of tablets - Mean (95% CI)	15·1 (14·3, 15·8)	15·3 (14·4, 16·2)
Week-3 n*	42	43
Number of tablets - Mean (95% CI)	17·8 (15·8, 19·9)	16·6 (14·7, 18·5)
Week-4 n*	30	31
Number of tablets - Mean (95% CI)	18·4 (15·5, 21·4)	16·9 (14·7, 19·2)
Week-5 n*	26	20
Number of tablets - Mean (95% CI)	18·0 (14·9, 21·2)	17·2 (14·4, 19·9)
Week-6 n*	16	14
Number of tablets - Mean (95% CI)	17·7 (13·6, 21·7)	19·4 (14·8, 23·9)
Cumulative dose (over entire treatment period) - n*	173	172
Number of tablets - Mean (95% CI)	35·3 (30·9, 39·6)	34·4 (30·3, 38·5)
Self-reported dose (tablets per week)		
Week-1 n*	87	104
Number of tablets - Mean (95% CI)	11·1 (10·1, 12·0)	11·2 (10·3, 12·1)
Week-2 n*	87	102
Number of tablets - Mean (95% CI)	9·3 (7·6, 11·1)	9·0 (7·3, 10·7)
Week-3 n*	57	51
Number of tablets - Mean (95% CI)	10·0 (7·5, 12·6)	10·0 (7·3, 12·7)
Week-4 n*	55	52
Number of tablets - Mean (95% CI)	9·7 (6·8, 12·6)	8·8 (6·2, 11·4)
Week-5 n*	44	45
Number of tablets - Mean (95% CI)	8·2 (5·2, 11·2)	8·6 (6·0, 11·2)

	Oxycodone/Naloxone (N=174)	Placebo (N=172)
Week-6 n*	43	44
Number of tablets - Mean (95% CI)	6·3 (3·6, 9·0)	5·5 (3·5, 7·5)
Cumulative dose (over entire treatment period) - n*	92	108
Number of tablets - Mean (95% CI)	38·2 (30·3, 46·1)	34·1 (28·0, 40·1)
Participants consuming >=80% of the prescribed doses[1]		
Less than 20%	11/91 (12·1%)	11/108 (10·2%)
20% - <50%	9/91 (9·9%)	15/108 (13·9%)
50% - <80%	21/91 (23·1%)	21/108 (19·4%)
80% or more	50/91 (54·9%)	61/108 (56·5%)
Participants returning <20% of the prescribed doses[2]		
Less than 20%	15/47 (31·9%)	11/50 (22·0%)
20% - <50%	1/47 (2·1%)	5/50 (10·0%)
50% - <80%	0/47 (0·0%)	2/50 (4·0%)
80% or more	31/47 (66·0%)	32/50 (64·0%)
Reasons for discontinuation by doctor		
Due to pain relieved	24/78 (30·8%)	26/81 (32·1%)
Due to adverse events	4/78 (5·1%)	7/81 (8·6%)
Due to other reason	10/78 (12·8%)	7/81 (8·6%)
Assessment of participant blinding		
Opioid	29/122 (23·8%)	17/118 (14·4%)
Placebo	29/122 (23·8%)	37/118 (31·4%)
Don't know	64/122 (52·5%)	64/118 (54·2%)

Appendix 13: Protocol deviations for randomised participants

Classification	Oxycodone/Naloxone Nevt Npt(%)	Placebo Nevt Npt(%)	Total Nevt Npt(%)
Participants with protocol deviations	44/174 (25.3%)	34/173 (19.7%)	78/347 (22.5%)
Became apparent post-randomisation that participant did not fill eligibility criteria	N=174	N=173	N=347
Had bony metastasis	0 0 (0·0%)	1 1 (0·6%)	1 1 (0·3%)
Pain duration >12 weeks	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Took opioid medicines for this episode	16 16(9·2%)	8 8 (4·6%)	24 24 (6·9%)
Did not receive treatment as allocated	N=174	N=173	N=347
Never collected medication kit	4 4 (2·3%)	4 4 (2·3%)	8 8 (2·3%)
Took concomitant opioid medication during treatment period	19 18 (10·3%)	15 13 (7·5%)	34 31 (8·9%)
Was dispensed medicine from incorrect kit	1 1 (0·6%)	2 2 (1·2%)	3 3 (0·9%)
Discrepancy in data collection of procedure	N=174	N=173	N=347
Baseline questionnaire completed > 72 hours after first presentation to study doctor	2 2 (1·2%)	1 1 (0·6%)	3 3 (0·9%)
No written screening form	2 2 (1·2%)	1 1 (0·6%)	3 3 (0·9%)
Obtained Brief Pain Inventory from a proxy	3 3 (1·7%)	4 4 (2·3%)	7 7 (2·0%)
Unable to obtain baseline data	1 1 (0·6%)	0 0 (0·0%)	1 1 (0·3%)
Verbal consent received prior to enrolment, written consent followed	2 2 (1·2%)	4 4 (2·3%)	6 6 (1·7%)

Nevt = number of events, Npt = number of patients reporting event