

Supplementary:

Table S1. Equivalency Conversion Table for Benzodiazepines

Table S2. ICD-9-CM and ICD-10-CM Codes of Diseases and Conditions Used in the Study

Table S3. Minimum and Maximum Standardized Mean Differences across Trajectory Group Comparisons

Table S4. Patterns of Opioid Use During 3-month Trajectory Measurement Period by Trajectory Group

Table S5. Patterns of Benzodiazepine Use During 3-month Trajectory Measurement Period by Trajectory Group

Table S6. Trajectories of Opioid and Benzodiazepine Use and Risk of Subsequent Injurious Falls among Medicare Beneficiaries

Table S7. E-values of Hazard Ratio Estimates for Injurious Falls among Medicare Beneficiaries

Figure S1. Sample Size Flowchart

Figure S2. Study Design Diagram

Figure S3. Trajectories of Opioid and Benzodiazepine Utilization Patterns and Risk of Injurious Falls: Sensitivity Analyses including Beneficiaries with Injurious Falls During the 6-month Trajectory Period (n=622,588)

**Table S1. Equivalency Conversion Table for Benzodiazepines**

|                        | Minimum diazepam<br>10 mg equivalent<br>dose | Type (by half-life) |
|------------------------|----------------------------------------------|---------------------|
| <b>Benzodiazepines</b> |                                              |                     |
| Alprazolam             | 0.5                                          | Short-acting        |
| Bromazepam             | 3                                            | Intermediate-acting |
| Chlordiazepoxide       | 10                                           | Long-acting         |
| Clonazepam             | 0.5                                          | Long-acting         |
| Clorazepate            | 7.5                                          | Long-acting         |
| Diazepam               | 10                                           | Long-acting         |
| Estazolam              | 1                                            | Intermediate-acting |
| Flurazepam             | 15                                           | Long-acting         |
| Lorazepam              | 1                                            | Intermediate-acting |
| Nitrazepam             | 2.5                                          | Long-acting         |
| Oxazepam               | 15                                           | Short-acting        |
| Quazepam               | 15                                           | Long-acting         |
| Temazepam              | 10                                           | Intermediate-acting |
| Triazolam              | 0.25                                         | Short-acting        |

**Table S2. ICD-9-CM and ICD-10-CM Codes of Diseases and Conditions Used in the Study**

| <b>Diseases (ordered alphabetically)</b>        | <b>ICD-9-CM</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>ICD-10-CM</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alcohol use disorders                           | 303.x, 305.0x, 291                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | F10.1, F10.121, F10.14, F10.15, F10.180, F10.182, F10.2, F10.221, F10.231, F10.232, F10.24, F10.25, F10.26, F10.27, F10.280, F10.282                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Anxiety disorders                               | 293.84, 300.0X, 300.10, 300.2X, 300.3X, 300.89, 300.9X, 308.X, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3X, 313.82, 313.83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | F06.4, F40.x, F41.x, F42.x, F43.0, F43.1x, F44.9, F45.8, F48.8, F48.9, F93.8, F99, R45.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Any cancers except for non-melanoma skin cancer | 140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 151.x, 152.x, 153.x, 154.x, 155.x, 156.x, 157.x, 158.x, 159.x, 160.x, 161.x, 162.x, 163.x, 164.x, 165.x, 170.x, 171.x, 172.x, 174.x, 175.x, 176.x, 179.x, 180.x, 181.x, 182.x, 183.x, 184.x, 185.x, 186.x, 187.x, 188.x, 189.x, 190.x, 191.x, 192.x, 193.x, 194.x, 195.x, 196.x, 197.x, 198.x, 199.x, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 210.x, 211.x, 212.x, 213.x, 214.x, 215.x, 216.x, 217.x, 218.x, 219.x, 220.x, 221.x, 222.x, 223.x, 224.x, 225.x, 226.x, 227.x, 228.x, 229.x, 230.x, 231.x, 232.x, 233.x, 234.x, 235.x, 236.x, 237.x, 238.x, 239.x | C00.x, C01.x, C02.x, C03.x, C04.x, C05.x, C06.x, C07.x, C08.x, C09.x, C10.x, C11.x, C12.x, C13.x, C14.x, C15.x, C16.x, C17.x, C18.x, C19.x, C20.x, C21.x, C22.x, C23.x, C24.x, C25.x, C26.x, C30.x, C31.x, C32.x, C33.x, C34.x, C37.x, C38.x, C39.x, C40.x, C41.x, C43.x, C4A.x, C45.x, C46.x, C47.x, C48.x, C49.x, C50.x, C51.x, C52.x, C53.x, C54.x, C55.x, C56.x, C57.x, C58.x, C60.x, C61.x, C62.x, C63.x, C64.x, C65.x, C66.x, C67.x, C68.x, C69.x, C70.x, C71.x, C72.x, C73.x, C74.x, C75.x, C76.x, C77.x, C78.x, C79.x, C80.x, C7A.x, C7B.x, C81.x, C82.x, C83.x, C84.x, C85.x, C86.x, C88.x, C90.x, C91.x, C92.x, C93.x, C94.x, C95.x, C96.x, D00.x, D01.x, D02.x, D03.x, D04.x, D05.x, D06.x, D07.x, D09.x, D10.x, D11.x, D12.x, D13.x, D14.x, D15.x, D16.x, D17.x, D18.x, D19.x, D20.x, D21.x, D22.x, D23.x, D24.x, D25.x, D26.x, D27.x, D28.x, D29.x, D30.x, D31.x, D32.x, D33.x, D34.x, D35.x, D36.x, D37.x, D38.x, D39.x, D40.x, D41.x, D42.x, D43.x, D44.x, D45.x, D46.x, D47.x, D48.x, D3A.x, D49.x |
| Injurious falls                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Falls                                           | E880-E888                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | W00-W19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Fractures                                       | 800-804, 805, 806, 807.0x-807.1x, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 831, 832, 833, 836                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | S02, S06, S12, S22, S32, S42, S43, S52, S53, S62, S63, S72, S81, S82, S92, T07, T148                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                 | Procedure codes (only for outpatient settings):<br>27230-27248, 27193-27194, 27215-27228, 21800, 21805, 21810, 23500-23515, 23600-23630, 23665-23680, 24500-24587 plus splint, 24586, 24587, 24620,                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                          | 24635, 24650-24685, 25500-25609, 25611, 25620, 25650-25652 plus cast or splint, 25622-25628 plus cast or splint, 26600, 26605, 26607, 26608, 26615, 26645, 26650, 26665, 26740, 26746 plus splint, 26720, 26725, 26727, 26735, 26740, 26742, 26746, 26750, 26755, 26756, 26765 plus splint, 27500-27514, 27530-27540, 27750-27759, 27780-27792, 27824-27828 plus cast or splint, 27520, 27524 plus splint, 27760-27769, 27808-27823, 28430-28445, 22305, 22310, 22315, 22318, 22319, 22325-22328, 22510-22515, 22520-22525, 27200, 27202, 72291, 72292, 76012, 76013, 77082, 77085, 77086, S2360-S2363 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Mood disorders                                           | 296.0x, 296.1x, 296.2x, 296.3x, 296.4x, 296.5x, 296.6x, 296.7x, 296.9x, 293.83, 296.80, 296.81, 296.82, 296.89, 311                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | F30.x, F32.x, F33.x, F31.x, F34.8, F39, F06.30, F31.9, F30.8, F32.8, F31.81, F32.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Musculoskeletal system and connective tissues conditions | 71y.x (y=0 to 9), 72y.x (y= 0 to 9), 73y.x (y=0 to 9),                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | M32.10, M33.20, M33.90, M34.0, M34.1, M34.9, M35.00, M35.01, M35.5, M35.8, M35.9, M11.20, M11.2x9 (x= 1 to 7), M11.28, M11.29, M11.80, M11.8x9 (x= 1 to 7), M11.88, M11.89, M11.9, M02.00, M02.20, M02.9, M12.80, M14.60, M14.80, M14.80, M36.2, M36.3, M36.4, M05.00, M05.10, M05.30, M05.60, M06.1, M06.4, M06.9, M08.00, M08.3, M08.40, M12.00, M15.x (x= 0 to 9), M16.10, M16.7, M16.9, M17.10, M17.5, M17.9, M18.9, M19.0x9 (x= 1 to 4, 7), M19.2x9 (x = 1 to 4, 7), M19.90, M19.91, M19.93, M12.10, M12.1x9 (x= 1 to 7), M12.18, M12.19, M12.50x, M12.8x, M12.9, M13.1x, M13.8x, M22.40, M23.009, M23.2x, M23.202, M23.205, M23.305, M23.3x9, M23.3x9 (x=1, 2, 3, 5, 6), M23.40, M23.50, M23.8x9, M24, M25, M45.9, M46.00, M46.1, M46.80, M46.90, M49.80, M47.10, M47.12, M47.14, M47.16, M47.812, M47.814, M47.817, M47.819, M48.10, M48.20, M48.30, M48.9, M46.45, M46.40, M46.47, M50.x0 (x=0 to 3, 8, 9), M51.0x, M51.2x, M51.3x, M51.4x, M51.8x, M51.9, M96.1, M43.6, M48.02, M53.0, M53.1, M53.82, M54.02, M54.12, M54.13, M54.2, M67.88, M43.27, M43.28, M43.8x9, M48.0x (x=0, 4, 6, 8), M53.2X7, M53.2X8, M53.3, M53.9, M54.08, M54.1x (x=4 to 7), M54.30, M54.5, M54.6, M54.89, M54.9, M35.3, M25.70, M25.729, M70.1x, M70.2x, M70.3x, M70.40, M70.5x. |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | M70.6x, M70.7x, M75.0x, M75.10x.<br>M75.2x, M75.3x, M75.4x, M75.5x,<br>M75.8x, M76.x0 (x=1, 2, 4, 5, 6), M76.829,<br>M76.899, M77.x0 (x=0 to 5, 8, 9), M67.47,<br>M70.30, D48.1, M20.10, M21.61, M21.62,<br>M65.00, M65.20, M65.30, M65.4, M65.80,<br>M65.849, M65.879, M65.9, M66.10,<br>M66.18, M66.2x9 (x =3 to 6). M66.339,<br>M66.349. M66.369, M66.829, M66.879,<br>M66.88, M66.9, M67.00, M67.4x (x=0 to<br>6), M67.50, M67.80. M67.88, M67.90,<br>M70.039, M70.40, M71.00, M71.20,<br>M71.x0 (x=3 to 5, 8, 9), M75.120, M24.20,<br>M35.7, M60.009, M60.10, M60.20,<br>M61.00, M61.10, M61.40, M61.59, M61.9,<br>M62.00, M62.10, M62.3, M62.40, M62.50,<br>M62.838, M62.84, M62.89, M62.9, M72.x<br>(x =0, 1, 2, 4, 6), M54.10, M60.9, M70.98,<br>M72.9. M79.0. M79.x (x= 1 to 5). M79.609.<br>M79.7, M79.81. M79.89, M79.9, R25.2,<br>R29.898, M46.20. M46.30, M86.1x,<br>M86.2x, M86.6x, M86.9. M86.9, M89.6x,<br>M90.8x, M88.9, M89.40. M89.70, M90.60,<br>M90.80, M42.00, M42.10, M91.80, M92.x0<br>(x = 3 to 8), M93.003, M93.1, M93.20,<br>M93.80, M93.90, M48.4, M48.50XA, M80,<br>M81.x, M84, M85, M87, M89, M89.00,<br>M89.30. M89.8X9, M94, M94.0, M94.8X9,<br>S02.91XK, S02.91XK, S02.92XK.<br>S12.000K, S12.001K, S12.100K, S12.101K,<br>S12.200K, S12.201K, S12.300K, S12.301K,<br>S12.400K, S12.401K, S12.500K. S12.501K,<br>S12.600K S12.601K, S22.9XXK. S32.9XXK.<br>S42.009K, S42.009P. S42.209K, S42.209P.<br>S42.90XK, S42.90XP, S52.90XK,<br>S52.90XM. S52.90XN, S52.90XP,<br>S52.90XQ, S52.90XR, S62.90XK.<br>S62.90XP. S72.90XK, S72.90XM,<br>S72.90XN, S72.90XP, S72.90XQ,<br>S72.90XR, S82.009P, S82.009Q, S82.009R,<br>S82.90XK, S82.90XM, S82.90XN,<br>S82.90XP, S82.90XQ, S82.90XR, S92.819K,<br>S92.819P, S92.909K, S92.909P, S92.919K.<br>S92.919P, S99.209K, S99.209P, S99.219K,<br>S99.219P, S99.229K, S99.229P, S99.239K,<br>99.239P, S99.249K, S99.249P, S99.299K, |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                    |                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                                                                                                                                                                                                                                                                                           | S99.299P, M21.40, M20.10. M20.20, M20.30, M20.40, M20.5X9, M20.60, M20.009. M20.019, M20.029. M20.039. M20.099, M21.029, M21.059. M21.069, M21.129. M21.159, M21.169, M21.339, M21.5x, M21.6X9, M21.759, M21.769, M21.80, M21.839, M21.859, M21.869, M21.90, M21.939, M21.959, M21.969, M40.00, M40.10, M40.209, M40.299. M40.40. M40.50. M41.x0 (x=0, 2, 3, 4, 5, 8), M41.9, M43.8X9, M43.8x9, M96.2, M96.3, M96.4, M96.5, M43.00, M43.10, M89.38, M89.8x8, M95.x, M99.83, M99.84, M99                                                                                                                                            |
| Non-opioid substance use disorders | 304.1x, 304.2x, 304.3x, 304.4x, 304.6x, 304.8x, 304.9x, 305.2x, 305.3x, 305.4x, 305.6x, 305.7x, 305.8x, 305.9x, V11.3, V79.1, 303.x, 305.0x,                                                                                                                                                              | F10.1x, F10.220, F12.x, F13.1x, F13.2x, F13.90, F14.1x, F14.2x, F14.90, F15.1x, F15.2x, F15.90, F16.x, F18.10, F18.120, F18.20, F18.21, F18.90, F19.1x, F19.90, F55.x, Z65.8, Z13.89                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Opioid use disorders               | 304.0x, 304.7x, 305.5x                                                                                                                                                                                                                                                                                    | F11.2x, F19.2x, F11.1x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Pain: abdominal pain               | 540.9, 553.1, 553.3, 564.1, 577.0, 533.90, 535.00, 550.90, 550.92, 553.2x (x=0,1,9), 590.80, 789.0x (x=0 to 7, 9), 541                                                                                                                                                                                    | K35.80, K35.89, K42.9, K44.9, K58.x (x=1, 2, 8, 9), K85.9x (x=0 to 2, 9) , K27.9, K29.00, K40.90, K40.20, K43.9, K43.2, K46.9, N12, R10.9, R10.11, R10.12, R10.31, R10.32, R10.33, R10.13, R10.84, R10.10, R10.2, R10.30, K37                                                                                                                                                                                                                                                                                                                                                                                                      |
| Pain: fibromyalgia                 | 729.1                                                                                                                                                                                                                                                                                                     | M60.9, M79.1, M79.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Pain: back pain                    | 721.42, 721.5-721.91, 722.10, 722.2, 722.30, 722.32, 722.52, 722.6, 722.73, 722.80, 722.83, 722.90, 722.93, 724.00, 724.02, 724.09, 724.2, 724.3, 724.4, 724.5, 724.6, 724.8, 724.9, 737.1x, 737.20, 737.3x, 738.4, 739.3, 739.4, 756.10, 756.12-756.19, 805.4, 805.6, 805.8, 846.0-846.9, 307.89, 996.4x | F45.42, M40.00, M40.209, M40.299, M40.40, M41.00, M41.20, M41.30, M41.80, M41.9, M43.00, M43.10, M43.27, M43.28, M43.8X9, M46.40, M46.47, M47.10, M47.16, M47.819, M48.00, M48.061, M48.08, M48.10, M48.20, M48.30, M48.9, M51.06, M51.26, M51.27, M51.34, M51.35, M51.36, M51.37, M51.46, M51.47, M51.86, M51.87, M51.9, M53.2X7, M53.3, M53.9, M54.08, M54.14, M54.15, M54.16, M54.17, M54.30, M54.5, M54.89, M54.9, M96.1, M96.2, M96.3, M96.5, M97.9XXA, M99.03, M99.04, S12.9XXA, S22.009A, S32.009A, S32.10XA, S32.2XXA, S33.6XXA, S33.8XXA, S33.9XXA, T84.019A, T84.029A, T84.039A, T84.059A, T84.069A, T84.099A, T84.119A, |

|                                                                    |                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                    |                                                                                                                                                                                                                       | T84.129A, T84.199A, T84.498A, Q76.0, Q76.1, Q76.2, Q76.419, Q76.49                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Pain: chest                                                        | 413.9, 786.5x (x=0 to 2, 9)                                                                                                                                                                                           | I20.8, I20.9, R07.9, R07.2, R07.1, R07.8x (x=1,2,9)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Pain: headache/<br>migraine                                        | 346.xx, 784.0x, 307.81,                                                                                                                                                                                               | G43.019, G43.109, G43.119, G43.711, 43.809, G43.819, G43.909, G43.919, G43.yx (y=A to D), G44.1, R51, G44.209                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Pain: neck pain                                                    | 723.xx, 721.0x, 721.1x, 722.0x, 722.4x, 839.0x, 839.1x, 847.0x, 722.x1 (x=3,7,8,9)                                                                                                                                    | M48.02, M53.0, M53.1, M54.2, M47.812, M47.12, M50.20, M50.30, M43.6, M53.82, M54.02, M54.12, M54.13, M67.88, S11.90XA, S11.90XA, S13.1x1A (x=0 to 8), S13.4XXA, S13.8XXA, M51.44, M51.45, M50.00, M96.1, M50.80, M50.90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Pain: osteoarthritis                                               | 715.x                                                                                                                                                                                                                 | M15.x, M16.x, M17.x, M18.x, M19.x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Pain: rheumatoid<br>arthritis                                      | 714.x                                                                                                                                                                                                                 | M05.x, M06.x, M08.yx (y=0,2,3,8,9), M12.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Pain:<br>temporomandibular<br>disorder pain                        | 524.6x (x=0 to 3, 9)                                                                                                                                                                                                  | M26.60x (x=1 to 3, 9), M26.69, M26.61x (x=1 to 3, 9), M26.62x (x=1 to 3, 9), M26.63x (x=1 to 3, 9)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Pain: pelvic (e.g.,<br>menstrual/<br>genital reproductive)<br>pain | 625.x (x=3,8,9), 626.6, 627.1, 627.2                                                                                                                                                                                  | N94.6, N94.89, R10.2, N92.1, N95.0, N95.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Other pain conditions                                              | 996.4x, 72y.xx (y=5 to 9), 382.9, 522.4, 522.5, 525.9, 565.1, 703.0, 706.2, 848.x (x=3,8,9), 379.91, 380.22, 380.23, 381.81, 388.70, 569.42, 604.90, 611.71, 611.79, 719.30, 786.52, 873.63, 470, 338.0, G89.2, 338.4 | M97.9XXA, T84.0x9A (x=1 to 3, 5, 6, 9), T84.099A, T84.1x9A (x=1,2,9), T84.498A, M35.3, M25.70, M25.729, M70.yx (y=1 to 3, 5 to 7), M70.40, M75.0x, M75.10x, M75.yx (y=2 to 5,8), M76.x0 (x=1,2,4 to 6), M76.829, M76.899, M77.x0 (x=0 to 5), M77.8, M77.9, M67.47, M70.30, D48.1, M20.10, M21.61, M21.62, M65.00, M65.20, M65.30, M65.4, M65.80, M65.80, M65.849, M65.879, M65.9, M66.10, M66.18, M66.2x9 (x=3 to 6), M66.3x9 (x=4 to 6), M66.349, M66.369, M66.829, M66.879, M66.88, M66.9, M67.00, M67.4x (x=0 to 6), M67.50, M67.80, M67.88, M67.90, M70.039, M70.40, M71.x0 (x=0,2 to 5,8), M71.9, M75.120, M24.20, M35.7, M60.009, M60.10, M60.20, M61.x0 (x=0,1,4), M61.59, M61.9, M62.x0 (x=0,1,4,5), M62.3, M62.838, M62.84, M62.89, M62.9, M72.x (x=0 to 2,4,6), M54.10, M60.9, M70.98, M72.9, M79.x (x=0 to 5), M79.609, M79.7, M79.81, |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                        |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 |                                                                                                                                                                                                                                                                                                                                                                                                 | M79.89, M79.9, R25.2, R29.898, H66.90, K04.4, K04.7, K08.9, K60.x (x=3 to 5), L60.0, L72.3, S23.41XA, S03.9XXA, S29.019A, S39.011A, T14.90XA, H57.13, H60.5x9 (x=0 to 5, 9), H60.60, H60.8X1, H60.90, H69.80, H92.09, K62.89, N45.x (x=1 to 3), N64.4, N64.5x (x=1 to 3, 9), M12.30, M12.40, R07.1, R07.81, S02.5XXA, S02.5XXB, J34.2, G89.x (x=0,2,4) |
| Sleep disorders | 291.82, 292.85, 307.4, 307.41, 307.42, 307.45, 307.46, 307.47, 307.48, 307.49, 327.11, 327.12, 327.2, 327.21, 327.23, 327.24, 327.26, 327.27, 327.29, 327.3, 327.31, 327.32, 327.33, 327.34, 327.35, 327.36, 327.37, 327.39, 327.42, 327.43, 327.52, 327.53, 327.59, 327.8, 333.94, 347.0, 347.00, 347.01, 347.10, 347.11, 780.5, 780.51, 780.53, 780.55, 780.56, 780.57, 780.58, 780.59, V69.4 | F51, F51.0, F51.1, F51.11, F51.13, F51.19, F51.2, F51.3, F51.4, F51.5, F51.8, F51.9, G25.8, G47, G47.0, G47.1, G47.10, G47.11, G47.12, G47.13, G47.14, G47.19, G47.2, G47.30, G47.31, G47.33, G47.34, G47.37, G47.39, G47.4, G47.411, G47.419, G47.421, G47.429, G47.8, G47.9, R06.81                                                                  |

**Table S3. Minimum and Maximum Standardized Mean Differences across Trajectory Group Comparisons**

|                            | Min*   |        | Max*  |       |
|----------------------------|--------|--------|-------|-------|
|                            | Unwt.  | Wt.    | Unwt. | Wt.   |
| <b>Socio-demographics</b>  |        |        |       |       |
| Age ≥65 years              | 0.001  | <0.001 | 0.554 | 0.034 |
| Female                     | 0.003  | 0.001  | 0.379 | 0.050 |
| Race/ethnicity group       |        |        |       |       |
| White                      | <0.001 | <0.001 | 0.273 | 0.059 |
| Black                      | 0.004  | <0.001 | 0.255 | 0.061 |
| Others                     | <0.001 | <0.001 | 0.168 | 0.039 |
| Disability status          | 0.002  | <0.001 | 0.543 | 0.030 |
| LIS/Dual eligibility       |        |        |       |       |
| No LIS/no dual eligibility | 0.005  | <0.001 | 0.482 | 0.051 |
| LIS or dual eligibility    | 0.003  | <0.001 | 0.296 | 0.039 |
| LIS and dual eligibility   | 0.003  | <0.001 | 0.420 | 0.046 |
| Metropolitan residence     | <0.001 | 0.001  | 0.166 | 0.046 |
| <b>Health status</b>       |        |        |       |       |
| Elixhauser index           | 0.008  | <0.001 | 0.370 | 0.033 |
| Opioid use disorder        | 0.001  | <0.001 | 0.203 | 0.028 |
| Alcohol use disorders      | 0.002  | 0.001  | 0.176 | 0.049 |
| Other non-opioid SUD       | 0.001  | <0.001 | 0.198 | 0.044 |
| Anxiety disorders          | 0.010  | <0.001 | 0.645 | 0.060 |
| Mood disorders             | 0.010  | 0.001  | 0.519 | 0.041 |
| Sleep disorders            | 0.001  | <0.001 | 0.279 | 0.029 |
| Musculoskeletal conditions | 0.005  | 0.001  | 0.752 | 0.069 |
| Pain conditions            |        |        |       |       |
| Osteoarthritis             | 0.004  | <0.001 | 0.551 | 0.062 |
| Back pain                  | 0.006  | <0.001 | 0.538 | 0.056 |
| Neck pain                  | 0.003  | <0.001 | 0.306 | 0.016 |
| Chest pain                 | <0.001 | <0.001 | 0.177 | 0.034 |
| Abdominal pain             | 0.002  | <0.001 | 0.278 | 0.043 |
| Rheumatoid arthritis       | 0.003  | <0.001 | 0.169 | 0.032 |
| Pelvic pain                | <0.001 | <0.001 | 0.127 | 0.043 |
| Headache/migraine          | <0.001 | <0.001 | 0.140 | 0.027 |
| TMJ                        | <0.001 | <0.001 | 0.059 | 0.062 |
| Others                     | 0.001  | <0.001 | 0.275 | 0.028 |
| <b>Health services use</b> |        |        |       |       |
| Any hospitalization        | 0.015  | 0.001  | 0.573 | 0.130 |
| ED visits                  |        |        |       |       |
| 0                          | 0.002  | <0.001 | 0.232 | 0.027 |
| 1                          | 0.001  | <0.001 | 0.202 | 0.024 |

|                                                     |        |        |       |       |
|-----------------------------------------------------|--------|--------|-------|-------|
| ≥2                                                  | 0.001  | <0.001 | 0.130 | 0.014 |
| Outpatient visits                                   |        |        |       |       |
| 0                                                   | 0.003  | <0.001 | 0.370 | 0.065 |
| 1                                                   | <0.001 | <0.001 | 0.034 | 0.034 |
| 2-5                                                 | 0.003  | 0.001  | 0.287 | 0.057 |
| >5                                                  | 0.002  | <0.001 | 0.191 | 0.046 |
| Urine drug test                                     | 0.001  | <0.001 | 0.034 | 0.040 |
| <b>Medication use related variables</b>             |        |        |       |       |
| Any high-risk medication use                        | 0.006  | <0.001 | 0.463 | 0.033 |
| Any alpha agonists                                  | <0.001 | <0.001 | 0.104 | 0.029 |
| Any alpha blockers                                  | <0.001 | <0.001 | 0.078 | 0.038 |
| Any antidysrhythmics                                | <0.001 | <0.001 | 0.033 | 0.035 |
| Any antiepileptics                                  | 0.001  | <0.001 | 0.407 | 0.037 |
| Any antihistamines                                  | <0.001 | <0.001 | 0.142 | 0.038 |
| Any antiPD                                          | 0.001  | <0.001 | 0.275 | 0.065 |
| Any antipsychotics                                  | <0.001 | <0.001 | 0.592 | 0.067 |
| Any antispasmodics                                  | 0.001  | <0.001 | 0.102 | 0.046 |
| Any antithrombotics                                 | <0.001 | <0.001 | 0.042 | 0.048 |
| Any anxiolytics                                     | <0.001 | <0.001 | 0.021 | 0.029 |
| Any barbiturates                                    | <0.001 | <0.001 | 0.065 | 0.039 |
| Any calcium channel blocker                         | <0.001 | <0.001 | 0.019 | 0.027 |
| Any hypnotic                                        | 0.002  | <0.001 | 0.243 | 0.032 |
| Any muscle relaxants                                | <0.001 | <0.001 | 0.317 | 0.046 |
| Any PPI                                             | <0.001 | <0.001 | 0.268 | 0.052 |
| Any SSRI                                            | <0.001 | <0.001 | 0.370 | 0.048 |
| Any TCA                                             | <0.001 | <0.001 | 0.110 | 0.020 |
| No. antidepressants                                 | 0.002  | <0.001 | 0.446 | 0.046 |
| No. antipsychotics                                  | 0.001  | <0.001 | 0.439 | 0.058 |
| No. gabapentinoids                                  | 0.006  | <0.001 | 0.303 | 0.034 |
| No. muscle relaxants                                | 0.007  | <0.001 | 0.194 | 0.042 |
| No. naltrexone                                      | 0.001  | <0.001 | 0.058 | 0.021 |
| Had polypharmacy (≥5 medications including OPI/BZD) | <0.001 | <0.001 | 0.390 | 0.025 |

Abbreviations: **ED**, emergency department; **LIS**, low-income subsidy; **No**, number of; **SD**, standard deviation;

**SMD**; standardized mean difference; **Unwt**, unweighted; **Wt**, weighted

\* Represents the minimum and maximum SMD across the 78 SMDs from group comparisons (the number of 2-combinations from the given 13 trajectories:  $C_2^{13} = 78$ ; i.e., group A vs B, group A vs C, group A vs D).

**Table S4. Patterns of Opioid Use During 3-month Trajectory Measurement Period by Trajectory Group**

| <b>OPI use patterns*</b>          | <b>Overall</b> | <b>A</b> | <b>B</b> | <b>C</b> | <b>D</b> | <b>E</b> | <b>F</b> | <b>G</b> | <b>H</b> | <b>I</b> | <b>J</b> | <b>K</b> | <b>L</b> | <b>M</b> |
|-----------------------------------|----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| No. beneficiaries                 | 622588         | 279263   | 93703    | 47851    | 24952    | 14225    | 71715    | 28109    | 19230    | 13013    | 17750    | 5601     | 3729     | 3447     |
| % of the overall cohort           | 100.0          | 44.9     | 15.1     | 7.7      | 4.0      | 2.3      | 11.5     | 4.5      | 3.1      | 2.1      | 2.9      | 0.9      | 0.6      | 0.6      |
| <b>Type of OPIs, %</b>            |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| SAO Schedule II only              | 59.5           | 66.6     | 30.3     | 64.1     | 24.4     | 49.5     | 0        | 0        | 0        | 0        | 65.3     | 55.1     | 54.2     | 52.3     |
| SAO Schedule III only             | 10.5           | 14.5     | 7.9      | 3.6      | 4.7      | 0.9      | 0        | 0        | 0        | 0        | 7.9      | 9.3      | 9.6      | 3.8      |
| SAO Schedule IV only              | 21.6           | 17.9     | 54.6     | 11.6     | 48.1     | 6.2      | 0        | 0        | 0        | 0        | 18.3     | 22.3     | 26.7     | 13.8     |
| LAO Schedule II only              | 0.1            | 0        | 0        | 0.2      | 0.1      | 2.5      | 0        | 0        | 0        | 0        | 0.1      | 0.1      | 0.3      | 1.3      |
| SAO mixed Schedules               | 7.5            | 0.9      | 6.9      | 19.4     | 21.2     | 30.2     | 0        | 0        | 0        | 0        | 7.8      | 12.8     | 8.5      | 18.7     |
| SAO and LAO mixed use             | 0.5            | 0        | 0.1      | 0.8      | 0.5      | 8.5      | 0        | 0        | 0        | 0        | 0.3      | 0.1      | 0.5      | 8.8      |
| Others                            | 0.3            | 0        | 0.2      | 0.4      | 1.1      | 2.1      | 0        | 0        | 0        | 0        | 0.3      | 0.3      | 0.3      | 1.2      |
| <b>OPI medication (top 10), %</b> |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Hydrocodone                       |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| SAO                               | 45.8           | 49.3     | 27.3     | 46.9     | 33.0     | 51.7     | 0        | 0        | 0        | 0        | 47.2     | 46.3     | 41.5     | 47.4     |
| Oxycodone SAO                     | 21.0           | 15.7     | 6.0      | 40.8     | 10.1     | 52.9     | 0        | 0        | 0        | 0        | 26.0     | 21.0     | 19.1     | 40.1     |
| Codeine SAO                       | 12.9           | 15.0     | 10.4     | 9.8      | 11.4     | 7.5      | 0        | 0        | 0        | 0        | 10.3     | 13.4     | 12.2     | 8.7      |
| Diphenoxylate                     | 2.2            | 2.1      | 3.9      | 1.2      | 3.9      | 0.6      | 0        | 0        | 0        | 0        | 1.5      | 3.1      | 3.0      | 1.7      |
| Hydromorphone                     |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| SAO                               | 0.9            | 0.4      | 0.2      | 2.3      | 0.4      | 4.9      | 0        | 0        | 0        | 0        | 1.4      | 1.2      | 1.1      | 3.8      |
| Fentanyl LAO                      | 0.2            | 0        | 0        | 0.4      | 0.1      | 3.6      | 0        | 0        | 0        | 0        | 0.1      | 0        | 0.2      | 3.4      |
| Morphine LAO                      | 0.2            | 0        | 0        | 0.4      | 0.1      | 1.4      | 0        | 0        | 0        | 0        | 0.6      | 0.3      | 0.4      | 2.3      |

|                                         |           |           |            |           |             |             |       |       |       |       |           |            |             |             |
|-----------------------------------------|-----------|-----------|------------|-----------|-------------|-------------|-------|-------|-------|-------|-----------|------------|-------------|-------------|
| Morphine SAO                            | 0.2       | 0         | 0          | 0.1       | 0.1         | 3.5         | 0     | 0     | 0     | 0     | 0.1       | 0          | 0.3         | 2.8         |
| Oxycodone LAO                           | 0.2       | 0         | 0          | 0.3       | 0           | 2.2         | 0     | 0     | 0     | 0     | 0.1       | 0.1        | 0.1         | 1.9         |
| Buprenorphine                           | 0         | 0         | 0.1        | 0         | 0.1         | 0.3         | 0     | 0     | 0     | 0     | 0         | 0          | 0.1         | 0.3         |
| <b>Other treatment patterns</b>         |           |           |            |           |             |             |       |       |       |       |           |            |             |             |
| First OPI                               |           |           |            |           |             |             |       |       |       |       |           |            |             |             |
| prescription's days supplied, mean (SD) | 8.2 (9.5) | 4.2 (2.3) | 21.4 (9.6) | 7.7 (5.4) | 24.2 (20.2) | 15.6 (12.8) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 6.9 (7.5) | 9.0 (10.1) | 11.6 (13.1) | 15.9 (13.6) |
| Mean OPI                                |           |           |            |           |             |             |       |       |       |       |           |            |             |             |
| prescription's days supplied, (SD)      | 8.4 (9.4) | 4.2 (2.3) | 21.6 (9.0) | 7.9 (5.1) | 26.2 (18.3) | 16.9 (10.9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 7.2 (7.4) | 9.2 (9.8)  | 12.1 (12.9) | 16.9 (12.4) |
| Mean daily OPI MME, (SD)                | 2.7 (5.1) | 1.3 (0.6) | 3.5 (1.7)  | 5.1 (3.0) | 8.3 (4.0)   | 23.7 (15.2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2.8 (2.9) | 3.1 (2.7)  | 3.9 (4.3)   | 18.6 (19.3) |
| Mean no. OPI fills, (SD)                | 1.4 (0.9) | 1.0 (0.2) | 1.3 (0.6)  | 1.8 (0.8) | 2.9 (1.3)   | 3.9 (1.9)   | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1.4 (0.7) | 1.6 (0.9)  | 1.5 (1.0)   | 3.1 (2.2)   |

Abbreviations: **LAO**, long-acting opioids; **No**, number of; **OPI**, opioid; **SAO**, short-acting opioids;

\* To facilitate the labeling of opioid and benzodiazepine dose levels for each trajectory, we defined opioid dosage use as: very-low- (SDD <25 MME), low- (25–50 MME), moderate- (51–90 MME), high- (91–150 MME), and very-high-dose (>150 MME). Similarly, we defined BZD dosage use as very-low- (<10 DME), low- (10–20 DME), moderate- (21–40 DME), high- (41–60 DME), and very-high-dose (>60 DME). Trajectory groups: **A**: Very-low OPI-only (early discontinuation); **B**: Low OPI-only (rapid decline); **C**: Very-low OPI-only (late discontinuation); **D**: Low OPI-only (gradual decline); **E**: Moderate OPI-only (rapid decline); **F**: Very-low BZD-only (late discontinuation); **G**: Low BZD-only (rapid decline); **H**: Low BZD-only (stable); **I**: Moderate BZD-only (gradual decline); **J**: Very-low OPI (rapid decline) / Very-low BZD (late discontinuation); **K**: Very-low OPI (rapid decline)/ Very-low BZD (increasing); **L**: Very-low OPI (stable)/Low BZD (stable); **M**: Low OPI (gradual decline)/ Low BZD (gradual decline).

**Table S5. Patterns of Benzodiazepine Use During 3-month Trajectory Measurement Period by Trajectory Group**

| <b>BZD use patterns*</b>        | <b>Overall</b> | <b>A</b> | <b>B</b> | <b>C</b> | <b>D</b> | <b>E</b> | <b>F</b> | <b>G</b> | <b>H</b> | <b>I</b> | <b>J</b> | <b>K</b> | <b>L</b> | <b>M</b> |
|---------------------------------|----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| No. beneficiaries               | 62258          | 27926    | 9370     | 4785     | 2495     | 1422     | 7171     | 2810     | 1923     | 1301     | 1775     | 5601     | 3729     | 3447     |
|                                 | 8              | 3        | 3        | 1        | 2        | 5        | 5        | 9        | 0        | 3        | 0        |          |          |          |
| % of the overall cohort         | 100            | 44.9     | 15.1     | 7.7      | 4.0      | 2.3      | 11.5     | 4.5      | 3.1      | 2.1      | 2.9      | 0.9      | 0.6      | 0.6      |
| <b>Type of BZD use, %</b>       |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| SA only                         | 34.3           | 0        | 0        | 0        | 0        | 0        | 29.1     | 24.7     | 58.2     | 33.0     | 44.5     | 35.4     | 38.5     | 35.8     |
| IA only                         | 33.3           | 0        | 0        | 0        | 0        | 0        | 39.4     | 35.1     | 21.3     | 23.8     | 28.1     | 32.1     | 26.7     | 31.8     |
| LA only                         | 29.5           | 0        | 0        | 0        | 0        | 0        | 30.9     | 35.1     | 18.3     | 33.8     | 25.6     | 28.6     | 27.9     | 23.8     |
| SA and IA mixed                 | 1.0            | 0        | 0        | 0        | 0        | 0        | 0.2      | 1.6      | 0.7      | 3.8      | 0.8      | 1.3      | 2.2      | 3.3      |
| SA and LA mixed                 | 0.9            | 0        | 0        | 0        | 0        | 0        | 0.2      | 2.0      | 0.6      | 2.7      | 0.4      | 1.0      | 2.5      | 2.5      |
| LA and IA mixed                 | 0.8            | 0        | 0        | 0        | 0        | 0        | 0.2      | 1.4      | 0.6      | 2.4      | 0.7      | 1.5      | 2.0      | 2.4      |
| SA, IA and LA mixed             | 0.1            | 0        | 0        | 0        | 0        | 0        | 0        | 0.1      | 0        | 0.4      | 0        | 0.1      | 0.2      | 0.4      |
| Missing                         | 0.1            | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0.3      | 0.1      | 0        | 0.1      | 0.1      | 0        |
| <b>BZD ingredients, %</b>       |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Alprazolam                      | 34.6           | 0        | 0        | 0        | 0        | 0        | 39.3     | 38.3     | 22.2     | 29.1     | 27.6     | 34.2     | 30.8     | 36.9     |
| Lorazepam                       | 25.9           | 0        | 0        | 0        | 0        | 0        | 30.0     | 26.1     | 18.4     | 19.5     | 23.8     | 23.9     | 23.0     | 19.5     |
| Diazepam                        | 17.2           | 0        | 0        | 0        | 0        | 0        | 20.7     | 7.5      | 5.6      | 3.0      | 40.9     | 21.7     | 10.5     | 21.3     |
| Clonazepam                      | 10.7           | 0        | 0        | 0        | 0        | 0        | 6.0      | 16.0     | 10.7     | 31.6     | 3.9      | 10.2     | 14.2     | 19.5     |
| Chlordiazepoxide                | 8.4            | 0        | 0        | 0        | 0        | 0        | 2.8      | 4.5      | 43.4     | 5.7      | 1.2      | 6.4      | 18.9     | 2.1      |
| Temazepam                       | 5.8            | 0        | 0        | 0        | 0        | 0        | 1.3      | 13.0     | 1.3      | 22.8     | 3.0      | 7.3      | 10.2     | 11.4     |
| Triazolam                       | 0.5            | 0        | 0        | 0        | 0        | 0        | 0.5      | 0.2      | 0.3      | 0.1      | 1.5      | 0.5      | 0.5      | 0.2      |
| Clobazam                        | 0.1            | 0        | 0        | 0        | 0        | 0        | 0        | 0.1      | 0.3      | 0.2      | 0        | 0.1      | 0.1      | 0        |
| Oxazepam                        | 0.1            | 0        | 0        | 0        | 0        | 0        | 0.1      | 0.1      | 0.1      | 0.1      | 0.1      | 0        | 0.1      | 0.1      |
| Flurazepam                      | 0              | 0        | 0        | 0        | 0        | 0        | 0        | 0.1      | 0        | 0.1      | 0        | 0        | 0.1      | 0        |
| Estazolam                       | 0              | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0.1      | 0.1      | 0.1      |
| <b>Other treatment patterns</b> |                |          |          |          |          |          |          |          |          |          |          |          |          |          |
| First BZD prescription's        | 23.7<br>(22.7) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 14.6     | 25.0     | 56.3     | 37.8     | 9.7      | 21.3     | 42.0     | 23.7     |

|                                                   |                |          |          |          |          |          |                    |                    |                    |                    |                   |                    |                    |                    |
|---------------------------------------------------|----------------|----------|----------|----------|----------|----------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|
| days supplied, mean<br>(SD)                       |                |          |          |          |          |          | (11.7<br>)         | (12.5<br>)         | (31.2<br>)         | (25.8<br>)         | (10.7<br>)        | (20.5<br>)         | (28.2<br>)         | (18.0<br>)         |
| Mean BZD<br>prescription's<br>days supplied, (SD) | 24.2<br>(22.5) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 14.6<br>(11.7<br>) | 25.9<br>(11.8<br>) | 57.6<br>(29.8<br>) | 39.3<br>(24.3<br>) | 9.8<br>(10.6<br>) | 21.9<br>(20.1<br>) | 43.5<br>(26.9<br>) | 24.6<br>(17.3<br>) |
| Mean daily BZD<br>DME,<br>(SD)                    | 1.3<br>(4.2)   | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 1.5<br>(1.1)       | 5.9<br>(2.9)       | 7.9<br>(2.5)       | 21.7<br>(10.4<br>) | 1.4<br>(1.7)      | 2.5<br>(2.4)       | 8.7<br>(4.3)       | 14.2<br>(14.4<br>) |
| Mean no. BZD fills,<br>(SD)                       | 1.5<br>(1.0)   | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 0<br>(0) | 1.1<br>(0.3)       | 1.7<br>(0.8)       | 2.3<br>(1.3)       | 2.9<br>(1.6)       | 1.1<br>(0.3)      | 1.3<br>(0.6)       | 2.4<br>(1.2)       | 2.1<br>(1.3)       |

Abbreviations: **BZD**, benzodiazepine; **IA**, intermediate-acting; **LA**, long-acting; **No**, number of; **SA**, short-acting;

\* To facilitate the labeling of opioid and benzodiazepine dose levels for each trajectory, we defined BZD dosage use as very-low- (<10 DME), low- (10–20 DME), moderate- (21–40 DME), high- (41–60 DME), and very-high-dose (>60 DME). Trajectory groups: **A**: Very-low OPI-only (early discontinuation); **B**: Low OPI-only (rapid decline); **C**: Very-low OPI-only (late discontinuation); **D**: Low OPI-only (gradual decline); **E**: Moderate OPI-only (rapid decline); **F**: Very-low BZD-only (late discontinuation); **G**: Low BZD-only (rapid decline); **H**: Low BZD-only (stable); **I**: Moderate BZD-only (gradual decline); **J**: Very-low OPI (rapid decline) / Very-low BZD (late discontinuation); **K**: Very-low OPI (rapid decline)/ Very-low BZD (increasing); **L**: Very-low OPI (stable)/Low BZD (stable); **M**: Low OPI (gradual decline)/ Low BZD (gradual decline)..

**Table S6. Trajectories of Opioid and Benzodiazepine Use and 6-month Risk of Subsequent Injurious Falls among Medicare Beneficiaries (N=622,588)**

| Trajectory Groups <sup>s</sup>                                        | Injurious Falls (n=5,167) |                                 |                   |                       |
|-----------------------------------------------------------------------|---------------------------|---------------------------------|-------------------|-----------------------|
|                                                                       | N (crude rate*)           | Days of follow-up, median (IQR) | Unadjusted        | Adjusted <sup>†</sup> |
| A. Very-low OPI-only (early discontinuation)                          | 1,930 (11.6)              | 83 (88.0)                       | Ref               | Ref                   |
| B. Low OPI-only (rapid decline)                                       | 641 (11.4)                | 91 (83.0)                       | 0.99 (0.91, 1.08) | 1.00 (0.92, 1.09)     |
| C. Very-low OPI-only (late discontinuation)                           | 583 (20.4)                | 69 (95.0)                       | 1.77 (1.61, 1.94) | 1.54 (1.40, 1.69)     |
| D. Low OPI-only (gradual decline)                                     | 354 (23.8)                | 71 (75.0)                       | 2.06 (1.84, 2.31) | 1.93 (1.72, 2.16)     |
| E. Moderate OPI-only (rapid decline)                                  | 185 (21.8)                | 66 (83.0)                       | 1.89 (1.63, 2.20) | 2.22 (1.93, 2.55)     |
| F. Very-low BZD-only (late discontinuation)                           | 521 (12.2)                | 87 (82.0)                       | 1.05 (0.95, 1.16) | 0.95 (0.86, 1.04)     |
| G. Low BZD-only (rapid decline)                                       | 237 (14.1)                | 90 (85.0)                       | 1.22 (1.07, 1.40) | 1.12 (0.98, 1.29)     |
| H. Low BZD-only (stable)                                              | 252 (22.0)                | 76 (93.5)                       | 1.90 (1.67, 2.17) | 1.82 (1.59, 2.07)     |
| I. Moderate BZD-only (gradual decline)                                | 143 (18.4)                | 101 (62.0)                      | 1.59 (1.34, 1.89) | 1.31 (1.09, 1.58)     |
| J. Very-low OPI (rapid decline) / Very-low BZD (late discontinuation) | 150 (14.2)                | 92 (68.0)                       | 1.22 (1.04, 1.44) | 1.08 (0.91, 1.28)     |
| K. Very-low OPI (rapid decline)/ Very-low BZD (increasing)            | 43 (12.8)                 | 109 (73.0)                      | 1.11 (0.82, 1.50) | 0.99 (0.73, 1.36)     |
| L. Very-low OPI (stable)/Low BZD (stable)                             | 80 (36.2)                 | 84 (74.5)                       | 3.13 (2.50, 3.91) | 2.64 (2.08, 3.36)     |

|                                   |           |           |                   |                   |
|-----------------------------------|-----------|-----------|-------------------|-------------------|
| <hr/>                             |           |           |                   |                   |
| M. Low OPI (gradual decline)/ Low |           |           |                   |                   |
| BZD (gradual decline)             | 48 (23.4) | 79 (68.0) | 2.02 (1.52, 2.69) | 1.72 (1.26, 2.35) |
| <hr/>                             |           |           |                   |                   |

Abbreviations: **CI**, confidence interval; **BZD**, benzodiazepines; **HR**, hazard ratio; **OPI**, opioid; **OPI-BZD**, concurrent opioid and benzodiazepine use;

§ To facilitate the labeling of opioid and benzodiazepine dose levels for each trajectory, we defined opioid dosage use as: very-low- (SDD <25 MME), low- (25–50 MME), moderate- (51–90 MME), high- (91–150 MME), and very-high-dose (>150 MME). Similarly, we defined BZD dosage use as very-low- (<10 DME), low- (10–20 DME), moderate- (21–40 DME), high- (41–60 DME), and very-high-dose (>60 DME).

\* The unit for crude rates is per 10,000 person-months.

† We excluded 11 beneficiaries with extreme IPTWs (>10) using trimming methods to increase validity of treatment effect estimates.

**Table S7. E-values of Hazard Ratio Estimates for 3-month Injurious Falls among Medicare Beneficiaries**

| Trajectory Groups <sup>§</sup>                                        | Injurious Falls       |                 |                          |
|-----------------------------------------------------------------------|-----------------------|-----------------|--------------------------|
|                                                                       | Adjusted HRs (95% CI) | E-value for HR* | E-value for lower 95% CI |
| A. Very-low OPI-only (early discontinuation)                          | Ref                   | Ref             | Ref                      |
| B. Low OPI-only (rapid decline)                                       | 0.92 (0.81, 1.03)     | 1.36            | 1.00                     |
| C. Very-low OPI-only (late discontinuation)                           | 1.78 (1.58, 2.01)     | 3.48            | 3.00                     |
| D. Low OPI-only (gradual decline)                                     | 2.24 (1.93, 2.59)     | 4.17            | 3.52                     |
| E. Moderate OPI-only (rapid decline)                                  | 2.60 (2.18, 3.09)     | 4.07            | 3.25                     |
| F. Very-low BZD-only (late discontinuation)                           | 0.93 (0.81, 1.07)     | 1.24            | 1.00                     |
| G. Low BZD-only (rapid decline)                                       | 1.02 (0.84, 1.24)     | 1.62            | 1.00                     |
| H. Low BZD-only (stable)                                              | 2.02 (1.70, 2.40)     | 3.54            | 2.87                     |
| I. Moderate BZD-only (gradual decline)                                | 1.03 (0.77, 1.36)     | 1.69            | 1.00                     |
| J. Very-low OPI (rapid decline) / Very-low BZD (late discontinuation) | 0.99 (0.78, 1.26)     | 1.46            | 1.00                     |
| K. Very-low OPI (rapid decline)/ Very-low BZD (increasing)            | 0.59 (0.34, 1.02)     | 2.35            | 1.00                     |
| L. Very-low OPI (stable)/Low BZD (stable)                             | 2.73 (1.98, 3.76)     | 6.42            | 4.66                     |
| M. Low OPI (gradual decline)/ Low BZD (gradual decline)               | 1.96 (1.32, 2.91)     | 3.64            | 2.24                     |

Abbreviations: **CI**, confidence interval; **BZD**, benzodiazepines; **HR**, hazard ratio; **OPI**, opioid;

<sup>§</sup> To facilitate the labeling of opioid and benzodiazepine dose levels for each trajectory, we defined opioid dosage use as: very-low (SDD <25 MME), low (25–50 MME), and moderate (51–90 MME). Similarly, we defined BZD dosage use as very-low (<10 DME), low (10–20 DME), and moderate (21–40 DME).

\* E-value is defined as the minimum strength of an association that an unmeasured confounder would need to have with the treatment and outcome to

fully account for a specific treatment-outcome association, conditioned on the measured covariates.

\* E-value is defined as the minimum strength of an association that an unmeasured confounder would need to have with the treatment and outcome to fully account for a specific treatment-outcome association, conditioned on the measured covariates.

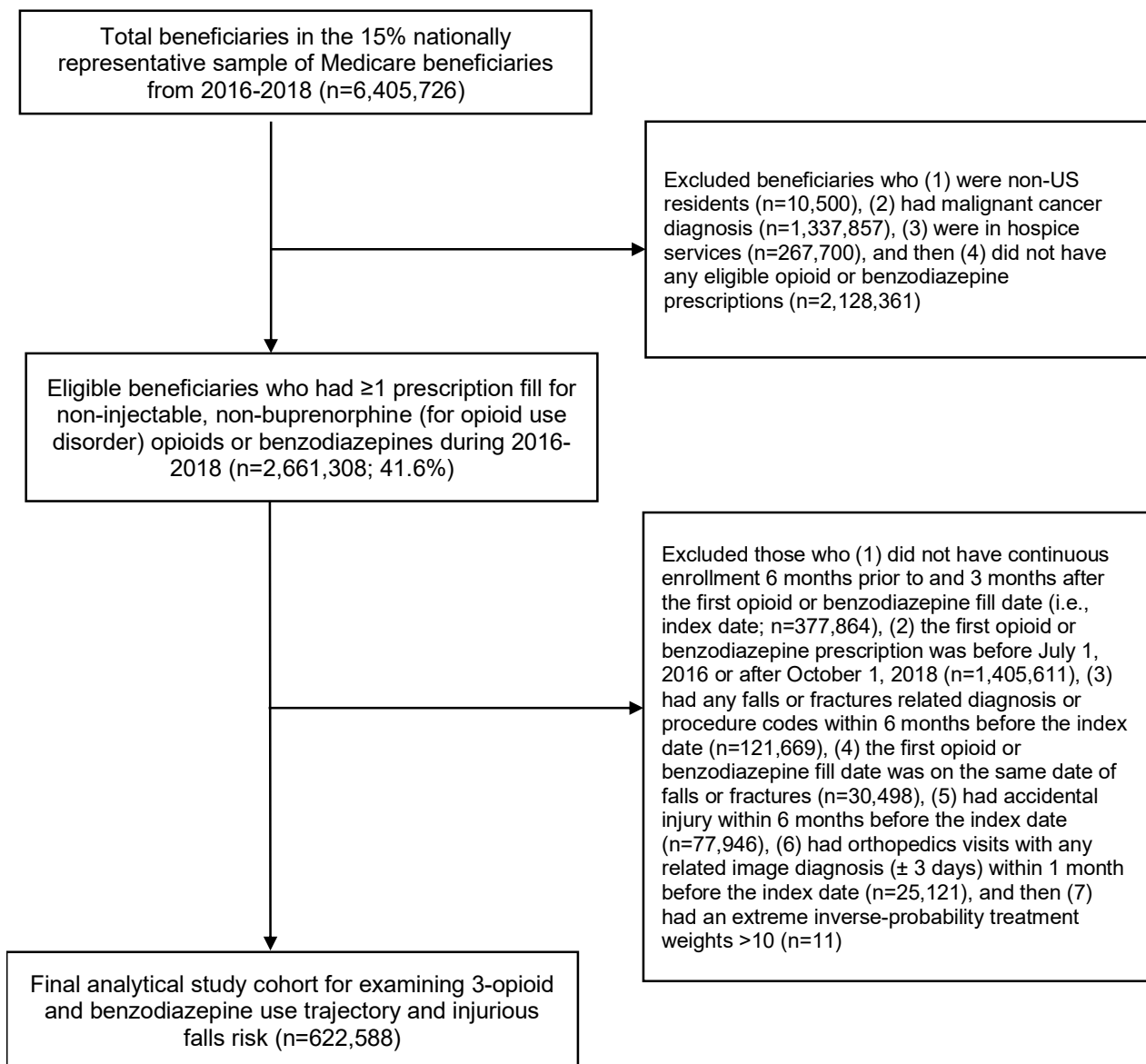
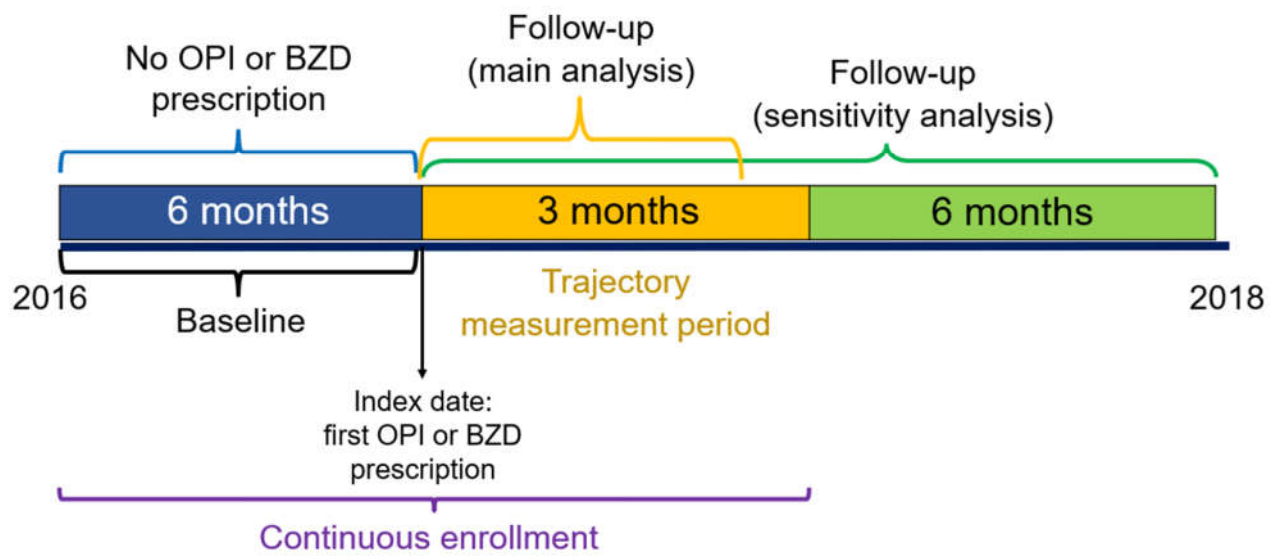
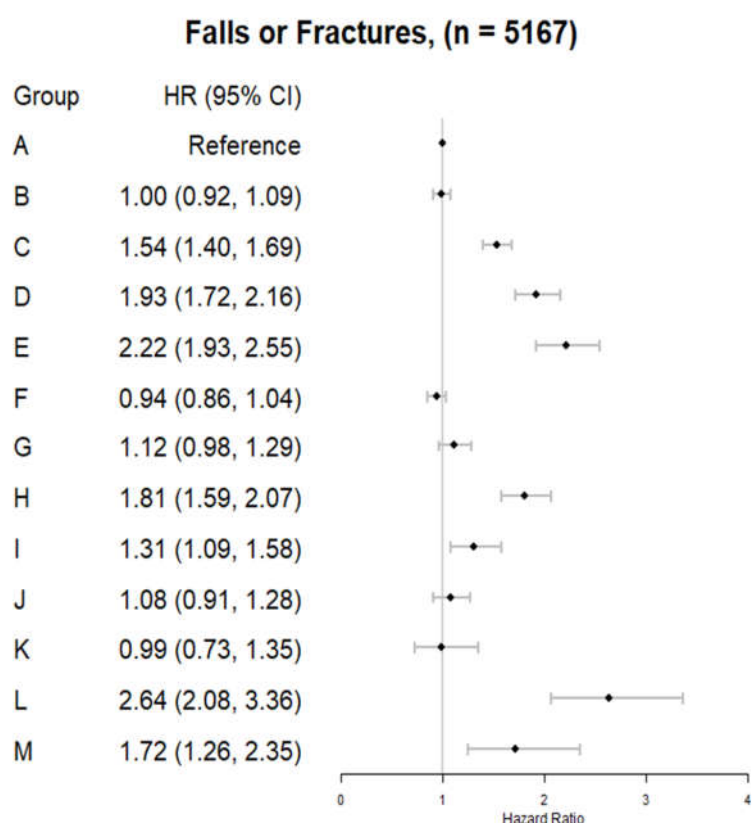


Figure S1. Sample Size Flowchart



**Figure S2. Study Design Diagram**

Abbreviations: **BZD**, benzodiazepines; **OPI**, opioids



A: Very-low OPI-only (rapid decline) (n=279,263, 44.9% of the cohort)  
 B: Low OPI-only (rapid decline) (n=93,703, 15.1%)  
 C: Very-low OPI-only (delayed decline) (n=47,851, 7.7%)  
 D: Low OPI-only (n=24,952, 4.0%)  
 E: Moderate OPI-only (n=14,225, 2.3%)  
 F: Very-low BZD-only (n=71,715, 11.5% of the cohort)  
 G: Low BZD-only (declining) (n=28,109, 4.5%)  
 H: Low BZD-only (stable) (n=19,230, 3.1%)  
 I: Moderate BZD-only (n=13,013, 2.1%)  
 J: Very-low OPI; Very-low BZD (n=17,750, 2.9% of the cohort)  
 K: Very-low OPI / Very-low BZD (n=5,601, 0.9%)  
 L: Very-low OPI; low BZD (stable) (n=3,729, 0.6%)  
 M: Low OPI; Low BZD (n=3,447, 0.6%)

**Figure S3. Trajectories of Opioid and Benzodiazepine Utilization Patterns and Risk of Injurious Falls: Sensitivity Analyses including Beneficiaries with Injurious Falls During the 6-month Trajectory Period (n=622,588)**

Abbreviations: **BZD**, benzodiazepine; **CI**, confidence intervals; **DME**, diazepam milligram equivalent; **HR**, hazard ratio; **MME**, morphine milligram equivalent; **OPI**, opioid; **OPI-BZD**, concurrent opioid

and benzodiazepine use; **SDD**, standardized daily dose

To facilitate the labeling of opioid and benzodiazepine dose levels for each trajectory, we defined opioid dosage use as: very-low- (SDD <25 MME), low- (25–50 MME), moderate- (51–90 MME), high- (91–150 MME), and very-high-dose (>150 MME). Similarly, we defined BZD dosage use as very-low- (<10 DME), low- (10–20 DME), moderate- (21–40 DME), high- (41–60 DME), and very-high-dose (>60 DME).