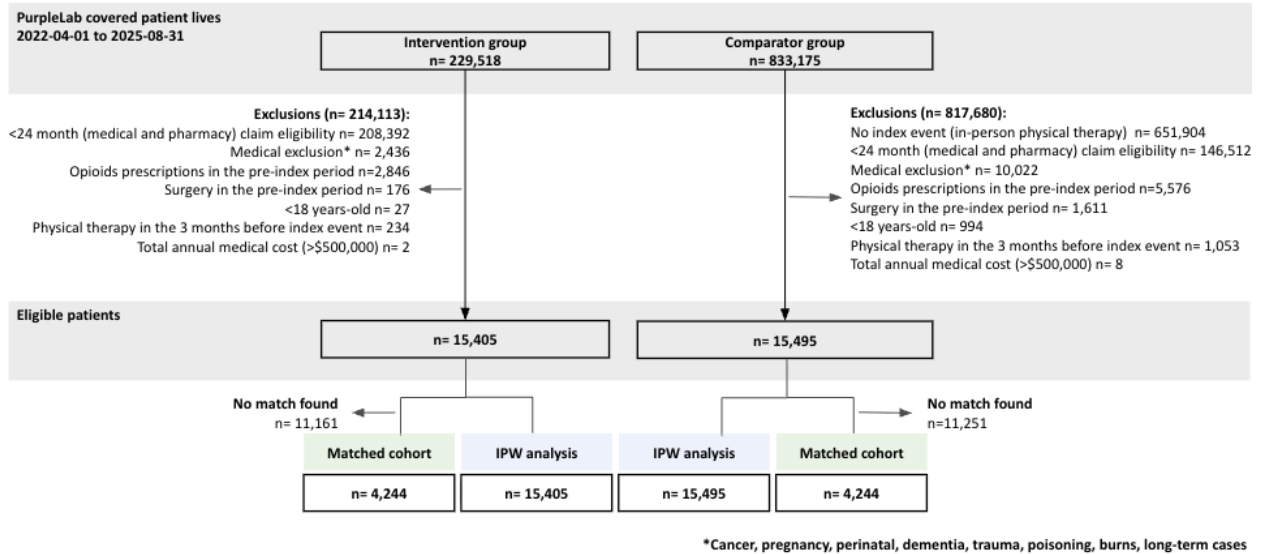


## SUPPLEMENTARY MATERIAL



**Supplementary Figure 1.** Flowchart of the study following the STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

**Abbreviations:** IPW, Inverse Probability Weighting.

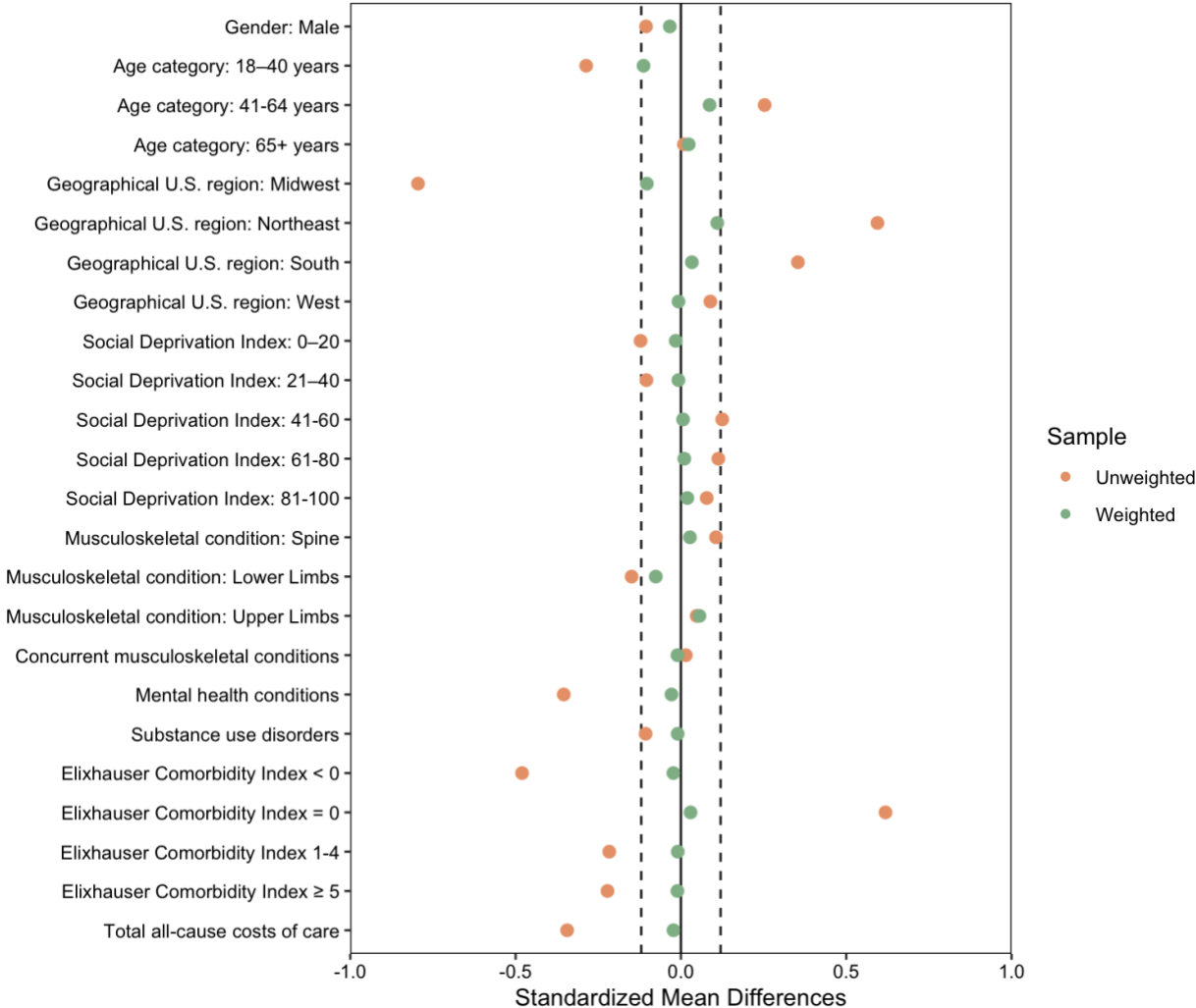
**Supplementary Table 1.** Baseline covariates included in the propensity score model used for inverse probability weighting and propensity score matching analyses.

Variables	Type	Description	Rationale for inclusion
Sex	Categorical	Female; Male	To account for differences in care access, cost structures, and treatment patterns.
Age	Categorical	18-40; 41-64; 65+	
Geographic region	Categorical	Midwest, Northeast, South, West	
Social Deprivation Index <sup>1,2</sup>	Categorical	0-20; 21-40; 41-60; 61-80; 81-100	To reflect the impact of social determinants of health.
MSK symptomatic anatomical site	Categorical	Spine (low back, upper back, neck) Lower limb (lower limb, hip, knee, ankle, foot) Upper limb (upper limb, shoulder, wrist, hand, elbow)	To reflect clinical presentation, influencing care needs
Concurrent MSK conditions	Categorical	0; 1+	To account for multimorbidity within MSK conditions, which may influence treatment intensity and prescribing patterns.
Weighted Elixhauser Comorbidity Index	Continuous	Weighted score calculated based on ICD-10 codes <sup>3,4</sup>	To account for general multimorbidity and overall health status and chronic disease complexity
Pre-index TCOC*	Continuous	Total healthcare costs for any cause	To account for overall health status and patient preferences in treatment-seeking behavior

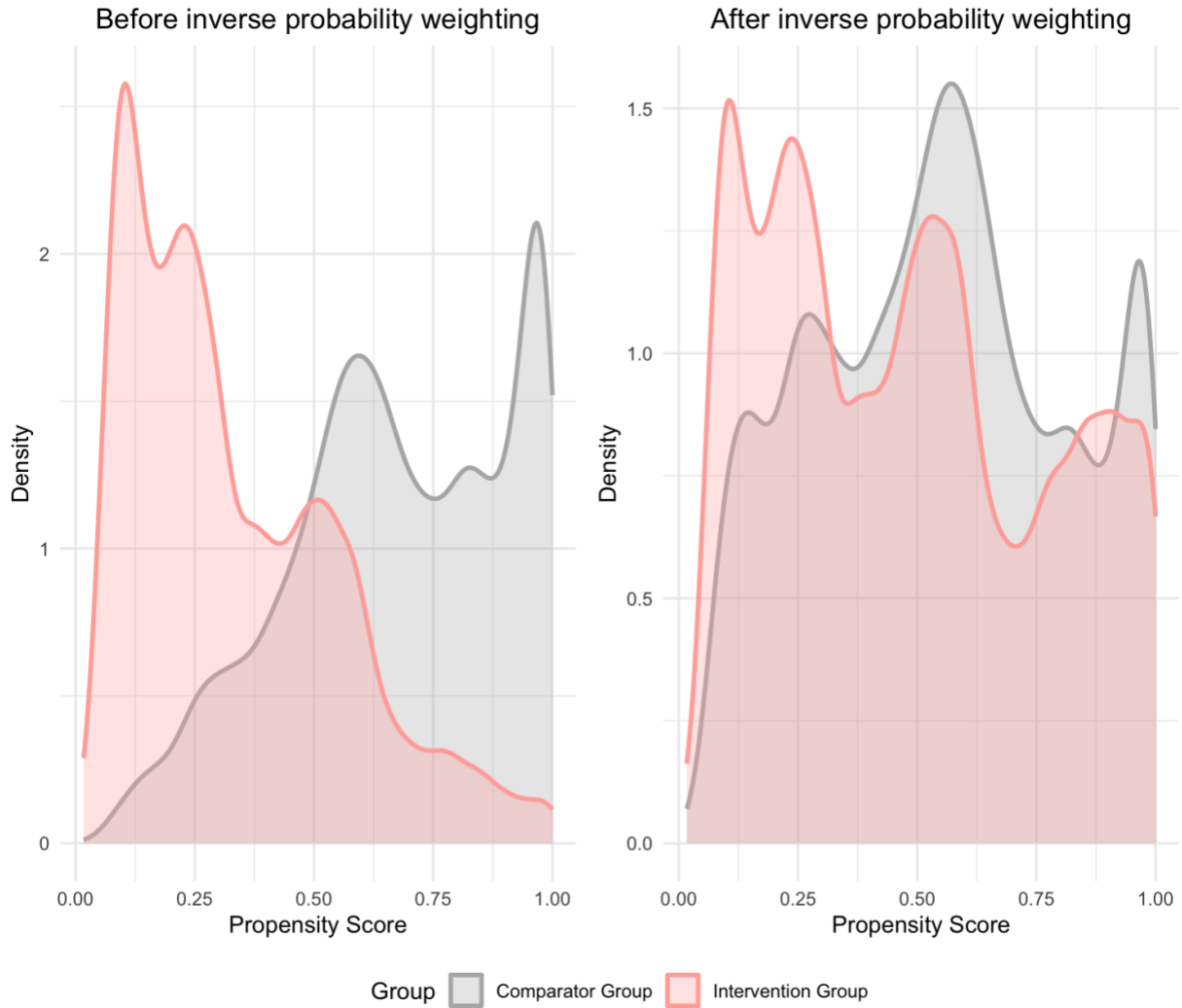
**Abbreviations:** MSK, Musculoskeletal; TCOC, Total all-cause costs of care.

**Note:** \*All costs were standardized using the Centers for Medicare & Medicaid Services (CMS) Fee Schedules and expressed in 2025 U.S. dollars.

Standardized mean differences before and after inverse probability weighting



**Supplementary Figure 2.** Standardized mean differences (SMDs) for baseline characteristics before and after inverse probability weighting.



**Supplementary Figure 3.** Distribution of propensity scores before and after inverse probability weighting.

**Supplementary Table 2.** Baseline characteristics of the intervention group (AI Care Program) and the comparator group (in-person physical therapy) in the unweighted (pre-weighting) cohort.

	Unweighted Cohort	
	Intervention Group (N=15,405)	Comparator Group (N=15,495)
<b>Demographic characteristics</b>		
<b>Sex, N (%):</b>		
Female	9,028 (58.6)	8,270 (53.4)
Male	6,377 (41.4)	7,225 (46.6)
<b>Age categories (years), N (%):</b>		
18-40	3,049 (19.8)	3,088 (19.7)
41-64	10,567 (68.6)	8,745 (56.4)
+65	1,789 (11.6)	1,755 (11.3)
<b>Geographic U.S. Region, N (%):</b>		
Midwest	5,483 (35.6)	11,221 (72.4)
Northeast	3,651 (23.7)	622 (4.0)
South	4,528 (29.4)	2,312 (14.9)
West	1,743 (11.3)	1,340 (8.6)
<b>Social Deprivation Index, N (%):</b>		
0-20	4,990 (32.4)	5,921 (38.4)
21-40	3,891 (25.3)	4,635 (29.9)
41-60	3,053 (19.8)	2,338 (15.1)
61-80	2,204 (14.3)	1,639 (10.6)
81-100	1,267 (8.2)	962 (6.2)
<b>Clinical data</b>		
<b>MSK symptomatic anatomical site, N (%):</b>		
Spine	6,661 (43.2)	5,894 (38.0)
Lower Limb	5,165 (33.5)	6,308 (40.7)
Upper Limb	3,579 (23.2)	3,293 (21.3)
<b>Concurrent MSK conditions, N (%):</b>		
0	12,981 (84.3)	13,141 (84.8)
1+	2,424 (15.7)	2,354 (15.2)

<b>Unweighted Cohort</b>		
	<b>Intervention Group</b> (N=15,405)	<b>Comparator Group</b> (N=15,495)
<b>Elixhauser Comorbidity Index, mean (SD)</b>	-0.1 (1.6)	-0.3 (3.1)
<b>Elixhauser Comorbidity Index, N (%):</b>		
<0	956 (6.2)	3,504 (22.6)
0	14,114 (91.6)	10,515 (67.9)
1-4	169 (1.1)	731 (4.7)
>5	166 (1.1)	745 (4.8)
<b>TCOC, mean (SD) (\$)</b>	746.2 (4,784.2)	3,981.8 (12,405.0)

**Abbreviations:** MSK, musculoskeletal; TCOC, total all-cause costs of care,

**Supplementary Table 3.** Comparison of opioid utilization outcomes between intervention and comparator groups using a broader definition of opioid initiation ( $\geq 1$  prescription), in the inverse probability weighted sample, adjusted for baseline covariates.

<b>Outcomes</b>	<b>Intervention group</b>	<b>Comparator group</b>	<b>Absolute Difference</b>	
	ESS = 8,977.1 Mean (95% CI)	ESS = 10,590.1 Mean (95% CI)	Mean (95% CI)	p
<b>Opioid initiation rates, %</b>	3.7 (3.1; 4.5)	7.4 (6.1; 8.8)	3.7 (2.9; 4.3)	<0.001
<b>Multiple prescriptions rates, %</b>	0.9 (0.6; 1.3)	2.3 (1.7; 3.2)	1.4 (0.9; 1.8)	<0.001
<b>Opioid prescriptions per 100 patients</b>	8.0 (4.9; 12.9)	16.7 (10.3; 27.1)	8.7 (4.1; 13.3)	0.001

**Abbreviations:** CI, confidence interval.

**Supplementary Table 4.** Comparison of unweighted (crude) opioid utilization outcomes between intervention and comparator groups ( $\geq 1$  prescription).

Outcomes	Intervention group N = 15,405 Mean (95% CI)	Comparator group N = 15,495 Mean (95% CI)	Absolute Difference	
			Mean/pp (95% CI)	p
Opioid initiation rates, %	4.9 (4.5; 5.2)	9.4 (8.9; 9.8)	4.5 (3.9; 5.1)	<0.001
Multiple prescriptions rates, %	1.4 (1.2; 1.6)	3.5 (3.2; 3.8)	2.1 (1.8; 2.5)	0.025
Opioid prescriptions per 100 patients	7.9 (7.1; 8.6)	16.8 (15.6; 18.0)	9.0 (7.6; 10.4)	<0.001

**Abbreviations:** CI, confidence intervals; DEA, Drug Enforcement Administration; MMEs, morphine milligram equivalents.

**Supplementary Table 5.** Comparison of unweighted (crude) opioid utilization outcomes between intervention and comparator groups, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

Outcomes	Intervention group	Comparator group	Absolute Difference	
	N = 15,405 Mean (95% CI)	N = 15,495 Mean (95% CI)	Mean/pp (95% CI)	p
<b>Opioid initiation rates, %</b>	2.9 (2.7;3.2)	5.1 (4.8; 5.5)	2.2 (1.8; 2.7)	<0.001
<b>Multiple prescriptions rates, %</b>	1.4 (1.2; 1.6)	3.0 (2.7; 3.2)	1.6 (1.3; 1.9)	<0.001
<b>Opioid prescriptions per 100 patients</b>	5.9 (5.2; 6.7)	11.9 (10.9; 13.1)	6.1 (4.7; 7.4)	<0.001

**Abbreviations:** CI, confidence intervals.

**Supplementary Table 6.** Subgroup analyses of opioid initiation rates in the inverse probability weighted sample, adjusted for baseline covariates, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

	ESS		Opioid initiation rates				Opioid initiation odds ratio	
	IG	CG	IG % (95% CI)	CG % (95% CI)	Absolute difference pp (95% CI)	p	Odds ratio (95% CI)	Adjusted p value <sup>1</sup>
<b>Sex</b>								
Female	5,192.7	5,523.7	2.0 (1.5; 2.7)	3.2 (2.4; 4.3)	1.2 (0.8; 1.6)	< 0.001	0.63 (0.56; 0.70)	< 0.001
Male	3,798.9	5,111.9	1.4 (1.1; 1.9)	3.3 (2.5; 4.4)	1.8 (1.3; 2.5)	< 0.001	0.42 (0.37; 0.49)	< 0.001
<b>Age</b>								
18-40	1,739.2	3,595.8	1.1 (0.8; 1.6)	2.2 (1.6; 2.9)	1.0 (0.6; 1.5)	< 0.001	0.52 (0.41; 0.67)	< 0.001
41-64	6,333.1	5,982.1	2.4 (1.7; 3.0)	4.1 (3.1; 5.5)	1.9 (1.3; 2.5)	< 0.001	0.53 (0.47; 0.59)	< 0.001
65+	9,86.8	1,213.8	3.3 (2.4; 4.5)	5.5 (4.1; 7.3)	2.2 (1.2; 3.2)	< 0.001	0.59 (0.48; 0.72)	< 0.001
<b>U.S. Region</b>								
Midwest	3,529.3	10,258.7	1.7 (1.3; 2.3)	3.6 (2.7; 4.8)	1.9 (1.3; 2.5)	< 0.001	0.46 (0.41; 0.52)	< 0.001
Northeast	3,224.6	437.8	2.4 (1.7; 3.3)	2.1 (1.5; 3.0)	-0.3 (-0.8; 0.3)	0.386	1.12 (0.86; 1.46)	0.437
South	3,219.4	1,739.9	1.8 (1.3; 2.5)	3.0 (2.2; 4.1)	1.2 (0.7; 1.8)	< 0.001	0.59 (0.49; 0.72)	< 0.001
West	1,151.0	1,049.1	1.6 (1.1; 2.3)	3.7 (2.7; 5.1)	2.1 (1.2; 3.0)	< 0.001	0.43 (0.32; 0.57)	< 0.001
<b>SDI</b>								
0-20	2,902.0	4,290.0	1.6 (1.2; 2.2)	2.8 (2.1; 3.8)	1.2 (0.7; 1.6)	< 0.001	0.58 (0.50; 0.69)	< 0.001
21-40	2,289.3	3,519.7	1.4 (1.0; 1.9)	2.6 (1.9; 3.5)	1.2 (0.7; 1.7)	< 0.001	0.54 (0.45; 0.64)	< 0.001
41-60	1,938.8	1,502.2	2.0 (1.5; 2.8)	3.8 (2.8; 5.1)	1.7 (1.0; 2.4)	< 0.001	0.53 (0.43; 0.64)	< 0.001

61-80	1,262.4	1,002.1	1.9 (1.3; 2.6)	4.2 (3.1; 5.7)	2.4 (1.5; 3.3)	< 0.001	0.43 (0.34; 0.54)	< 0.001
81-100	706.1	653.7	1.9 (1.3; 2.7)	2.8 (2.0; 4.0)	0.9 (0.2; 1.7)	< 0.001	0.66 (0.48; 0.91)	0.016
<b>MSK symptomatic anatomical site</b>								
Spine	3,899.9	3,928.1	1.7 (1.3; 2.3)	2.7 (2.0; 3.6)	1.0 (0.6; 1.4)	< 0.001	0.64 (0.55; 0.74)	< 0.001
Lower Limb	2,986.0	4,452.6	1.8 (1.3; 2.4)	4.1 (3.1; 5.4)	2.4 (1.6; 3.3)	< 0.001	0.42 (0.36; 0.48)	< 0.001
Upper Limb	2,112.7	2,278.9	1.9 (1.4; 2.6)	2.9 (2.2; 4.0)	1.0 (0.5; 1.5)	< 0.001	0.65 (0.54; 0.78)	< 0.001
<b>Mental health conditions, %:</b>								
No	9,210.8	9,311.7	2.1 (1.6; 2.8)	3.7 (2.8; 4.8)	1.6 (1.1; 2.0)	< 0.001	0.56 (0.51; 0.61)	< 0.001
Yes	314.0	1,623.8	1.0 (0.7; 1.5)	3.4 (2.5; 4.7)	2.4 (1.5; 3.3)	< 0.001	0.29 (0.21; 0.42)	< 0.001
<b>Substance use disorders, %:</b>								
No	9,013.5	1,0454.7	2.2 (1.9; 2.5)	4.0 (3.5; 4.5)	1.8 (1.5; 2.1)	<.001	0.54 (0.50; 0.59)	< 0.001
Yes	32.7	149.4	0.4 (0.1; 0.9)	3.7 (2.1; 6.4)	3.3 (1.2; 5.4)	<.001	0.11 (0.02; 0.54)	0.010

**Abbreviations:** CG, comparator group; CI, confidence interval; ESS, effective sample size; IG, intervention group; MSK, musculoskeletal; pp, percentage points; SDI, Social Deprivation Index.

**Note:** <sup>1</sup>To account for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg.

**Supplementary Table 7.** Comparison of opioid prescribing patterns among opioid users using a broader definition of opioid initiation ( $\geq 1$  prescription), among opioid users in the inverse probability weighted sample, adjusted for baseline covariates.

Outcomes	Intervention group	Comparator group	Absolute difference	
	ESS = 415.2 Mean (95% CI)	ESS = 1,015.3 Mean (95% CI)	Mean/pp (95% CI)	p
<b>MMEs per day</b>	35.5 (28.7; 43.9)	38.2 (30.9; 47.3)	2.7 (0.2; 5.1)	0.044
<b>MMEs per day<sup>1</sup> rates</b>				
$\geq 50$	17.8 (10.2; 29.2)	21.2 (12.5; 33.5)	3.3 (-1.2; 7.8)	0.159
$\geq 90$	2.1 (0.7; 5.9)	5.4 (2.2; 12.6)	3.3 (-0.3; 6.2)	0.044
<b>Opioid potency relative to morphine<sup>2</sup> rates</b>				
Lower potency than morphine	33.3 (20.5; 49.2)	23.5 (13.7; 37.1)	-9.9 (4.0; 15.7)	0.002
Equivalent to morphine	27.7 (17.1; 41.5)	28.0 (17.9; 40.9)	0.3 (-5.8; 5.3)	0.921
Greater potency than morphine	39.6 (27.2; 53.6)	53.1 (39.8; 65.9)	13.4 (7.4; 19.5)	<0.001
<b>DEA Schedule classification<sup>3</sup> rates</b>				
Schedule IV	31.3 (18.9; 47.1)	22.8 (13.2; 36.4)	8.5 (2.7; 14.3)	0.007
Schedule III	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.159
Schedule II	67.6 (50.6; 80.9)	79.5 (66.0; 88.6)	11.9 (5.3; 18.6)	0.001

**Abbreviations:** CI, confidence interval; DEA, Drug Enforcement Administration; MME, morphine milligram equivalent.

**Note:** <sup>1</sup> MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 23). <sup>2</sup>Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 24). <sup>3</sup>Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup> (Supplementary Table 24).

**Supplementary Table 8.** Comparison of unweighted (crude) opioid utilization outcomes between intervention and comparator groups ( $\geq 1$  prescription), among opioid users.

Outcomes	Intervention group N = 749	Comparator group N = 1,452	Absolute Difference	
	Mean (95% CI)	Mean (95% CI)	Mean/pp (95% CI)	p
<b>MMEs<sup>1</sup> per day</b>	37.1 (35.2; 39.0)	39.6 (38.2; 40.9)	2.5 (0.2; 4.8)	0.037
<b>MMEs<sup>1</sup> per day thresholds rates,</b>				
$\geq 50$	18.7 (15.9; 21.5)	22.4 (20.2; 24.5)	-3.7 (-7.2; -0.2)	0.044
$\geq 90$	3.2 (1.9; 4.5)	6.9 (5.6; 8.2)	-3.7 (-1.9; -0.3)	<0.001
<b>Opioid potency relative to morphine<sup>2</sup> rates</b>				
Lower potency than morphine	38.1 (34.8; 41.7)	26.4 (24.2; 28.7)	11.8 (7.7; 16.0)	<0.001
Equivalent to morphine	23.8 (20.9; 26.9)	24.2 (22.0; 26.4)	-0.4 (-4.2; -3.4)	0.831
Greater potency than morphine	49.0 (45.4; 52.6)	65.4 (62.9; 67.8)	-16.4 (-20.7; 12.0)	<0.001
<b>DEA schedule classification<sup>3</sup> rates</b>				
Schedule IV	32.8 (29.6; 36.3)	22.2 (20.2; 24.5)	10.6 (6.6; 14.6)	<0.001
Schedule III	5.3 (3.9; 7.2)	3.2 (2.4; 4.2)	2.2 (-0.3; 4.0)	0.021
Schedule II	68.8 (65.3; 72.0)	82.4 (80.3; 84.2)	-13.6 (-17.5; -9.8)	<0.001

**Abbreviations:** CI, confidence intervals; DEA, Drug Enforcement Administration; MMEs, morphine milligram equivalents.

**Notes:** <sup>1</sup>MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 17). <sup>2</sup>Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 16). <sup>3</sup>Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup> (Supplementary Table 16).

**Supplementary Table 9.** Comparison of opioid prescribing patterns among opioid users using a broader definition of opioid initiation, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

Outcomes	Intervention group	Comparator group	Absolute difference	
	ESS = 415.2 Mean (95% CI)	ESS = 1,015.3 Mean (95% CI)	Mean/pp (95% CI)	p
<b>MMEs per day</b>	43.6 (34.2; 55.6)	45.3 (35.7; 57.5)	1.7 (-1.6; 5.0)	0.377
<b>MMEs per day<sup>1</sup> rates</b>				
$\geq 50$	29.9 (16.6; 47.8)	31.1 (17.8; 48.4)	1.1 (-6.3; 8.6)	0.791
$\geq 90$	0.0 (0.0; 0.5)	0.1 (0.0; 0.5)	0.0 (-0.0; 0.1)	0.625
<b>Opioid potency relative to morphine<sup>2</sup> rates</b>				
Lower potency than morphine	33.8 (19.6; 51.7)	29.8 (17.1; 46.7)	-4.0 (-11.0; 3.1)	0.341
Equivalent to morphine	35.0 (19.1; 55.1)	34.3 (19.8; 52.5)	-0.7 (-8.8; 7.5)	0.868
Greater potency than morphine	42.3 (27.0; 59.3)	49.9 (34.3; 65.4)	7.5 (-0.3; 15.3)	0.082
<b>DEA Schedule classification<sup>3</sup> rates</b>				
Schedule IV	29.8 (16.4; 47.9)	27.4 (15.0; 44.6)	-2.4 (-9.1; 4.4)	0.538
Schedule III	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (-0.0; 0.0)	0.389
Schedule II	74.4 (55.8; 86.9)	79.2 (62.8; 89.5)	4.7 (-1.8; 11.3)	0.204

**Note:** <sup>1</sup> MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 23). <sup>2</sup> Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 24). <sup>3</sup> Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup> (Supplementary Table 24).

**Abbreviations:** CI, confidence interval; DEA, Drug Enforcement Administration; MME, morphine milligram equivalent.

**Supplementary Table 10.** Comparison of unweighted (crude) opioid utilization outcomes between intervention and comparator groups, among opioid users, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

Outcomes	Intervention group	Comparator group	Absolute Difference	
	N = 451 Mean (95% CI)	N = 751 Mean (95% CI)	Mean/pp (95% CI)	P
<b>MMEs<sup>1</sup> per day</b>	40.8 (38.7; 42.9)	41.5 (39.9; 43.2)	0.8 (-1.9; 3.4)	0.577
<b>MMEs<sup>1</sup> per day thresholds rates,</b>				
$\geq 50$	22.6 (18.8; 26.5)	24.6 (21.6; 27.6)	1.9 (-2.9; 6.9)	0.432
$\geq 90$	4.4 (2.6; 6.3)	3.9 (2.6; 5.2)	-0.1 (-1.8; 1.7)	0.640
<b>Opioid potency relative to morphine<sup>2</sup> rates</b>				
Lower potency than morphine	42.6 (38.1; 47.2)	34.8 (31.5; 38.1)	-7.8 (-13.5; 2.2)	0.007
Equivalent to morphine	22.8 (19.2; 26.9)	25.2 (22.3; 28.4)	2.4 (-2.5; 7.0)	0.342
Greater potency than morphine	52.3 (47.7; 56.9)	64.5 (61.1; 67.7)	12.2 (6.5; 17.8)	<0.001
<b>DEA schedule classification<sup>3</sup> rates</b>				
Schedule IV	37.9 (33.6; 42.5)	31.1 (28.0; 34.4)	-6.8 (-12.3; -1.3)	0.016
Schedule III	4.9 (3.2; 7.3)	3.8 (2.6; 5.3)	-1.1 (-3.5; 1.3)	0.360
Schedule II	68.7 (64.3; 72.8)	79.3 (76.3; 82.0)	10.6 (5.4; 15.7)	<0.001

**Abbreviations:** CI, confidence intervals; DEA, Drug Enforcement Administration; MMEs, morphine milligram equivalents.

**Notes:** <sup>1</sup>MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 23). <sup>2</sup>Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 24). <sup>3</sup>Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup> (Supplementary Table 24).

**Supplementary Table 11.** Subgroup analyses of mean daily MMEs and high-dose thresholds ( $\geq 50$  and  $\geq 90$  MMEs/day) rates among opioid users in the inverse probability weighted sample, adjusted for baseline covariates, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

ESS		Mean MMEs/day				Rates for MMEs/day thresholds								
						$\geq 50$ MMEs/day				$\geq 90$ MMEs/day				
IG	CG	IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference		
		Mean (95% CI)	Mean (95% CI)	Diff (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	% 1(95% CI)	% (95% CI)	pp (95% CI)	p	
<b>Sex</b>														
Female	156.6	300.4	41.6 (32.5; 53.1)	45.4 (35.6; 57.8)	3.8 (-0.2; 7.8)	0.063	24.8 (13.4; 41.2)	31.5 (17.7; 48.9)	6.5 (-2.6; 15.6)	0.164	0.1 (0.0; 0.6)	0.1 (0.0; 0.8)	0.1 (-0.1; 0.2)	0.252
Male	92.9	92.9	46.8 (36.1; 60.6)	44.9 (34.9; 57.9)	-1.8 (- 7.0; 3.4)	0.500	37.3 (20.2; 58.4)	29.9 (16.5; 47.9)	-7.4 (- 19.5; 4.7)	0.231	0.1 (0.0; 0.4)	0.1 (0.0; 0.4)	-0.1 (-0.2; 0.1)	0.433
<b>Age</b>														
18-40	29.5	110.0	37.9 (29.8; 49.7)	43.4 (33.9; 55.6)	5.5 (-0.8; 11.8)	0.086	24.8 (13.4; 47.3)	30.8 (15.8; 51.2)	6.0 (- 12.5; 24.5)	0.524	1.0 (0.1; 7.4)	3.4 (0.5; 18.3)	2.2 (-3.0; 7.3)	0.417
41-64	180.3	180.3	45.0 (35.2; 57.6)	45.4 (35.6; 57.9)	0.4 (-6.5; 5.7)	0.843	34.6 (20.4; 52.8)	32.5 (19.3; 50.2)	-1.7 (- 10.8; 7.5)	0.721	3.9 (0.7; 19.3)	3.2 (0.7; 13.4)	-0.7 (-4.2; 2.7)	0.675
65+	40.5	101.1	48.2 (37.1; 62.6)	52.8 (40.7; 68.3)	4.5 (-2.4; 11.3)	0.242	34.9 (15.5; 61.9)	42.5 (24.9; 62.1)	7.5 (- 11.9; 26.9)	0.449	4.4 (0.8; 23.7)	10.1 (2.3; 35.5)	5.7 (-3.9; 15.4)	0.243
<b>U.S. Region</b>														

ESS			Mean MMEs/day				Rates for MMEs/day thresholds							
							≥50 MMEs/day				≥90 MMEs/day			
Midwest	96.8	546.2	43.1 (33.9; 54.9)	43.5 (34.7; 54.4)	0.4 (-3.9; 4.6)	0.871	36.9 (20.5; 56.9)	33.1 (19.8; 50.2)	-3.6 (- 14.1; 6.9)	0.506	0.1 (0.0; 0.5)	0.1 (0.0; 0.4)	0.0 (-0.1; 0.1)	0.573
Northeast	124.4	16.7	41.6 (32.5; 53.3)	38.6 (29.5; 50.4)	-3.0 (- 9.6; 3.6)	0.352	21.0 (9.9; 39.2)	10.1 (2.6; 32.1)	-10.9 (- 26.0; 4.2)	0.155	0.0 (0.0; 0.4)	0.1 (0.0; 1.0)	0.1 (-0.1; 0.3)	0.528
South	135.0	71.0	40.8 (31.9; 52.3)	47.9 (37.1; 61.9)	7.0 (1.3; 13.7)	0.035	26.2 (13.2; 45.3)	44.4 (24.9; 65.9)	18.3 (2.2; 34.4)	0.026	0.1 (0.0; 0.6)	0.1 (0.0; 0.6)	0.0 (-0.1; 0.1)	0.989
West	15.6	51.0	47.7 (35.5; 63.9)	52.1 (38.2; 71.2)	4.5 (-5.1; 18.1)	0.517	37.7 (17.5; 63.2)	41.1 (21.9; 63.3)	3.4 (- 19.7; 26.5)	0.773	0.2 (0.0; 1.2)	0.1 (0.0; 1.0)	-0.0 (-0.3; 0.2)	0.820
<b>SDI</b>														
0-20	83.4	221.5	42.5 (32.9; 54.9)	44.9 (35.0; 57.4)	2.4 (-3.8; 8.5)	0.451	31.4 (16.8; 50.9)	28.7 (15.6; 46.6)	-2.7 (- 15.7; 10.3)	0.684	0.0 (0.0; 0.3)	0.2 (0.0; 0.9)	0.1 (-0.1; 0.4)	0.262
21-40	68.0	142.2	45.6 (35.3; 58.9)	49.6 (38.5; 64.0)	4.0 (-2.3; 10.4)	0.210	36.2 (17.8; 59.8)	37.7 (21.6; 50.2)	1.5 (- 14.7; 17.7)	0.855	0.1 (0.0; 0.6)	0.2 (0.0; 1.0)	0.1 (-0.1; 0.3)	0.318
41-60	63.5	98.3	45.2 (34.7; 58.9)	44.5 (34.5; 57.4)	-0.7 (- 8.2; 6.0)	0.827	33.9 (17.6; 55.2)	29.4 (15.5; 48.7)	-4.5 (- 19.3; 10.2)	0.549	0.2 (0.0; 1.0)	0.0 (0.0; 0.3)	-0.1 (-0.4; 0.1)	0.353
61-80	27.3	82.5	43.3 (32.9; 56.9)	43.5 (33.3; 56.9)	0.2 (-6.7; 6.9)	0.946	20.5 (8.5; 41.8)	29.6 (15.5; 49.1)	9.0 (-7.1; 25.2)	0.273	0.1 (0.0; 0.8)	0.1 (0.0; 0.7)	-0.0 (-0.2; 0.2)	0.778
81-100	15.5	33.8	42.5 (30.5; 59.4)	44.5 (33.9; 58.3)	2.0 (-7.3; 13.4)	0.744	20.1 (6.4; 48.3)	36.8 (17.2; 62.0)	16.7 (- 8.3; 41.7)	0.191	0.3 (0.0; 1.8)	0.0 (0.0; 0.0)	-0.3 (-0.8; 0.2)	0.320

MSK symptomatic anatomical site	ESS		Mean MMEs/day				Rates for MMEs/day thresholds							
							≥50 MMEs/day				≥90 MMEs/day			
Spine	99.1	192.2	43.3 (34.4; 54.6)	41.1 (32.8; 51.5)	-2.2 (- 6.0; 2.5)	0.360	28.7 (14.9; 47.9)	25.9 (13.7; 43.5)	-2.7 (- 14.9; 9.4)	0.659	0.1 (0.0; 0.6)	0.0 (0.0; 0.2)	-0.1 (-0.2; 0.1)	0.408
Lower Limb	135.4	270.2	48.5 (38.1; 61.8)	50.9 (40.5; 64.2)	2.5 (-3.1; 8.1)	0.390	42.9 (25.0; 62.8)	39.9 (24.0; 58.4)	-2.9 (- 14.5; 8.7)	0.621	0.2 (0.0; 1.2)	0.3 (0.1; 1.3)	0.1 (-0.1; 0.3)	0.487
Upper Limb	41.6	103.0	36.9 (28.9; 47.1)	39.8 (31.4; 50.4)	2.9 (-3.6; 8.4)	0.296	13.8 (5.4; 31.0)	20.9 (9.5; 39.9)	7.1 (-5.6; 19.8)	0.270	0.0 (0.0; 0.3)	0.1 (0.0; 0.4)	0.1 (-0.1; 0.2)	0.395
<b>Mental health conditions, %:</b>														
No	253.6	495.1	43.3 (34.5; 54.3)	44.5 (35.7; 55.5)	1.4 (-1.4; 4.2)	0.335	29.5 (16.9; 46.3)	30.9 (18.1; 47.6)	1.4 (-6.1; 9.0)	0.708	0.1 (0.0; 0.4)	0.1 (0.0; 0.4)	0.0 (-0.0; 0.1)	0.697
Yes	5.8	95.6	38.2 (27.6; 52.9)	46.9 (35.7; 61.7)	8.7 (-2.1; 18.8)	0.091	34.4 (6.6; 79.4)	30.3 (15.3; 51.1)	-4.1 (- 45.8; 37.6)	0.849	0.0 (0.0; 0.0)	0.2 (0.0; 0.8)	0.2 (-0.1; 0.4)	0.236
<b>Substance use disorders, %:</b>														
No	247.5	557.3	37.4 (33.8; 41.5)	38.8 (35.0; 43.1)	1.4 (-4.2; 3.9)	0.335	15.9 (9.6; 25.3)	16.5 (10.3; 25.4)	0.6 (-4.2; 5.4)	0.809	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)	0.0 (-0.0; 0.1)	0.570
Yes	5.8	10.7	18.5 (15.9; 23.0)	57.3 (37.0; 88.8)	38.8 (14.0; 63.7)	0.002	0.0 (0.0; 0.0)	57.6 (26.9; 83.4)	57.6 (25.7; 89.5)	< 0.001	0.0 (0.0; 0.0)	0.2 (0.0; 2.7)	0.2 (-0.3; 0.6)	0.494

**Abbreviations:** CG, comparator group; CI, confidence interval; ESS, effective sample size; IG, intervention group; MME, morphine milligram equivalent; MSK, musculoskeletal; pp, percentage points; SDI, Social Deprivation Index.

**Note:** MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 23).

**Supplementary Table 12.** Subgroup analyses of opioid potency rates relative to morphine among opioid-receiving patients in the inverse probability weighted sample, adjusted for baseline covariates, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

ESS		Opioid potency relative to morphine												
		Lower potency than morphine				Equivalent to morphine				Greater potency than morphine				
IG	CG	IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference		
		% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	
<b>Sex</b>														
Female	156.6	300.4	36.8 (21.5; 55.3)	27.9 (15.7; 44.7)	-8.9 (- 18.0; 0.3)	0.057	30.7 (16.2; 50.4)	33.6 (19.2; 51.9)	2.9 (-6.7; 12.5)	0.555	41.3 (25.7; 59.0)	53.2 (36.8; 68.9)	11.8 (1.9; 21.8)	0.020
Male	92.9	267.3	28.7 (15.3; 47.2)	32.7 (18.7; 50.7)	4.0 (-5.7; 13.7)	0.419	40.9 (22.0; 63.0)	34.6 (19.6; 53.4)	-6.4 (- 19.1; 6.4)	0.328	45.2 (28.2; 63.5)	45.8 (29.9; 62.6)	0.6 (- 10.6; 11.7)	0.921
<b>Age</b>														
18-40	29.5	110	34.6 (17.3; 57.1)	24.7 (12.8; 42.4)	-9.8 (- 26.4; 6.8)	0.247	28.4 (11.2; 55.3)	39.4 (22.2; 59.6)	11.0 (- 10.1; 32.1)	0.306	38.7 (19.5; 62.2)	52.1 (34.5; 69.2)	13.4 (- 7.6; 34.4)	0.210
41-64	180.3	362.3	41.9 (25.8; 60.0)	37.9 (22.9; 55.6)	-4.0 (- 13.1; 5.1)	0.387	33.2 (18.3; 52.4)	32.7 (18.9; 50.3)	-0.5 (- 9.4; 8.4)	0.909	42.9 (28.2; 59.0)	46.3 (31.6; 61.7)	3.4 (-5.7; 12.4)	0.468
65+	40.5	101.1	37.1 (19.3; 59.2)	34.4 (19.2; 53.5)	-2.7 (- 19.1; 13.6)	0.743	37.3 (17.9; 61.7)	28.8 (15.2; 47.8)	-8.4 (- 27.1; 10.2)	0.376	39.3 (22.5; 59.1)	58.5 (40.7; 74.4)	19.2 (2.5; 35.9)	0.024
<b>U.S. Region</b>														

ESS		Opioid potency relative to morphine												
		Lower potency than morphine				Equivalent to morphine				Greater potency than morphine				
IG	CG	IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference		
				% (95% CI)	% (95% CI)			pp (95% CI)	p			% (95% CI)	% (95% CI)	pp (95% CI)
Midwest	96.8	546.2	29.8 (16.5; 47.8)	28.5 (16.9; 44.0)	-1.3 (-10.3; 7.8)	0.781	33.3 (17.1; 54.8)	34.1 (19.9; 52.0)	0.8 (-9.7; 11.4)	0.878	54.2 (36.5; 71.0)	55.9 (40.7; 70.1)	1.7 (-9.1; 12.5)	0.762
Northeast	124.4	16.7	31.7 (17.3; 50.8)	26.8 (9.9; 54.9)	-5.0 (-26.7; 16.7)	0.653	25.7 (12.2; 46.2)	22.2 (7.6; 50.0)	-3.4 (-23.6; 16.7)	0.740	49.0 (31.3; 67.0)	61.8 (34.0; 83.5)	12.7 (-12.4; 37.8)	0.320
South	135	71	48.6 (30.3; 67.3)	32.5 (17.4; 52.4)	-16.1 (-30.2; -1.9)	0.026	35.8 (19.1; 56.7)	26.2 (12.6; 46.8)	-9.5 (-23.9; 4.8)	0.194	26.0 (14.5; 42.1)	48.3 (30.3; 66.8)	22.3 (8.2; 36.4)	0.002
West	15.6	51	22.9 (8.5; 48.5)	30.2 (15.4; 50.8)	7.3 (-13.1; 27.8)	0.481	44.4 (16.9; 75.8)	55.5 (33.0; 76.0)	11.1 (-20.1; 42.3)	0.486	43.5 (20.4; 69.8)	40.5 (23.5; 60.2)	-3.0 (-28.0; 22.0)	0.815
<b>SDI</b>														
0-20	83.4	221.5	29.3 (15.5; 48.3)	27.2 (14.8; 44.6)	-2.0 (-12.4; 8.4)	0.703	38.3 (19.1; 61.9)	33.0 (18.0; 52.5)	-5.3 (-19.7; 9.2)	0.477	54.9 (35.2; 73.2)	52.2 (34.8; 69.1)	-2.8 (-15.5; 10.0)	0.672
21-40	68	142.2	21.3 (10.0; 39.7)	25.9 (13.9; 43.2)	4.6 (-6.3; 15.6)	0.408	36.2 (18.4; 58.8)	32.0 (17.0; 52.0)	-4.2 (-18.6; 10.2)	0.568	44.7 (26.3; 64.6)	56.3 (38.3; 72.7)	11.6 (-2.7; 25.9)	0.113
41-60	63.5	98.3	51.4 (31.0; 71.3)	28.8 (14.8; 48.4)	-22.6 (-37.8; -7.3)	0.004	30.8 (14.4; 54.1)	35.7 (19.2; 56.5)	4.9 (-10.1; 19.9)	0.523	26.1 (12.9; 45.6)	55.5 (36.5; 73.0)	29.4 (14.1; 44.6)	0.000
61-80	27.3	82.5	32.2 (15.4; 55.4)	30.4 (16.1; 50.0)	-1.7 (-20.0; 16.5)	0.851	28.6 (12.3; 53.3)	37.8 (20.0; 59.6)	9.3 (-8.9; 27.4)	0.317	53.7 (32.4; 73.7)	48.7 (30.2; 67.6)	-5.0 (-23.7; 13.7)	0.600

ESS			Opioid potency relative to morphine											
			Lower potency than morphine				Equivalent to morphine				Greater potency than morphine			
IG	CG		IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference	
			% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p
81-100	15.5	33.8	36.3 (15.0; 64.8)	41.7 (21.3; 65.4)	5.4 (-22.2; 33.0)	0.701	37.9 (14.6; 68.7)	36.1 (16.8; 61.2)	-1.8 (- 31.8; 28.1)	0.904	32.6 (14.0; 59.1)	31.0 (14.9; 53.6)	-1.6 (- 26.1; 22.9)	0.897
<b>MSK symptomatic anatomical site</b>														
Spine	99.1	192.2	31.1 (17.5; 48.9)	35.0 (20.6; 52.8)	4.0 (-6.6; 14.5)	0.464	39.7 (21.5; 61.4)	36.0 (20.2; 55.6)	-3.7 (- 16.6; 9.2)	0.572	44.7 (28.0; 62.6)	43.6 (27.9; 60.7)	18.6 (7.9; 29.3)	0.853
Lower Limb	135.4	270.2	43.7 (26.4; 62.7)	30.1 (17.3; 47.0)	-13.6 (- 24.5; -2.7)	0.015	30.4 (15.7; 50.8)	32.7 (18.3; 51.2)	2.3 (-8.3; 12.8)	0.677	35.0 (20.4; 53.1)	53.6 (37.3; 69.2)	-1.1 (- 12.3; 10.2)	0.001
Upper Limb	41.6	103	27.0 (13.1; 47.6)	21.3 (10.5; 38.3)	-5.8 (- 20.3; 8.7)	0.433	30.9 (13.7; 55.7)	29.8 (15.3; 49.8)	-1.1 (- 17.7; 15.5)	0.896	48.5 (28.5; 69.0)	52.7 (34.3; 70.4)	4.2 (- 13.9; 22.3)	0.650
<b>Mental health conditions, %:</b>														
No	253.6	495.1	38.5 (23.4; 56.2)	33.3 (19.9; 50.0)	-5.2 (- 12.8; 2.4)	0.176	30.5 (16.3; 49.7)	30.9 (17.4; 48.7)	0.4 (-7.1; 7.9)	0.909	41.4 (26.5; 58.0)	49.6 (34.4; 64.8)	8.2 (0.3; 16.1)	0.041
Yes	5.8	95.6	18.4 (3.5; 58.5)	29.1 (15.1; 48.6)	10.7 (- 16.4; 37.9)	0.439	50.7 (15.1; 85.7)	35.9 (19.4; 56.6)	-14.8 (- 56.2; 26.6)	0.483	52.6 (16.4; 86.2)	48.3 (30.3; 66.7)	-4.3 (- 45.5; 37.0)	0.840
<b>Substance use disorders, %:</b>														

ESS			Opioid potency relative to morphine											
			Lower potency than morphine				Equivalent to morphine				Greater potency than morphine			
IG	CG		IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference	
			% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p
No	247.5	557.3	31.0 (21.7; 42.2)	27.1 (19.0; 37.1)	-3.9 (- 10.6; 2.7)	0.248	27.4 (17.6; 39.9)	27.0 (19.0; 36.9)	-0.4 (- 7.5; 6.8)	0.921	54.6 (42.4; 66.3)	61.8 (51.0; 71.6)	7.2 (-0.6; 15.0)	0.070
Yes	1	10.7	0.0 (0.0; 0.0)	39.2 (15.5; 69.3)	39.2 (9.2; 69.1)	0.010	100.0 (100.0; 100.0)	33.9 (10.0; 70.4)	-66.1 (- 100.4; - 31.8)	0.000	0.0 (0.0; 0.0)	42.5 (18.9; 70.2)	42.5 (14.2; 70.8)	0.003

**Abbreviations:** CG, comparator group; CI, confidence interval; ESS, effective sample size; IG, intervention group; MSK, musculoskeletal; pp, percentage points; SDI, Social Deprivation Index.

**Note:** Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 24).

**Supplementary Table 13.** Subgroup analyses of opioid prescribing rates by Drug Enforcement Administration (DEA) schedule classification among opioid-receiving patients in the inverse probability weighted sample, adjusted for baseline covariates, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

ESS			DEA schedule classification											
			Schedule IV				Schedule III				Schedule II			
IG	CG		IG	CG	Absolute difference		IG	CG	Absolute difference		IG	CG	Absolute difference	
			% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p	% (95% CI)	% (95% CI)	pp (95% CI)	p
<b>Sex</b>														
Female	156.6	300.4	32.9 (18.3; 51.9)	26.1 (14.0; 43.2)	-6.8 (-15.7; 2.0)	0.131	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.430	72.4 (52.9; 85.9)	81.7 (65.8; 91.2)	9.3 (0.5; 18.1)	0.038
Male	92.9	267.3	24.8 (12.6; 43.1)	29.6 (16.1; 48.0)	4.8 (-4.5; 14.1)	0.310	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.497	78.5 (59.9; 89.9)	75.7 (57.2; 87.9)	-2.7 (-11.5; 6.0)	0.540
<b>Age</b>														
18-40	29.5	110	32.0 (15.4; 54.9)	20.1 (9.8; 36.9)	-11.8 (-28.0; 4.3)	0.150	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.626	68.7 (44.9; 85.6)	87.2 (72.9; 94.5)	18.4 (1.5; 35.3)	0.033
41-64	180.3	362.3	35.3 (20.3; 53.9)	34.1 (19.6; 52.4)	-1.2 (-10.0; 7.6)	0.787	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.266	68.0 (48.5; 82.7)	71.0 (52.3; 84.6)	3.1 (-5.6; 11.7)	0.489
65+	40.5	101.1	35.5 (18.1; 57.9)	33.1 (17.9; 52.7)	-2.4 (-18.4; 13.6)	0.766	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.754	70.7 (47.7; 86.5)	76.7 (57.4; 89.0)	6.1 (-9.7; 21.8)	0.451
<b>U.S. Region</b>														

ESS			DEA schedule classification											
			Schedule IV				Schedule III				Schedule II			
Midwest	96.8	546.2	26.8 (14.1; 44.8)	28.0 (16.1; 44.1)	1.2 (-7.6; 10.1)	0.785	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.393	80.9 (64.4; 90.8)	82.0 (67.9; 90.7)	1.1 (-6.5; 8.7)	0.778
Northeast	124.4	16.7	30.7 (16.2; 50.3)	23.2 (7.6; 52.4)	-7.5 (- 29.3; 14.3)	0.500	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.554	75.8 (56.2; 88.5)	84.2 (56.3; 95.6)	8.4 (- 10.2; 26.9)	0.377
South	135	71	40.0 (22.9; 59.9)	27.9 (14.1; 47.9)	-12.0 (- 25.8; 1.7)	0.086	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.230	58.0 (36.8; 76.6)	74.0 (53.6; 87.6)	16.0 (1.9; 30.1)	0.026
West	15.6	51	22.2 (8.3; 47.4)	25.5 (12.2; 45.9)	3.3 (- 16.0; 22.6)	0.734	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.348	82.8 (59.5; 94.1)	78.7 (58.8; 90.6)	-4.1 (- 20.7; 12.5)	0.630
<b>SDI</b>														
0-20	83.4	221.5	26.1 (13.1; 45.1)	23.4 (12.1; 40.4)	-2.7 (- 12.6; 7.3)	0.597	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.842	78.3 (59.5; 89.9)	79.9 (63.1; 90.3)	1.6 (-7.7; 10.9)	0.735
21-40	68	142.2	19.3 (8.5; 38.0)	23.7 (12.2; 41.1)	4.4 (-6.1; 15.0)	0.410	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.884	81.3 (62.1; 92.0)	82.5 (66.5; 91.8)	1.2 (-9.3; 11.7)	0.820
41-60	63.5	98.3	39.3 (21.2; 61.0)	27.8 (13.8; 48.1)	-11.5 (- 26.4; 3.4)	0.130	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.134	58.8 (36.2; 78.3)	82.0 (63.9; 92.1)	23.1 (6.4; 39.9)	0.007
61-80	27.3	82.5	31.3 (14.4; 55.1)	27.5 (13.8; 47.3)	-3.8 (- 21.7; 14.2)	0.681	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.314	82.3 (62.9; 92.7)	77.1 (57.6; 89.3)	-5.2 (- 18.5; 8.1)	0.444
81-100	15.5	33.8	31.9 (12.8; 59.9)	38.2 (18.4; 62.8)	6.3 (- 19.0; 31.5)	0.626	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.778	69.2 (42.8; 87.0)	67.1 (41.7; 85.4)	-2.0 (- 24.6; 20.5)	0.860

ESS				DEA schedule classification																	
				Schedule IV				Schedule III				Schedule II									
<b>MSK symptomatic anatomical site</b>																					
Spine	99.1	192.2		28.3 (15.4; 46.1)	32.2 (18.2; 50.4)	-13.2 (- 24.1; - 2.3)	0.459	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.483	76.3 (57.4; 88.5)	74.5 (55.8; 87.2)	12.7 (1.5; 24.0)	0.702						
Lower Limb	135.4	270.2		40.8 (23.6; 60.7)	27.6 (15.2; 44.8)	3.9 (-6.5; 14.4)	0.018	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.564	68.5 (47.1; 84.2)	81.2 (65.4; 90.8)	-1.8 (- 10.8; 7.3)	0.027						
Upper Limb	41.6	103		18.7 (8.0; 37.7)	17.6 (8.1; 34.1)	-1.1 (- 13.7; 11.6)	0.871	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.153	78.2 (57.4; 90.5)	81.7 (62.9; 92.2)	3.5 (- 10.3; 17.4)	0.615						
<b>Mental health conditions, %:</b>																					
No	253.6	495.1		34.0 (19.7; 51.9)	31.1 (18.0; 48.1)	-2.9 (- 10.3; 4.4)	0.436	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.213	74.9 (57.5; 86.8)	79.9 (64.8; 89.5)	5.0 (-1.7; 11.6)	0.142						
Yes	5.8	95.6		21.5 (4.1; 63.9)	25.0 (12.1; 44.6)	3.5 (- 26.6; 33.6)	0.821	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.181	77.8 (35.3; 95.8)	77.6 (57.0; 90.1)	-0.2 (- 30.4; 30.0)	0.990						
<b>Substance use disorders, %:</b>																					
No	247.5	557.3		25.9 (17.5; 36.6)	23.6 (16.0; 33.4)	-2.3 (-8.5; 3.8)	0.458	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)	-0.0 (- 0.1; 0.0)	0.315	76.8 (66.2; 84.8)	81.3 (72.3; 87.9)	4.5 (-1.4; 10.4)	0.134						
Yes	1.0	10.7		0.0 (0.0; 0.0)	38.0 (14.1; 69.6)	38.0 (7.0; 69.0)	0.016	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (-0.0; 0.0)	0.792	100.0 (100.0; 100.0)	72.6 (39.6; 91.4)	-27.4 (- 55.2; 0.3)	0.053						

**Abbreviations:** CG, comparator group; CI, confidence interval; DEA, Drug Enforcement Administration; ESS, effective sample size; IG, intervention group; MSK, musculoskeletal; pp, percentage points; SDI, Social Deprivation Index.

**Note:** Drug schedule categorized according to U.S. Drug Enforcement Administration (DEA) controlled substance schedules<sup>8,9</sup> (Supplementary Table 24).

**Supplementary Table 14.** Comparison of unweighted (crude) engagement.

<b>Engagement</b>	<b>Intervention group</b> N = 15,405	<b>Comparator group</b> N = 15,495
<b>Sessions, Median (IQR)</b>	13 (9; 23)	6 (3; 11)
<b>Proportion of patients with <math>\leq 3</math> sessions, N (%)</b>	983 (6.4)	4,993 (32.2)

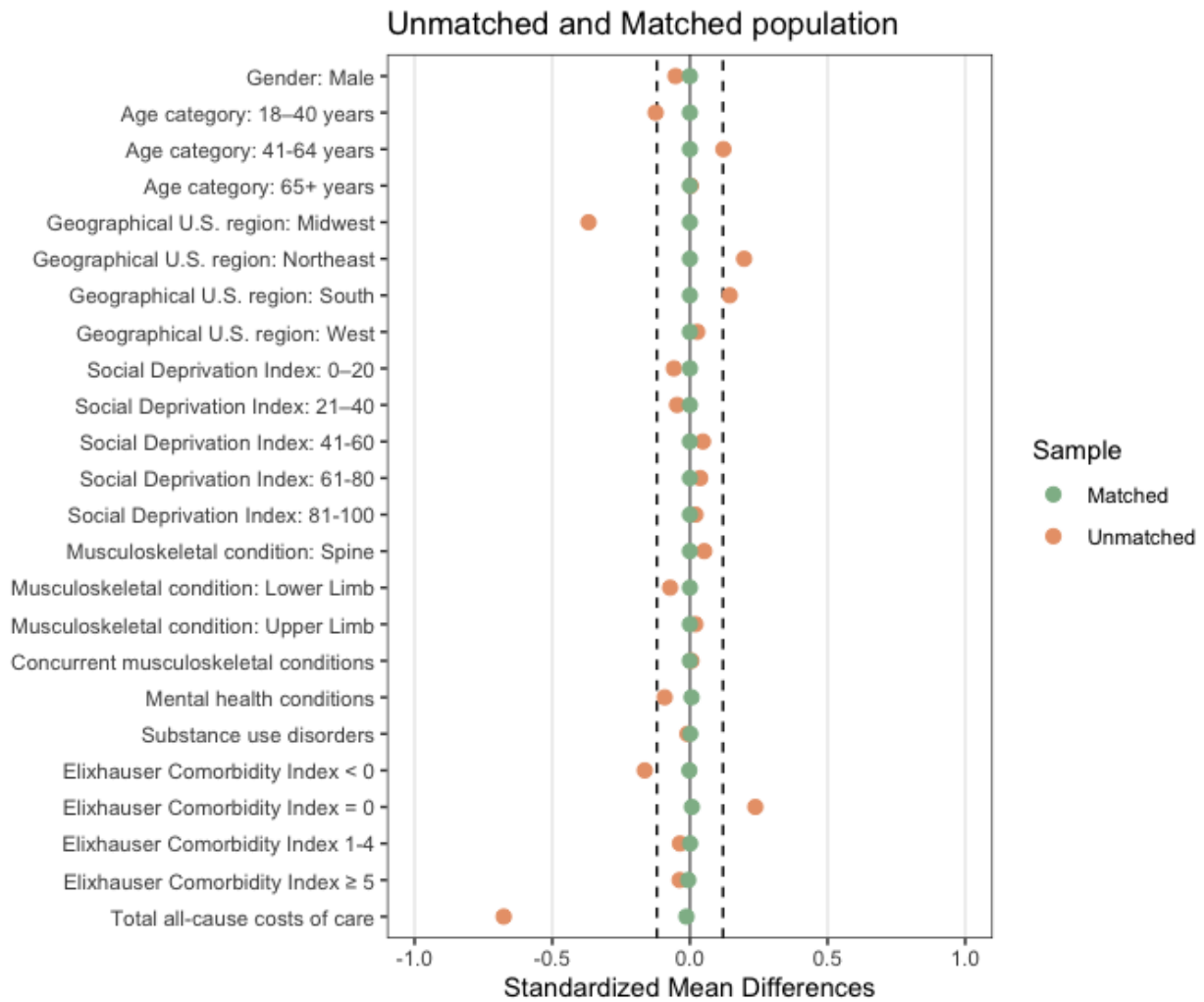
**Abbreviations:** Interquartile range.

**Supplementary Table 15.** Baseline characteristics of the intervention group (AI Care Program) and the comparator group (in-person physical therapy) in the matched population.

	<b>Intervention Group</b> (N=4,244)	<b>Comparator Group</b> (N=4,244)	<b>P</b>
<b>Demographic characteristics</b>			
<b>Sex, N (%):</b>			1.00
Female	2,431 (57.3)	2,431 (57.3)	
Male	1,813 (42.7)	1,813 (42.7)	
<b>Age categories (years), N (%):</b>			1.00
18-40	1,026 (24.2)	1,026 (24.2)	
41-64	2,854 (67.2)	2,854 (67.2)	
+65	364 (8.6)	364 (8.6)	
<b>Geographic U.S. Region, N (%):</b>			1.00
Midwest	3,283 (77.4)	3,283 (77.4)	
Northeast	94 (2.2)	94 (2.2)	
South	631 (14.9)	631 (14.9)	
West	236 (5.6)	236 (5.6)	
<b>Social Deprivation Index, N (%):</b>			1.00
0-20	1,673 (39.4)	1,673 (39.4)	
21-40	1,162 (27.4)	1,162 (27.4)	
41-60	687 (16.2)	687 (16.2)	
61-80	454 (10.7)	454 (10.7)	
81-100	268 (6.3)	268 (6.3)	
<b>Clinical data</b>			
<b>MSK symptomatic anatomical site, N (%):</b>			1.00
Spine	1,829 (43.1)	1,829 (43.1)	
Lower Limb	1,509 (35.6)	1,509 (35.6)	
Upper Limb	906 (21.3)	906 (21.3)	
<b>Concurrent MSK conditions, N (%):</b>			1.00
0	3397 (80.0)	3397 (80.0)	
1+	847 (20.0)	847 (20.0)	

	<b>Intervention Group (N=4,244)</b>	<b>Comparator Group (N=4,244)</b>	<b>P</b>
<b>Mental health conditions, N (%):</b>			0.266
No	3984 (93.9)	4009 (94.5)	
Yes	260 (6.1)	235 (5.5)	
<b>Substance use disorders, N (%):</b>			0.478
No	4216 (99.3)	4222 (99.5)	
Yes	28 (0.7)	22 (0.5)	
<b>Elixhauser Comorbidity Index, mean (SD)</b>	-0.3 (2.2)	-0.2 (2.1)	0.099
<b>Elixhauser Comorbidity Index, N (%):</b>			0.331
<0	581 (13.7)	590 (13.9)	
0	3,475 (81.9)	3,445 (81.2)	
1-4	101 (2.4)	97 (2.3)	
≥5	87 (2.0)	112 (2.6)	
<b>TCOC, mean (SD) (\$)</b>	1,108.3 (1,729.4)	1,168.6 (1,705.4)	0.106

**Abbreviations:** MSK, musculoskeletal; TCOC, total all-cause costs of care.



**Supplementary Figure 4.** Standardized mean differences for all matching variables.

**Supplementary Table 16.** Comparison of opioid utilization outcomes between intervention and comparator groups in the matched population, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

<b>Outcomes</b>	<b>Intervention group</b>	<b>Comparator group</b>	<b>Absolute Difference</b>	
	N = 4, 244 Mean (95% CI)	N = 4, 244 Mean (95% CI)	Mean (95% CI)	p
<b>Opioid initiation rates, %</b>	2.2 (1.8; 2.7)	5.0 (4.4; 5.7)	2.8 (2.0; 3.6)	<0.001
<b>Multiple prescriptions rates, %</b>	1.1 (0.8; 1.4)	2.9 (2.4; 3.4)	1.8 (1.2; 2.4)	<0.001
<b>Opioid prescriptions per 100 patients</b>	4.7 (3.4; 6.0)	11.8 (9.8; 13.7)	7.1 (4.7; 9.4)	<0.001

**Abbreviations:** CI, confidence interval.

**Supplementary Table 17.** Comparison of opioid prescribing patterns among opioid users in the matched population, using a more stringent definition of opioid initiation ( $\geq 2$  prescriptions or  $\geq 1$  prescription with higher-tablet counts).

Outcomes	Intervention group	Comparator group	Absolute difference	
	N = 94 Mean (95% CI)	N = 213 Mean (95% CI)	Mean/pp (95% CI)	p
<b>MMEs per day</b>	37.9 (34.2; 41.6)	43.3 (40.1; 46.5)	5.4 (0.1; 10.8)	0.054
<b>MMEs per day<sup>1</sup> rates</b>				
$\geq 50$	21.3 (13.0; 29.6)	28.2 (22.1; 34.2)	6.9 (-3.8; 17.6)	0.206
$\geq 90$	2.1 (-0.8; 5.0)	4.2 (1.5; 6.9)	2.1 (-2.4; 6.6)	0.364
<b>Opioid Potency relative to morphine<sup>2</sup> rates</b>				
Lower potency than morphine	34.0 (24.5; 43.6)	33.8 (27.5; 40.2)	-0.2 (-11.8; 11.3)	0.968
Equivalent to morphine	27.7 (18.6; 36.7)	23.9 (18.2; 29.7)	-3.7 (-14.3; 6.9)	0.490
Greater potency than morphine	60.6 (50.8; 70.5)	61.5 (55.0; 68.0)	0.9 (-11.0; 12.8)	0.887
<b>DEA Schedule classification<sup>3</sup> rates</b>				
Schedule IV	33.0 (23.5; 42.5)	31.5 (25.2; 37.7)	-1.5 (-12.9; 9.9)	0.793
Schedule III	1.1 (-1.0; 3.1)	2.8 (0.6; 5.0)	1.8 (-1.9; 5.4)	0.345
Schedule II	76.6 (68.0; 85.2)	73.7 (67.8; 79.6)	-2.9 (-13.5; 7.8)	0.594

**Abbreviations:** CI, confidence interval; DEA, Drug Enforcement Administration; MME, morphine milligram equivalent. **Note:** <sup>1</sup>MMEs were obtained by converting each dispensed opioid prescription using published conversion factors<sup>5-7</sup> based on opioid type, strength, and quantity dispensed (Supplementary Table 23). <sup>2</sup>Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup> (Supplementary Table 24). <sup>3</sup> Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup> (Supplementary Table 24).

**Supplementary Table 18.** Negative control analysis comparing numbers of non-MSK-related drugs (metformin and simvastatin) between the intervention and comparator groups across methodologies.

Procedure	Intervention group		Comparator group		Difference in differences	
	Pre-index, mean (95% CI)	Post-index, mean (95% CI)	Pre-index, mean (95% CI)	Post-index, mean (95% CI)	Mean (95% CI)	p
<b>Inverse Probability Weighting + Multivariable Regression§</b>						
<b>Metformin</b>	0.36 (0.36; 0.36)	0.37 (0.37; 0.38)	0.22 (0.22; 0.22)	0.24 (0.24; 0.24)	0.00 (-0.03; 0.02)	0.860
<b>Simvastatin</b>	0.07 (0.07; 0.07)	0.06 (0.06; 0.06)	0.05 (0.05; 0.05)	0.04 (0.04; 0.04)	0.01 (-0.00; 0.01)	0.171
<b>Propensity Score Matching</b>						
<b>Metformin</b>	0.28 (0.23; 0.33)	0.31 (0.26; 0.36)	0.17 (0.13; 0.20)	0.17 (0.13; 0.21)	0.02 (-0.07; 0.10)	0.682
<b>Simvastatin</b>	0.07 (0.05; 0.09)	0.06 (0.05; 0.08)	0.04 (0.02; 0.05)	0.03 (0.02; 0.05)	0.00 (-0.04; 0.03)	0.814

**Abbreviations:** CI, Confidence Interval; CG, comparator group; IG, intervention group.

**Supplementary Table 19.** STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

Item			
No		Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	Page 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 17-18; Figure 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 17-22; Supplementary Notes 1-2
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 18-22; Supplementary Figure 1; Supplementary Table 20-21
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Pages 24-25; Supplementary Table 1 & 15; Supplementary Figure 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 21-25; Figure 1;

			Supplementary Tables 1 & 20-24
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 20-25; Supplementary Tables 1 & 22-24; Supplementary Notes 1-2
Bias	9	Describe any efforts to address potential sources of bias	Pages 22-25; Figure 1; Supplementary Tables 1
Study size	10	Explain how the study size was arrived at	Pages 17-21; Supplementary Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 21-25
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Pages 22-25; Supplementary Tables 1
		(b) Describe any methods used to examine subgroups and interactions	Pages 23-24; Supplementary Tables 23-24
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	Pages 24-25; Supplementary Tables 1 & 22
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 4-5 & 11; Supplementary Figure 1; Supplementary Tables 20-21

		(b) Give reasons for non-participation at each stage	Pages 4-5 & 11
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 4-5; Table 1; Supplementary Table 2; Supplementary Figure 2-3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	Page 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 6-12; Figure 2; Supplementary Tables 2-18
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 6-12; Figure 2; Table 1; Supplementary Figure 2-3 Supplementary Tables 2-14
		(b) Report category boundaries when continuous variables were categorized	Pages 9-11; Figure 2; Table 1; Supplementary Tables 2 & 7-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 7-12; Figure 2; Supplementary Figure 4; Supplementary Tables 6 & 11-13 & 15-18

Discussion

Key results	18	Summarise key results with reference to study objectives	Pages 12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 26

\*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

**Supplementary Table 20.** Categorized ICD-10 Codes used to identify patients eligible for the study.

<b>ICD-10 Major Category (3-digit)</b>	<b>Diagnostic Category</b>	<b>Full ICD-10 Codes</b>
G54	Nerve root and plexus disorders	G54, G540, G541, G542, G543, G544
G56	Mononeuropathies of upper limb	G56, G5600, G5601, G5602, G5603, G5611, G5612, G5613, G5620, G5621, G5622, G5623, G5630, G5631, G5632, G5633, G5640, G5641, G5642, G5643, G5680, G5681, G5682, G5683, G5690, G5691, G5692, G5693
G57	Mononeuropathies of lower limb	G57, G5700, G5701, G5702, G5703, G5710, G5711, G5712, G5713, G5720, G5721, G5722, G5723, G5730, G5731, G5732, G5733, G5740, G5741, G5742, G5743, G5750, G5751, G5752, G5753, G5760, G5761, G5762, G5763, G5770, G5771, G5772, G5773, G5780, G5781, G5782, G5783, G5790, G5791, G5792, G5793
M12	Other and unspecified arthropathy	M12, M123, M1230, M1231, M1232, M1233, M1234, M1235, M1236, M1237, M1238, M1239, M124, M1240, M1241, M1242, M1243, M1244, M1245, M1246, M1247, M1248, M1249, M125, M1250, M1251, M1252, M1253, M1254, M1255, M1256, M1257, M1258, M1259, M128, M1280, M1281, M1282, M1283, M1284, M1285, M1286, M1287, M1288, M1289, M129
M13	Other arthritis	M13, M1310, M1311, M1312, M1313, M1314, M1315, M1316, M1317, M1380, M1381, M1382, M1383, M1384, M1385, M1386, M1387, M1388, M1389
M14	Arthropathies in other diseases	M14, M146, M1460, M1461, M1462, M1463, M1464, M1465, M1466, M1467, M1468, M1469, M148, M1480, M1481, M1482, M1483, M1484, M1485, M1486, M1487, M1488, M1489
M15	Polyarthrosis	M15, M150, M151, M152, M153, M154, M158, M159
M16	Osteoarthritis of hip	M16, M160, M1610, M1611, M1612, M162, M1630, M1631, M1632, M164, M1650, M1651, M1652, M166, M167, M169
M17	Osteoarthritis of knee	M17, M170, M1710, M1711, M1712, M172, M1730, M1731, M1732, M174, M175, M179
M19	Other and unspecified osteoarthritis	M19, M1901, M1902, M1903, M1904, M1907, M1909, M1911, M1912, M1913, M1914, M1917, M1919, M1921, M1922, M1923, M1924, M1927, M1929, M1990, M1991, M1992, M1993
M21	Other acquired deformities of limbs	M21, M2100, M2102, M2105, M2106, M2107, M211, M2110, M2112, M2115, M2116, M2117, M212, M2120, M2121, M2122, M2123, M2124, M2125, M2126, M2127
M22	Disorder of patella	M22, M2200, M2201, M2202, M2210, M2211, M2212, M222X, M223X,

		M2240, M2241, M2242, M228X, M2290, M2291, M2292
M23	Internal derangement of knee	M23, M230, M2300, M2301, M2302, M2303, M2304, M2305, M2306, M232, M2320, M2321, M2322, M2323, M2324, M2325, M2326, M233, M2330, M2331, M2332, M2333, M2334, M2335, M2336, M234, M2340, M2341, M2342, M235, M2350, M2351, M2352, M236, M2360, M2361, M2362, M2363, M2364, M2367, M238, M238X, M239, M2390, M2391, M2392
M24	Other specific joint derangements	M24, M240, M2400, M2401, M2402, M2403, M2404, M2405, M2407, M241, M2410, M2411, M2412, M2413, M2414, M2415, M2417, M242, M2420, M2421, M2422, M2423, M2424, M2425, M2427, M2428, M2429, M243, M2430, M2431, M2432, M2433, M2434, M2435, M2436, M2437, M2439, M2440, M2441, M2442, M2443, M2444, M2445, M2446, M2447, M245, M2450, M2451, M2452, M2453, M2454, M2455, M2456, M2457, M247, M248, M2480, M2481, M2482, M2483, M2484, M2485, M2487, M2489, M249
M25	Other joint disorder, not elsewhere classified	M25, M251, M2511, M2512, M2513, M2514, M2515, M2516, M2517, M2518, M253, M2530, M2531, M2532, M2533, M2534, M2535, M2536, M2537, M2539, M254, M2540, M2541, M2542, M2543, M2544, M2545, M2546, M2547, M2548, M255, M2550, M2551, M2552, M2553, M2554, M2555, M2556, M2557, M256, M2560, M2561, M2562, M2563, M2564, M2565, M2566, M2567, M2569, M257, M2570, M2571, M2572, M2573, M2574, M2575, M2576, M2577, M2578, M258, M2580, M2581, M2582, M2583, M2584, M2585, M2586, M2587, M259
M40	Kyphosis and lordosis	M40, M4000, M4003, M4004, M4005, M4010, M4012, M4013, M4014, M4015, M4020, M4029, M4030, M4035, M4036, M4037, M4040, M4045, M4046, M4047, M4050, M4055, M4056, M4057
M41	Scoliosis	M41, M4100, M4102, M4103, M4104, M4105, M4106, M4107, M4108, M4111, M4112, M4120, M4122, M4123, M4124, M4125, M4126, M4127, M4130, M4134, M4135, M4140, M4141, M4142, M4143, M4144, M4145, M4146, M4147, M4150, M4152, M4153, M4154, M4155, M4156, M4157, M4180, M4182, M4183, M4184, M4185, M4186, M4187
M42	Spinal osteochondrosis	M42, M4200, M4201, M4202, M4203, M4204, M4205, M4206, M4207, M4208, M4209, M4210, M4211, M4212, M4213, M4214, M4215, M4216, M4217, M4218, M4219, M429
M43	Other deforming dorsopathies	M43, M431, M4310, M4311, M4312, M4313, M4314, M4315, M4316, M4317, M4318, M4319, M432, M4320, M4321, M4322, M4323, M4324, M4325, M4326, M4327, M4328, M435, M435X, M438, M438X, M439
M45	Ankylosing spondylitis	M45, M450, M451, M452, M453, M454, M455, M456, M457, M458, M459
M46	Other inflammatory spondylopathies	M46, M460, M4600, M4601, M4602, M4603, M4604, M4605, M4606, M4607, M4608, M4609, M461, M468, M4680, M4681, M4682, M4683, M4684, M4685, M4686, M4687, M4688, M4689, M469, M4690, M4691, M4692, M4693, M4694, M4695, M4696, M4697, M4698, M4699

M47	Spondylosis	M47, M4720, M4721, M4722, M4723, M4724, M4725, M4726, M4727, M4728, M4781, M4789, M479
M48	Other spondylopathies	M4820, M4821, M4822, M4823, M4824, M4825, M4826, M4827, M4830, M4831, M4832, M4833, M4834, M4835, M4836, M4837, M4838, M488X, M489
M49	Spondylopathies in diseases classified elsewhere	M4980, M4981, M4982, M4983, M4984, M4985, M4986, M4987, M4988, M4989
M50	Cervical disc disorders	M5010, M5011, M5012, M5013, M5020, M5021, M5022, M5023, M5030, M5031, M5032, M5033, M5080, M5081, M5082, M5083, M5090, M5091, M5092, M5093
M51	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	M5114, M5115, M5116, M5117, M5124, M5125, M5126, M5127, M5134, M5135, M5136, M5137, M5144, M5145, M5146, M5147, M5184, M5185, M5186, M5187, M519
M53	Other and unspecified dorsopathies, not elsewhere classified	M530, M531, M532X, M533, M5380, M5381, M5382, M5383, M5384, M5385, M5386, M5387, M5388, M539
M54	Dorsalgia	M5410, M5411, M5412, M5413, M5414, M5415, M5416, M5417, M5418, M542, M5430, M5431, M5432, M5440, M5441, M5442, M545, M5450, M5451, M5459, M546, M549
M62	Other disorders of muscle	M6200, M6201, M6202, M6203, M6204, M6205, M6206, M6207, M6208, M6211, M6212, M6213, M6214, M6215, M6216, M6217, M6240, M6241, M6242, M6243, M6244, M6245, M6246, M6247, M6248, M6249, M6251, M6254, M6255, M6256, M6257, M6258, M6259, M6281, M6283, M6289, M629
M65	Synovitis and tenosynovitis	M6520, M6522, M6523, M6524, M6525, M6526, M6527, M6528, M654, M6580, M6581, M6582, M6583, M6584, M6585, M6586, M6587, M6588, M659
M66	Spontaneous rupture of synovium and tendon	M6611, M6612, M6613, M6614, M6615, M6617, M6620, M6621, M6622, M6623, M6624, M6625, M6626, M6627, M6628, M6629, M6630, M6631, M6632, M6633, M6634, M6635, M6636, M6637, M6638, M6639, M6680, M6681, M6682, M6683, M6684, M6685, M6686, M6687, M6688, M6689, M669
M67	Other disorders of synovium and tendon	M6700, M6701, M6702, M6720, M6721, M6722, M6723, M6724, M6725, M6726, M6727, M6728, M6729, M6730, M6731, M6732, M6733, M6734, M6735, M6736, M6737, M6738, M6739, M6740, M6741, M6742, M6743, M6744, M6745, M6746, M6747, M6748, M6749, M6750, M6751, M6752, M6780, M6781, M6782, M6783, M6784, M6785, M6786, M6787, M6788, M6789, M6790, M6791, M6792, M6793, M6794, M6795, M6796, M6797, M6798
M70	Soft tissue disorders	M7003, M7004, M7010, M7011, M7012, M7020, M7021, M7022, M7030,

	related to use, overuse and pressure	M7031, M7032, M7040, M7041, M7042, M7050, M7051, M7052, M7060, M7061, M7062, M7070, M7071, M7072, M7080, M7081, M7082, M7083, M7084, M7085, M7086, M7087, M7088, M7089, M7090, M7091, M7092, M7093, M7094, M7095, M7096, M7097, M7098, M7099
M71	Other bursopathies	M7120, M7121, M7122, M7130, M7131, M7132, M7133, M7134, M7135, M7137, M7138, M7139, M7140, M7142, M7143, M7144, M7145, M7146, M7147, M7148, M7149, M7150, M7152, M7153, M7154, M7155, M7156, M7157, M7158, M7180, M7181, M7182, M7183, M7184, M7185, M7186, M7187, M7188, M7189, M719
M75	Shoulder lesions	M7500, M7501, M7502, M7510, M7511, M7512, M7520, M7521, M7522, M7530, M7531, M7532, M7540, M7541, M7542, M7550, M7551, M7552, M7580, M7581, M7582, M7590, M7591, M7592
M76	Enthesopathies, lower limb, excluding foot	M7600, M7601, M7602, M7610, M7611, M7612, M7620, M7621, M7622, M7630, M7631, M7632, M7640, M7641, M7642, M7650, M7651, M7652, M7660, M7661, M7662, M7670, M7671, M7672, M7681, M7682, M7689, M769
M77	Other enthesopathies	M7700, M7701, M7702, M7710, M7711, M7712, M7720, M7721, M7722, M7750, M7751, M7752, M778, M779
M79	Other and unspecified soft tissue disorders, not elsewhere classified	M7912, M7918, M794, M7960, M7962, M7963, M7964, M7965, M7966, M7967
M84	Disorder of continuity of bone	M8430, M8431, M8432, M8433, M8434, M8435, M8436, M8437
M93	Other osteochondropathies	M9320, M9321, M9322, M9323, M9324, M9325, M9326, M9327, M9328, M9329, M9380, M9381, M9382, M9383, M9384, M9385, M9386, M9387, M9388, M9389
M94	Other disorders of cartilage	M9420, M9421, M9422, M9423, M9424, M9425, M9426, M9427, M9428, M9429, M9435, M948X
M95	Other acquired deformities of musculoskeletal system and connective tissue	M953, M955
M96	Intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified	M961
M99	Biomechanical lesions, not elsewhere	M9901, M9902, M9903, M9904, M9905, M9906, M9911, M9912, M9913, M9914, M9915, M9916, M9961, M9962, M9963, M9964, M9965, M9966,

	classified	M9967, M9969, M9970, M9971, M9972, M9973, M9974, M9975, M9976, M9977
S13	Dislocation and sprain of joints and ligaments at neck level	S134X, S138X, S139X
S16	Injury of muscle, fascia and tendon at neck level	S161X, S168X, S169X
S30	Superficial injury of abdomen, lower back, pelvis and external genitals	S300X
S33	Dislocation and sprain of joints and ligaments of lumbar spine and pelvis	S335X, S336X, S338X, S339X
S34	Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level	S3421, S3422
S39	Other and unspecified injuries of abdomen, lower back, pelvis and external genitals	S3901, S3909, S3982, S3992
S40	Superficial injury of shoulder and upper arm	S4001, S4002
S43	Dislocation and sprain of joints and ligaments of shoulder girdle	S4330, S4340, S4341, S4342, S4343, S4349, S4350, S4351, S4352, S4380, S4381, S4382, S4390, S4391, S4392
S44	Injury of nerves at shoulder and upper arm level	S4400, S4401, S4402, S4410, S4411, S4412, S4420, S4421, S4422, S4430, S4431, S4432, S4440, S4441, S4442, S448X, S4490, S4491, S4492
S46	Injury of muscle, fascia and tendon at shoulder and upper arm level	S4600, S4601, S4609, S4610, S4611, S4619, S4620, S4621, S4629, S4630, S4631, S4639, S4680, S4681, S4689, S4690, S4691, S4699
S50	Superficial injury of elbow and forearm	S5000, S5001, S5002, S5010, S5011, S5012
S53	Dislocation and sprain of joints and ligaments	S5340, S5341, S5342, S5343, S5344, S5349

	of elbow	
S54	Injury of nerves at forearm level	S5400, S5401, S5402, S5410, S5411, S5412, S5420, S5421, S5422, S548X, S5490, S5491, S5492
S56	Injury of muscle, fascia and tendon at forearm level	S5620, S5621, S5629
S59	Other and unspecified injuries of elbow and forearm	S5980, S5981, S5990, S5991
S60	Superficial injury of wrist, hand and fingers	S6021, S6022
S63	Dislocation and sprain of joints and ligaments at wrist and hand level	S6350, S6351, S6352, S6359
S70	Superficial injury of hip and thigh	S7000, S7001, S7002, S7010, S7011, S7012
S73	Dislocation and sprain of joint and ligaments of hip	S7310, S7311, S7312, S7319
S76	Injury of muscle, fascia and tendon at hip and thigh level	S7600, S7601, S7609, S7610, S7611, S7619, S7620, S7621, S7629, S7630, S7631, S7639, S7680, S7681, S7682, S7689, S7690, S7691, S7699
S83	Fracture of lower leg, including ankle	S8320, S8321, S8322, S8323, S8324, S8325, S8326, S8327, S8328, S8330, S8331, S8332, S8340, S8341, S8342, S8350, S8351, S8352, S8360, S8361, S8362, S838X, S8390, S8391, S8392
S86	Injury of muscle, fascia and tendon at lower leg level	S8600, S8601, S8609, S8610, S8611, S8619, S8620, S8621, S8629, S8630, S8631, S8639, S8680, S8681, S8682, S8689, S8690, S8691, S8692, S8699
S89	Other and unspecified injuries of lower leg	S8980, S8981, S8982, S8990, S8991, S8992
S90	Superficial injury of ankle, foot and toes	S9000, S9001, S9002
S93	Dislocation and sprain of joints and ligaments at ankle, foot and toe level	S9340, S9341, S9342, S9343, S9349, S9360, S9369
S94	Injury of nerves at ankle and foot level	S9400, S9401, S9402, S9410, S9411, S9412, S9420, S9421, S9422, S9430, S9431, S9432, S948X, S9490, S9491, S9492
S99	Other and unspecified injuries of ankle and foot	S9981, S9991

Z96	Presence of other functional implants	Z9661, Z9662, Z9663, Z9664, Z9665, Z9666
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**Abbreviation:** ICD-10, International Classification of Diseases, Tenth Revision.

**Supplementary Table 21.** Categorized ICD-10 Codes used to identify patients with conditions that warrant exclusion from the study.

<b>Diagnostic Category</b>	<b>Full Codes</b>
Neoplasms	NEO001-NEO025, NEO028-NEO071 (except NEO073)
Perinatal period, and Pregnancy, Childbirth and the Puerperium	PNL001-PNL013, PRG001-PRG030
Dementia, Cognitive impairment or Intellectual disabilities	F01-F03, F70-F79, G20, G30, G71, R26
Traumatic injuries	S00–S99
Poisoning, burns, and other injury complications	T00–T88
Transport accidents	V00–V99
Falls and environmental injuries	W00–W99
Exposure, toxic effects, and self-harm	X00–X99
Assault and other external causes	Y00–Y99
Severe neurologic or systemic conditions	G82, R57
Severe stress disorders	F43
Encounter/status exclusions	Z90

**Abbreviation:** ICD-10, International Classification of Diseases, Tenth Revision.

**Supplementary Note 1.** Brief description of PurpleLab data source.

PurpleLab is one of the largest claims data repositories in the US (covering millions of lives) and aggregates fully adjudicated, payer sourced claims via direct feeds and partnerships rather than purchasing a commercial database license. In practice, that means:

**Third-Party Administrators (TPAs) & Self-Insured Employers**

Clients deliver member eligibility & claims extracts (medical, pharmacy, ancillary) via secure SFTP or API. These feeds span both national administrators and large regional/local TPAs.

**National & Regional Carrier Partnerships**

For fully insured groups, PurpleLab ingests de-identified claims from major carriers under data-share agreements.

Key data elements available:

1. Enrollment files: demographics, eligibility history (coverage dates, plan tier, employer ID);
2. Medical claims: inpatient, outpatient, office, emergency room, imaging, surgery, ancillary; includes ICD-10, CPT/HCPCS, place-of-service, provider National Provider Identifier, billed/allowed/paid amounts;
3. Pharmacy claims: Outpatient prescription dispensing records including National Drug Codes (NDC), drug name and class, dispensing date, quantity, days of supply, refill information, pharmacy identifier, and paid amounts.

4. Ancillary & lab: select lab orders/results, Durable Medical Equipment (DME), home health;
5. Longitudinal linkage via de-identified member & claim IDs.

## **Supplementary Note 2. Claims Classification and Validation Procedures.**

To ensure accurate and consistent classification of musculoskeletal (MSK)-related claims, we applied a standardized data validation protocol aligned with established recommendations for retrospective claims analyses<sup>10,11</sup>.

MSK-related diagnoses within the scope of physical therapy were identified using ICD-10 codes. Misclassified or clinically irrelevant codes were excluded, and consistency checks were performed to flag implausible sequences (e.g., surgery preceding diagnosis). All cost data were normalized using CMS Fee Schedules to reduce payer-level variability and ensure comparability across claims.

**Supplementary Table 22.** Opioid Drug Families and Associated National Drug Codes (NDC) and Current Procedural Terminology/Healthcare Common Procedure Coding System (CPT/HCPCS).

Opioid family	NDC/CPT/HCPCS
<b>Pharmacy claims</b>	
<b>Buprenorphine</b>	121101930, 121203830, 12496075701, 12496075705, 228315303, 228315603, 409201203, 409201232, 42023017901, 42023017905, 42858035340, 42858049340, 42858050103, 42858050203, 42858058640, 42858075040, 42858083940, 47781040604, 47781040704, 47781040804, 47781041904, 50383092493, 50383093093, 50742037204, 50742037304, 50742037404, 50742037504, 50742037604, 54017613, 54017713, 59011075004, 59011075104, 59011075204, 59011075704, 59011075804, 59385002160, 59385002201, 59385002260, 59385002360, 59385002401, 59385002460, 59385002501, 59385002560, 59385002660, 59385002760, 60505707505, 60505707605, 60505707705, 60505707805, 60505707905, 60687048111, 60687048121, 60687049211, 60687049221, 62756045983, 62756046083, 63481051960, 69238120202, 69238120302, 69238120402, 69238120502, 69238150502, 71335095003, 71335116303, 72888018230, 72888018330, 904715404, 904715504, 93323921, 93323940, 93360140, 93360321, 93360340, 93365621, 93365640, 93365740, 93365840, 93365940
<b>Codeine</b>	121050400, 121050404, 121050405, 121050416, 121050440, 121100840, 13107005801, 13107005901, 13107005999, 13107006001, 13107006005, 13107006099, 17856006501, 21695025860, 33358000160, 349232401, 406048301, 406048401, 406048403, 406048410, 406048423, 406048462, 406048501, 406048505, 42195084010, 43063055424, 49999002660, 50090301101, 50090461000, 50090520004, 50383007906, 50383007916, 50383033913, 50458051380, 51079016101, 51079016120, 51991007301, 51991007401, 51991007405, 52544008201, 527131201, 527169801, 52959000325, 52959000328, 52959044630, 536322705, 54569002502, 55289000598, 55887030930, 603233721, 603233821, 603233832, 603255321, 60687060401, 60687061501, 615043053, 61919032830, 63187010615, 63629118501, 63629118701, 63629149403, 63629149406, 63629294501, 63629303101, 63629685102, 63739000410, 63874020290, 64380044601, 64380044701, 64380044801, 64850064101, 64850064201, 64850064301, 64950037416, 65162003310, 65162003311, 66267000120, 66267099704, 66992084010, 67544000253, 67544000260, 67544000353, 68084037201, 68084037211, 68115000112, 68115000190, 69238199301, 71335033606, 71335054509, 71610011145, 71610011146, 71610011160, 71610011170, 71930005412, 71930005452, 71930005512, 71930005552, 71930005612, 71930005652, 72162200201, 72189037660, 76420010330, 879000252, 93005001, 93015001, 93015010, 157042101, 580045201, 719003310, 781166005
<b>Fentanyl</b>	10019003725, 10019003727, 143939110, 143939210, 17478003002, 17478003005, 17478006702, 378911998, 378912116, 378912198, 378912298, 378912316, 378912398, 378912498, 378912598, 378912616, 378912698, 378912798, 38779175603, 38779175604, 406900076, 406901276, 406902576, 406903776, 406905076, 406906276, 406907576, 406910076, 406911276, 406912576, 406915076, 406917576, 406920230, 409127603, 409127632, 409338221, 409909309, 409909311, 409909332, 409909335, 409909337, 409909345, 409909409, 409909411, 409909412, 409909418, 409909422, 409909425, 409909428, 409909431, 409909441, 409909461, 47781042347, 47781042447, 47781042647, 47781042747, 47781042847, 50742054905, 50742055005, 50742055105, 50742055201, 50742055205, 50742055405, 50742055605, 51552068704, 51552068705, 51862063528, 51862063728, 51862063828, 55887089005, 60505700602, 60505700702, 60505701002, 60505708002, 60505708102, 60505708202, 60505708300, 60505708302, 60505708402, 60505708502, 60505708702, 61553030328, 62991140504, 63323072301,

<b>Opioid family</b>	<b>NDC/CPT/HCPCS</b>
	63323072303, 63323072401, 63323072405, 63323080601, 63323080602, 63323080605, 63323080611, 63323080612, 63323080613, 63323080801, 63323080811, 63629476503, 63629549601, 641602410, 641602501, 641602510, 641602701, 641602725, 641602801, 641602825, 641602901, 641603001, 641624701, 641624725, 641624801, 641624810, 67457019803, 67457019805, 67457019810, 67457091201, 68071137405, 68071137505, 68258201103, 69374052620, 70004020232, 70092109337, 70092109949, 70092110537, 70092116037, 70092140043, 70092150935, 71266505001, 71266917001, 71266922701, 71449001305, 71500000230, 71500000430, 71500000830, 72078003401, 72572017001, 72572017025, 72572017125, 72572017201, 73177010203, 81371201005, 81565020502, 82393011807, 93786565, 93786665, 20482001230
<b>Hydrocodone</b>	10544031602, 10702018901, 10702018910, 10702018950, 10702019001, 10702019010, 10702019050, 10702019101, 10702019110, 10702019150, 10702019201, 10702019301, 10702019401, 121077204, 121077216, 121154440, 121231615, 121231640, 121477115, 121477205, 121477240, 13107000401, 13107001901, 13107001905, 13107002001, 13107002005, 13107002101, 13107002105, 13107002199, 13811065710, 16590049430, 17478045016, 21695027016, 23600201, 247007990, 247034215, 247061350, 254203401, 27808003501, 27808003502, 27808003503, 27808003601, 27808003602, 27808003603, 27808003701, 27808003702, 27808003703, 27808011401, 27808011501, 27808011502, 27808011601, 31722094101, 31722094105, 31722094201, 31722094205, 31722094301, 31722094305, 31722099601, 31722099605, 31722099701, 31722099705, 33261005412, 33261005607, 33261005636, 33261037990, 35356079590, 35356079630, 406012301, 406012305, 406012310, 406012312, 406012323, 406012330, 406012362, 406012401, 406012405, 406012410, 406012412, 406012423, 406012462, 406012501, 406012505, 406012510, 406012512, 406012523, 406012560, 406012562, 406036523, 406036762, 406037601, 406037605, 406037701, 406037705, 406037801, 406037805, 40893019104, 42291033201, 42858004001, 42858013901, 42858020101, 42858020150, 42858020201, 42858020301, 42858020350, 42858023801, 43063009120, 43063068610, 43063068698, 43353015957, 43353073454, 43353073480, 43386035101, 43386035201, 43386035301, 43386035601, 43386035610, 43386035701, 43386035710, 43386035801, 43386035810, 440761006, 47463036273, 47679082901, 47781039260, 47781039360, 47781039460, 47781039560, 47781039660, 47781039760, 47781040960, 47781041060, 47781041160, 47781041260, 47781041360, 47781041460, 50268040011, 50268040015, 50268040111, 50268040115, 50268040211, 50268040215, 50436261204, 51079077720, 51862058505, 52246007520, 52493019130, 52544096960, 52959032401, 52959048440, 52959052112, 52959053330, 53217026790, 53746010901, 53746010905, 53746010910, 53746011001, 53746011005, 53746011010, 53746011701, 53746014501, 53746014601, 54084363, 54124095818, 54569030300, 54868007108, 54868497403, 55289094460, 55700065221, 55700065230, 57664012613, 57664012688, 57664017013, 57664017088, 57664017688, 58016063221, 58118017607, 59011027160, 59011027260, 59011027360, 59011027460, 59011027560, 59011027660, 59011027760, 591217101, 591217205, 591320201, 603388721, 603388728, 603388732, 603388804, 603389021, 603389028, 603389032, 603389121, 603389128, 603389132, 603389721, 60429059001, 60429059005, 60429059101, 60429059201, 60429059205, 60687039601, 60687039611, 60687040701, 60687040711, 60687041744, 60687041801, 60687041811, 60951064170, 61919011872, 61919049430, 61919061826, 63629153206, 63629193801, 63629193901, 63629194101, 63629229201, 63629229801, 63629229901, 63629230001, 63629295805, 63629473101, 63629542203, 63717089516, 63739032610, 63739053210, 63739070410, 63874020335, 63874023030, 63874029525, 63874083450, 64376064016, 64376064301, 64376064801, 64380044001, 64380044101, 64380044201, 64850063001, 64850063101, 64850063201, 64850063301, 64950034316, 64950037316, 64950037516, 65162011510, 65162011511,

Opioid family	NDC/CPT/HCPCS
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<b>Hydromorphone</b>	13107010901, 13811070110, 13811070210, 13811070310, 13811070410, 31722011901, 31722012001, 31722012101, 31722012201, 38779073105, 406324301, 406324401, 406324901, 409128303, 409128304, 409128305, 409128309, 409128310, 409128317, 409128331, 409128337, 409130403, 409131203, 409131210, 409131230, 409131236, 409180501, 409255201, 409255211, 409263401, 409263405, 409263450, 409335601, 409335611, 409336501, 409336510, 409336511, 409426401, 409426411, 42858012201, 42858023401, 42858030101, 42858030125, 42858030201, 42858030225, 42858030250, 42858030301, 42858030416, 44101201, 44105301, 49999083590, 527135301, 527135401, 527135501, 54038663, 54437025, 54835016, 574029301, 574029401, 574029501, 574722406, 59011044110, 59011044225, 60687057901, 60687057911, 60687059001, 61553045474, 61553051069, 61553061219, 61553070268, 62991309207, 63275210008, 63323085115, 63323085203, 63323085225, 63323085303, 63323085325, 641012121, 641012125, 641234141, 641615101, 641615125, 641616901, 68084042301, 70092111536, 70092111850, 70092154635, 70092911148, 70092911450, 70092940550, 7030111303, 73177010403, 74131212, 76045000901, 76045000905, 76045000906, 76045000910, 76045000911, 76045000996, 76045001001, 76045001010, 76045001011, 76045012101, 76045012111, 82393011908
<b>Levorphanol</b>	406222401, 527323637, 527323737, 54043825, 57664076288, 69543041210, 69543041710, 72989041710
<b>Meperidine</b>	409117603, 409117630, 409117803, 409117830, 409118069, 409118130, 409125301, 409125512, 409125601, 409136201, 409136211, 409141801, 42806005030, 54354563, 548192710, 54868515101, 641605201, 641605225, 641605301, 641605325, 641605401, 641605425, 64950021403, 904197840, 24036404
<b>Methadone</b>	13107008801, 13107008901, 16590067015, 31722094601, 31722094701, 406052710, 406412303, 406575501, 406575562, 406577101, 406577162, 406622105, 406622505, 406872510, 527192736, 54070920, 54070925, 54071020, 54071025, 54355344, 54355563, 54355663, 54457025, 54457125, 54855424, 54868285400, 57866707005, 63629102701, 66689069479, 66689082010, 66689083699, 67457021720, 67877011601, 67877065901, 68084073801, 68084073811, 70166028401, 72865012001, 904653061, 904741761
<b>Morphine</b>	10544042328, 115127701, 121082501, 228309011, 228309111, 228309211, 228309311, 228311611, 228311711, 228350106, 228350206, 228350306, 228427011, 228427111, 228431111, 228432311, 27808008201, 27808008202, 34052203, 35356083730, 38779067305, 38779067307, 406152153, 406511801, 406511901, 406800312, 406800315, 406800324, 406800330, 406831501, 406831523, 406831562, 406832001, 406833001, 406833023, 406833062, 406838001, 406838062, 406839001, 406839062, 409113403, 409126069, 409176230, 409189001, 409189003, 409189010, 409189011, 409189013, 409189023, 409189101, 409189103, 409189110, 409189111, 409189113, 409189123, 409189203, 409189301, 409189303, 409189313, 409381411, 409381412, 409381511, 409381512, 42858051501, 42858063101, 42858080101, 42858080201, 42858080301,

Opioid family	NDC/CPT/HCPCS
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<b>Nalbuphine</b>	409146301, 409146349, 409146371, 409146401, 409146461, 409146701, 409146761, 54868360800, 70069067101, 70069067110
<b>Oxycodone</b>	10702000801, 10702000850, 10702000901, 10702000950, 10702001801, 10702001850, 10702002301, 10702005601, 10702005650, 10702005701, 10702005750, 10702018401, 10702018501, 10702018550, 10702018601, 10702018701, 10702018750, 10702080101, 10702080301, 115155801, 115156001, 121082601, 121482705, 13107004401, 13107004405, 13107004501, 13107004505, 13107004601, 13107004605, 13107005501, 13107005601, 13107005701, 16590061960, 23635058110, 23635058210, 24510011010, 24510011510, 24510012010, 24510013010, 24510014010, 29033040535, 31722010901, 31722011001, 31722011101, 31722019101, 31722019205, 31722019301, 31722019401, 31722091701, 31722091705, 31722091801, 31722091805, 31722094801, 31722094901, 31722094905, 31722095001, 31722095005, 31722095101, 31722095105, 33261019606, 339407112, 35356080130, 35356083930, 378710401, 378710601, 406051201, 406051205, 406051223, 406051262, 406052201, 406052205, 406052223, 406052262, 406052301, 406052305, 406052323, 406052362, 406055201, 406055223, 406055262, 406056201, 406851001, 406851023, 406851062, 406851501, 406851523, 406851562, 406852001, 406853001, 406853062, 406855605, 406855730, 42806000501, 42806000601, 42806000701, 42858000101, 42858000110, 42858000201, 42858000210, 42858000301, 42858000401, 42858000501, 42858010201, 42858010250, 42858010301, 42858010350, 42858010401, 42858010450, 43063065340, 43386043001, 43386043201, 43386043301, 43386049305, 47781019601, 47781019605, 47781022901, 47781022905, 47781023001, 47781023005, 47781023063, 47781026301, 47781026305, 47781026401, 47781026405, 47781026501, 47781026505, 49884013701, 49999085105, 49999085405, 49999085460, 50268064411, 50268064415, 50268064611, 50268064615, 50383096134, 50383096430, 527166905, 527167105, 527177401, 53746020301, 53746020305, 53746020401, 53746020405, 54039041, 54039063, 54055125, 54868471000, 54868539008, 55048056230, 55700049801, 55700055730, 57664015588, 57664018788, 57664022388, 57664037088, 57866993601, 59011041010, 59011041020, 59011041510, 59011041520, 59011042010, 59011042020, 59011043010, 59011043020, 59011044010, 59011044020, 59011046010, 59011046020, 59011048010, 59011048020, 591269301, 591270801, 603497821, 603498221, 603499828, 60429051601, 60429051701, 60432070605, 60687040667, 60687064201, 60687064211, 60951060270, 60951060285, 60951070070, 60951070170, 60951071270, 61919087130, 62559015116, 62559016701, 63481062370, 63481062870,

Opioid family	NDC/CPT/HCPCS					
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	71335142201,	71335142202,	71335142203,	71335142204,	71930002243,	71930002330,
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<b>Oxymorphone</b>	10702007001,	10702007006,	10702007101,	10702007106,	13107010301,	13107010401,
	16590076756,	31722092901,	31722093001,	54028325,	54028425,	63481061275,
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	64896069801,	64896069813,	64896069901,	64896069913,	64896070001,	64896070013,
	64896070101,	64896070113				
<b>Pentazocine</b>	43386068001,	591039501,	60346066040,	63874022035		
<b>Tapentadol</b>	24510005010,	24510005860,	24510007510,	24510010010,	24510011660,	24510017460,
	24510023260,	24510029160,	35356052530,	35356059330,	50458082002,	69865022002
<b>Tramadol</b>	10135051905,	10147090103,	10370022211,	12634094060,	13811068930,	13811069030,
	13811069130,	16571071601,	16571071610,	16571071650,	16590089228,	16714048102,
	185031110,	21695013278,	23490758602,	29300035501,	29300035505,	29300035510,
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	43353007292,	440857091,	47335053183,	47335053188,	47335053383,	47335053388,
	47335053783,	47335053788,	47335085983,	47335086083,	47335086183,	50090080601,
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Opioid family	NDC/CPT/HCPCS
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**Medical Claims**

<b>Buprenorphine</b>	J0571, J0592, G2079
<b>Codeine</b>	J0745
<b>Fentanyl</b>	J3010, J0216, J1810
<b>Hydromorphone</b>	J1170
<b>Meperidine</b>	J2175, J2180
<b>Methadone</b>	J1230, G2078
<b>Morphine</b>	J2270, J2272, J2274
<b>Nalbuphine</b>	J2300

**Abbreviation:** CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Codes.

**Supplementary Table 23.** Opioid conversion factors used to calculate oral Morphine Milligram Equivalents (MMEs).

<b>Opioid</b>	<b>Route of administration</b>	<b>Conversion factor</b>	<b>Reference</b>
<b>Codeine (mg)</b>	Oral	0.15	6,7
<b>Buprenorphine (mg)</b>	IV	75	5
	Transdermal	2.2	6
<b>Fentanyl (mcg)</b>	IV	0.2	5
<b>Hydrocodone (mg)</b>	Oral	1	6,7
<b>Hydromorphone (mg)</b>	Oral	5	6,7
	IV	17.5	5
<b>Meperidine (mg)</b>	IV	0.4	5
<b>Methadone (mg)</b>	Oral	4.7	6,7
	IV	13.5	5
<b>Morphine (mg)</b>	Oral	1	6,7
	IV	3	5
<b>Nalbuphine (mg)</b>	IV	3	5
<b>Oxycodone (mg)</b>	Oral	1.5	6,7
<b>Tramadol (mg)</b>	Oral	0.2	6,7

**Abbreviation:** IV, intravenous; mg, milligram; mcg, microgram.

**Supplementary Table 24.** Classification of opioid medications by potency relative to morphine and U.S. Drug Enforcement Administration (DEA) schedule.

<b>Opioids</b>	
<b>Opioid potency relative to morphine<sup>1</sup></b>	
Lower potency than morphine	Codeine, Meperidine, Tramadol
Equivalent to morphine	Hydrocodone, Morphine
Greater potency than morphine	Buprenorphine, Fentanyl, Hydromorphone, Methadone, Oxycodone
<b>DEA schedule classification<sup>2</sup></b>	
Schedule IV	Tramadol
Schedule III	Buprenorphine, Codeine
Schedule II	Fentanyl, Hydrocodone, Hydromorphone, Meperidine, Methadone, Morphine, Oxycodone

**Abbreviation:** DEA, U.S. Drug Enforcement Administration.

**Notes:** <sup>1</sup>Drug potency relative to morphine considering published equianalgesic dose conversion factors<sup>5-7</sup>. <sup>2</sup>Drug schedule categorized according to the U.S. DEA controlled substance schedules<sup>8,9</sup>

**Supplementary Table 25.** Negative control drugs and associated National Drug Codes (NDC).

Negative control	NDC
<b>Metformin</b>	64764015860, 45802016972, 45802021172, 50090599300, 66993036160, 66993036230, 93745501, 93745601, 93745701, 378313301, 23155011501, 23155011601, 23155011701, 62135073360, 68382018401, 68382018501, 68382018601, 87606005, 87606313, 87606413, 87607005, 87607111, 55045250401, 49999066030, 68012000316, 68012000450, 228275250, 23155023301, 23155023401, 23155023501, 23155023505, 51138047330, 57237002301, 57237002401, 57237002405, 57237002501, 57237002505, 65862008001, 65862008005, 65862008101, 65862008105, 65862008201, 65862008205, 50458054060, 50458054160, 50458054260, 50458054360, 50458094001, 50458094101, 50458094201, 50458094301, 6007861, 6007862, 6007882, 6008061, 6008062, 6008082, 6008131, 6008154, 6008182, 6057561, 6057562, 6057582, 6057761, 6057762, 6057782, 597014618, 597014660, 597014718, 597014760, 597014818, 597014860, 597014860, 597027073, 597027094, 597027533, 597027581, 64764033560, 64764033760, 310612560, 310613530, 310614595, 72205040701, 72205040802, 72205040901, 93104801, 93721201, 93726701, 93726710, 378035001, 378035205, 378600191, 378600291, 378718505, 378718605, 378718705, 591241101, 591241219, 591272060, 603446921, 904668961, 904669161, 904716261, 904716361, 904716461, 10544024802, 10544052130, 11788003760, 23155010201, 23155010205, 23155010206, 23155010209, 23155010210, 23155010301, 23155010305, 23155010309, 23155010310, 23155010401, 23155010405, 23155010409, 23155010410, 23155084101, 23155084105, 23155084110, 23155084201, 23155084205, 23155084210, 23155084301, 23155084305, 23155084310, 24658029218, 24658079010, 24658079105, 24658079205, 24979014604, 24979015304, 25000010112, 25000010212, 27241018860, 27241018960, 27241024001, 27241024190, 29033003106, 29033003206, 29033005501, 29033005601, 29300038901, 29300038905, 29300039901, 31722004247, 33342023911, 38779212605, 42291049710, 42291049718, 42291049736, 42291049750, 42291049790, 42291049801, 42291049818, 42291049850, 42291059318, 42291061001, 42291082450, 42291082490, 42291082510, 42291082512, 42291082518, 42291082536, 42291082590, 42385090210, 42385090410, 42385094701, 42385094705, 42385094711, 42385094801, 42385094805, 42385094811, 42385094901, 42385094905, 42385094911, 42385097701, 42385097705, 42385097711, 42385097790, 42385097801, 42571033301, 42571033490, 42571036007, 42571036010, 42806021305, 42806031305, 42806031505, 42806040660, 42806063201, 42806063205, 42806063301, 43353008260, 43353008280, 43353008292, 43353008296, 43353089430, 43353098230, 43353098253, 43353098260, 43353098270, 43353098280, 43353098296, 43353098730, 43353098745, 43353098753, 43353098760, 43353098773, 43353098780, 43353098786, 43353098796, 43547035950, 47335030588, 47335030688, 49483062001, 49483062010, 49483062081, 49483062110, 49483062181, 49483062201, 49483062210, 49483062250, 49483062281, 49483062301, 49483062309, 49483062310, 49483062350, 49483062401, 49483062450, 49999010660, 50090208104, 50090305002, 50090505200, 50090685603, 50090685805, 50090685806, 50228010501, 50228010505, 50228010510, 50228010530, 50228010601, 50228010605, 50228010701, 50228010705, 50228010710, 50228010730, 50228044501, 50228044690, 50228050460, 50742015405, 50742015490, 50742015501, 50742063360, 50742063460, 51079017201, 51224000750, 51224000760, 51224002050, 51224002060, 51224002070, 51224010750, 51224010760, 51224012050, 51224012060, 51224012070, 51224022050, 51224022060, 51224022070, 51991080605, 51991080705, 52817082050, 53002142200, 53746017805, 53746017810, 53746021801, 55289061590, 55700066990, 57664039751, 57664039753, 57664039758, 57664039788, 57664043551, 57664043553, 57664043558, 57664047451, 57664047453, 57664047458, 57664047488, 59651004260, 59651004360, 59651085401, 59651085405, 59651085499, 59651085501, 59651085505, 59651085601,

Negative control	NDC					
59651085605, 59651085699, 60429011101, 60429011110, 60429011136, 60429011145, 60429011205, 60429011218, 60429011227, 60429011260, 60429011301, 60429011305, 60429011318, 60505026001, 60505470001, 60505470109, 60687014301, 60687015501, 60687015511, 60687016201, 60687016211, 60760052360, 61442036110, 61442036301, 62037057110, 62135068005, 62135068130, 62135068230, 62135068418, 62584025901, 62756014201, 62756014202, 62756014301, 62991304901, 63629139704, 63629139705, 63629914701, 65862000801, 65862000805, 65862000899, 65862000901, 65862000905, 65862001001, 65862001005, 65862001046, 65862001099, 65862029101, 65862029105, 66336088414, 66689031816, 67877015901, 67877015905, 67877015910, 67877041301, 67877041305, 67877041390, 67877041401, 67877056101, 67877056105, 67877056110, 67877056201, 67877056205, 67877056210, 67877056301, 67877056305, 67877056310, 68094048060, 68094048070, 68094068860, 68094068870, 68094080450, 68094080460, 68094090450, 68094090460, 68180033607, 68180033707, 68180033801, 68180033909, 68382075801, 68382075805, 68382075810, 68382075901, 68382075905, 68382075910, 68382076001, 68382076005, 68382076010, 68462052001, 68462052190, 68645030059, 68645054459, 68645054559, 68645054759, 68645058259, 68645058359, 68645058459, 68645059559, 68682001890, 68682002150, 68788720409, 69238212601, 69315041001, 69315041005, 69367018001, 69367018005, 69367018010, 69367018101, 69367018105, 69367018201, 69367018205, 69367018210, 69367038101, 69367038105, 69367038110, 69367038205, 69367038301, 69367038305, 69367038310, 69452038088, 70010006301, 70010006305, 70010006309, 70010006310, 70010006401, 70010006405, 70010006409, 70010006410, 70010006499, 70010006501, 70010006505, 70010006509, 70010006510, 70010006599, 70010049101, 70010049105, 70010049109, 70010049110, 70010049201, 70010049210, 70010049601, 70010049709, 70934013630, 71093013204, 71093013205, 71093013206, 71093013305, 71093013404, 71093013405, 71205088260, 71205088478, 71335029304, 71335128902, 71335128903, 71335183301, 71335183308, 71610021080, 71610044153, 71610045453, 71610045760, 71610045770, 71610045792, 71610045794, 71610046760, 71610055430, 71610055453, 71610055460, 71610055470, 71610055480, 71610055494, 71610057860, 71610058770, 71610058794, 71610061330, 71610061353, 71610061360, 71610061370, 71610061380, 71610065230, 71610065253, 71610065260, 71610065270, 71610065280, 71610065294, 71610066660, 71610066680, 71610067280, 71610074053, 71610074080, 71610083730, 71610083753, 71610083760, 71610083770, 71610083794, 71610085830, 71610085853, 71610085860, 71610085870, 71610085880, 71610085894, 71610086753, 71610086780, 71610092080, 71610092392, 71656001704, 71717010611, 72336006430, 72336009530, 72578003601, 72789009730, 72789010590, 72789010593, 72789010595, 72789010601, 72789010682, 72789010690, 72789010693, 72789040060, 72789040090, 75834050001, 75834050005, 76385012810, 76385012901, 82009004610, 82009004710, 83301000801, 83301000802, 83301000803, 83301000902, 83301000903, 83301001001, 83301001002, 83301001003, 67877093001, 67877093005, 67877093101, 67877093205, 10135082305, 82009011710, 82009011801, 71610094160, 13668028160, 33342017609, 33342017657, 33342017709, 33342017757, 57237021760, 57237021860, 65862052518, 65862052560, 65862052618, 65862052660, 10631001917, 10631020601, 378817593, 378817691, 378817793, 43598061860, 43598061930, 43598062030, 6536903, 6536906, 6537003, 6537006, 6537303, 6537306, 6537403, 6537406, 70710198606, 70710198706, 597015918, 597015960, 597016818, 597016860, 597017518, 597017560, 597018018, 597018060, 597028073, 597028090, 597029059, 597029074, 597029578, 597029588, 597030045, 597030093, 310622560, 310625030, 310626060, 310627030, 310628030, 70710178706						
<b>Simvastatin</b>	115138702, 16714077801, 16714077802, 16714077901, 16714077902, 16714078001, 16714078002, 16714078101, 16714078102, 43598058330, 43598074210, 43598074230, 43598074290, 43598074305, 43598074330, 43598074390, 43598074410, 43598074430,					

Negative control	NDC					
	43598074490,	43598074505,	43598074530,	43598074590,	45963056608,	45963056630,
	45963056708,	45963056730,	51407019230,	62559070030,	62559070090,	62559070130,
	62559070190,	62559070230,	62559070290,	62559070330,	67877050730,	67877050790,
	67877050830,	67877050890,	67877050930,	67877050990,	67877051030,	67877051090,
	68462032130,	68462032190,	68462032230,	68462032290,	68462032330,	68462032390,
	68462032430,	68462032490,	69238115503,	69238115603,	69238115609,	69238115703,
	69238115803,	29273040104,	93715410,	93715619,	16714068101,	16714068102,
	16714068201,	16714068202,	16714068203,	16714068301,	16714068302,	16714068303,
	16714068401,	16714068402,	16714068403,	16714068501,	16714068502,	16714068503,
	16729000415,	16729000417,	16729000510,	16729000515,	16729000517,	16729000610,
	16729000615,	16729000617,	16729000715,	16729000717,	16729015615,	16729015617,
	24658050010,	24658050090,	24658050110,	24658050130,	24658050145,	24658050190,
	24658050210,	24658050230,	24658050245,	24658050290,	24658050310,	24658050330,
	24658050345,	24658050390,	24658050410,	24658050445,	24658050490,	31722051010,
	31722051090,	31722051110,	31722051210,	31722051310,	31722051390,	43353086115,
	47463077430,	52343002299,	52343002330,	52343002345,	52343002399,	52343002430,
	52343002499,	52343002599,	54868562903,	55111019790,	55111019805,	55111019830,
	55111019890,	55111019905,	55111019910,	55111019990,	55111020005,	55111020030,
	55111020090,	55111026830,	55111026890,	60687021001,	60687021011,	61919071090,
	63304079330,	63629338502,	63739057010,	63739057110,	63739057210,	63739057310,
	65862005030,	65862005090,	65862005130,	65862005190,	65862005199,	65862005230,
	65862005290,	65862005299,	65862005330,	65862005390,	65862005399,	65862005430,
	65862005490,	68084051101,	68084051111,	68084051201,	68084051211,	68180046403,
	68180046406,	68180046409,	68180046503,	68180046506,	68180046509,	68180047801,
	68180047802,	68180047803,	68180047901,	68180047902,	68180047903,	68382006516,
	68645047054,	68645052754,	68788743703,	70377000114,	70377000115,	70377000214,
	70377000215,	70377000312,	70377000314,	70377000315,	70377000412,	70377000414,
	70377000415,	70377000514,	70377000515,	71610060945,	71610061045,	71610061145,
	71610061545,	82009001210,	82009001310,	82009001410,	82009001510,	82009001605,
	78206017401,	78206017501,	78206017502,	78206017601,	78206017602,	6054331,
	6073531,	6074031,	6074931,	78206018001,	78206018002,	78206018101,
	78206018102,	78206018201,	78206018202			

**Abbreviation:** NDC, National Drug Codes.

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