**Supplementary Online Content**

Ballreich J, Mansour O, Hu E, et al. Modeling mitigation strategies to reduce opioid-related morbidity and mortality in the US. *JAMA Netw Open*. 2020;3(11):e2023677. doi:10.1001/jamanetworkopen.2020.23677



This supplementary material has been provided by the authors to give readers additional information about their work.

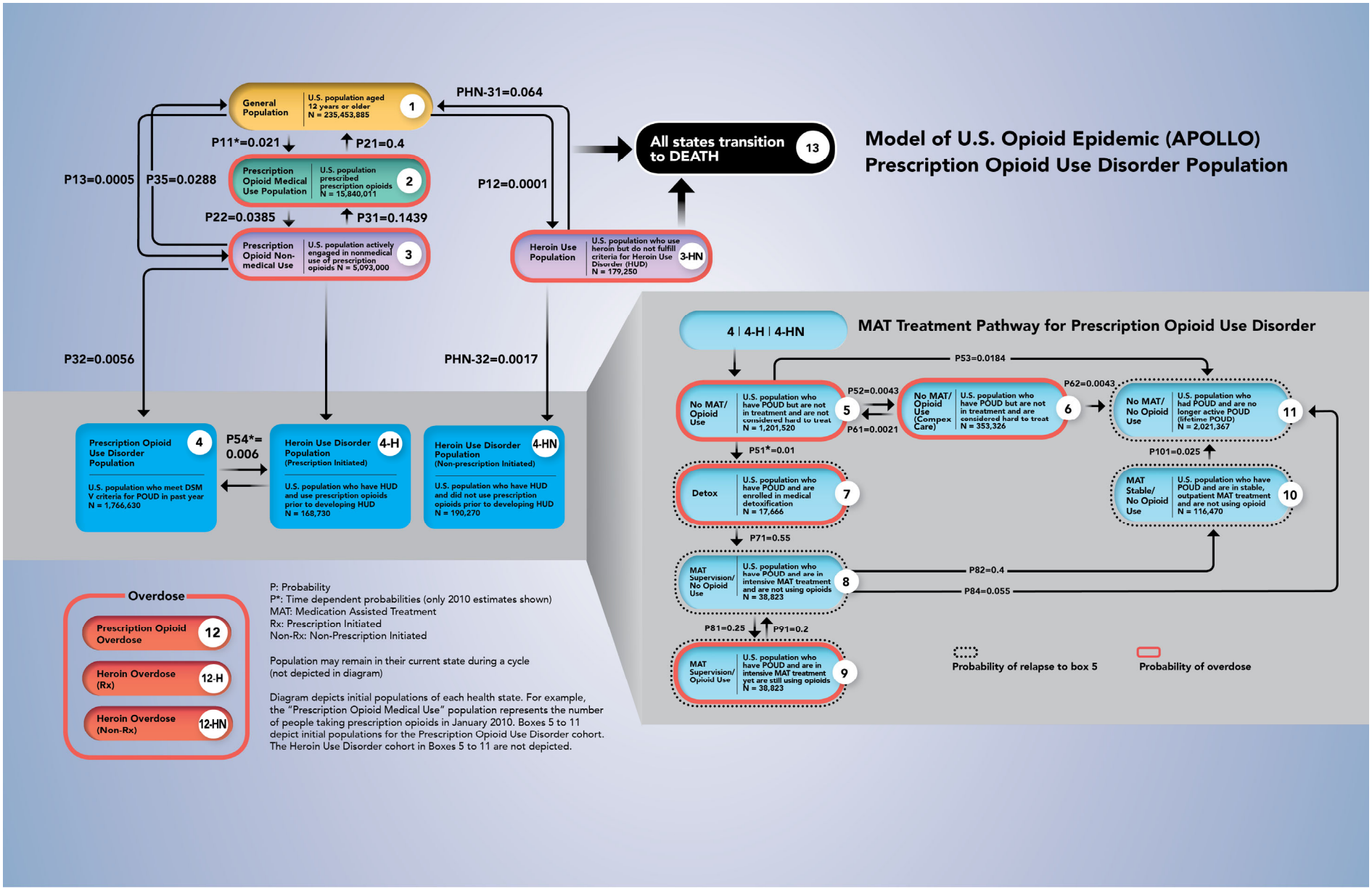
**eTable.** Calibration of major populations included in APOLLO.

| Population | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | Source |
|---|---|---|---|---|---|---|---|---|---|---|
| Total Population ACTUAL[1] | 260,124,362 | 262,607,802 | 265,092,889 | 267,352,435 | 270,131,237 | 272,700,371 | 275,286,656 | 276,833,437 | 279,169,227 | U.S. Census |
| Total Population MODEL | 263,111,944 | 265,808,868 | 268,189,332 | 270,276,191 | 272,444,888 | 274,688,229 | 276,940,252 | 279,076,689 | 281,098,692 | |
| Percent Difference | 1.1% | 1.2% | 1.2% | 1.1% | 0.9% | 0.7% | 0.6% | 0.8% | 0.7% | |
| Total Active OUD ACTUAL | 2,280,000 | 2,194,000 | 2,523,000 | 2,396,000 | 2,504,000 | 2,629,000 | 2,379,000 | 2,330,000 | 2,220,000 | Sum of POUD |
| Total Active OUD MODEL | 2,286,192 | 2,381,148 | 2,439,679 | 2,476,505 | 2,493,686 | 2,507,812 | 2,508,149 | 2,498,998 | 2,481,576 | |
| Percent Difference | 0.3% | 8.5% | -3.3% | 3.4% | -0.4% | -4.6% | 5.4% | 7.3% | 11.8% | |
| Prescription OUD ACTUAL | 1,921,000 | 1,768,000 | 2,056,000 | 1,879,000 | 1,918,000 | 2,038,000 | 1,753,000 | 1,678,000 | 1,694,000 | NSDUH pain |
| Prescription OUD MODEL | 1,828,059 | 1,848,147 | 1,853,231 | 1,849,709 | 1,835,089 | 1,823,242 | 1,812,760 | 1,801,040 | 1,782,891 | |
| Percent Difference | -4.8% | 4.5% | -9.9% | -1.6% | -4.3% | -10.5% | 3.4% | 7.3% | 5.2% | |
| Total HUD ACTUAL | 359,000 | 426,000 | 467,000 | 517,000 | 586,000 | 591,000 | 626,000 | 652,000 | 526,000 | NSDUH |
| Total HUD MODEL | 458,133 | 533,001 | 586,448 | 626,796 | 658,597 | 684,570 | 695,389 | 697,958 | 698,686 | |
| Percent Difference | 27.6% | 25.1% | 25.6% | 21.2% | 12.4% | 15.8% | 11.1% | 7.0% | 32.8% | |
| Total Overdose Deaths ACTUAL | 21,089 | 22,784 | 23,166 | 25,052 | 28,647 | 33,091 | 42,249 | 47,600 | 46,802 | CDC WONDER |
| Total Overdose Deaths MODEL | 22,397 | 23,352 | 24,843 | 26,839 | 28,778 | 32,081 | 41,950 | 46,927 | 46,814 | |
| Percent Difference | 6.2% | 2.5% | 7.2% | 7.1% | 0.5% | -3.1% | -0.7% | -1.4% | - | |
| Rx Opioid Deaths ACTUAL | 14,583 | 15,140 | 14,240 | 14,145 | 14,838 | 15,281 | 17,087 | 17,029 | - | CDC WONDER |
| Rx Opioid Deaths MODEL | 17,012 | 16,527 | 16,403 | 16,694 | 16,780 | 16,766 | 16,776 | 16,602 | 16,396 | |
| Percent Difference | 16.7% | 9.2% | 15.2% | 18.0% | 13.1% | 9.7% | -1.8% | -2.5% | - | |
| Heroin Deaths ACTUAL | 6,506 | 7,644 | 8,926 | 10,907 | 13,809 | 17,810 | 25,162 | 30,571 | - | CDC WONDER |
| Heroin Deaths MODEL | 5,384 | 6,825 | 8,441 | 10,145 | 11,998 | 15,315 | 25,174 | 30,325 | 30,418 | |
| Percent Difference | -17.2% | -10.7% | -5.4% | -7.0% | -13.1% | -14.0% | 0.0% | -0.8% | - | |
| Total MAT ACTUAL | 691,595 | 727,994 | 766,310 | 806,642 | 849,097 | 893,786 | 983,165 | - | - | CBHSQ |
| Total MAT MODEL | 601,191 | 595,756 | 654,812 | 724,944 | 814,372 | 871,918 | 932,895 | 1,002,150 | 1,089,022 | |
| Percent Difference | -13.1% | -18.2% | -14.5% | -10.1% | -4.1% | -2.4% | -5.1% | - | - | |

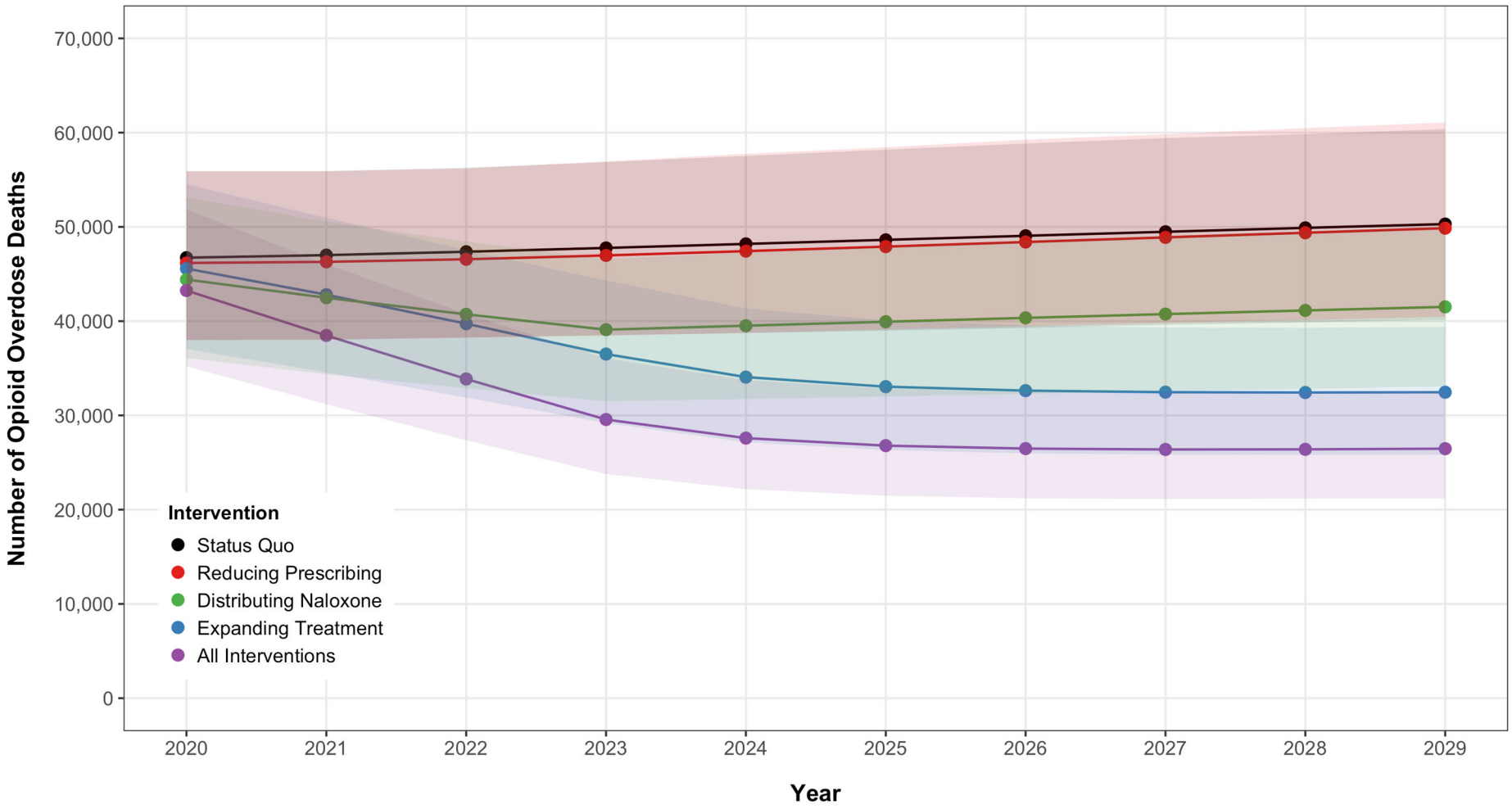
[1] Includes all populations within model

POUD Prescription Opioid Use Disorder; HUD Heroin Use Disorder; NSDUH National Survey on Drug Use and Health; CDC Centers for Disease Control and Prevention; WONDER Wide-ranging Online Data for Epidemiologic Research; MAT Medications for Addiction Treatment; CBHSQ Center for Behavioral Health Statistics and Quality

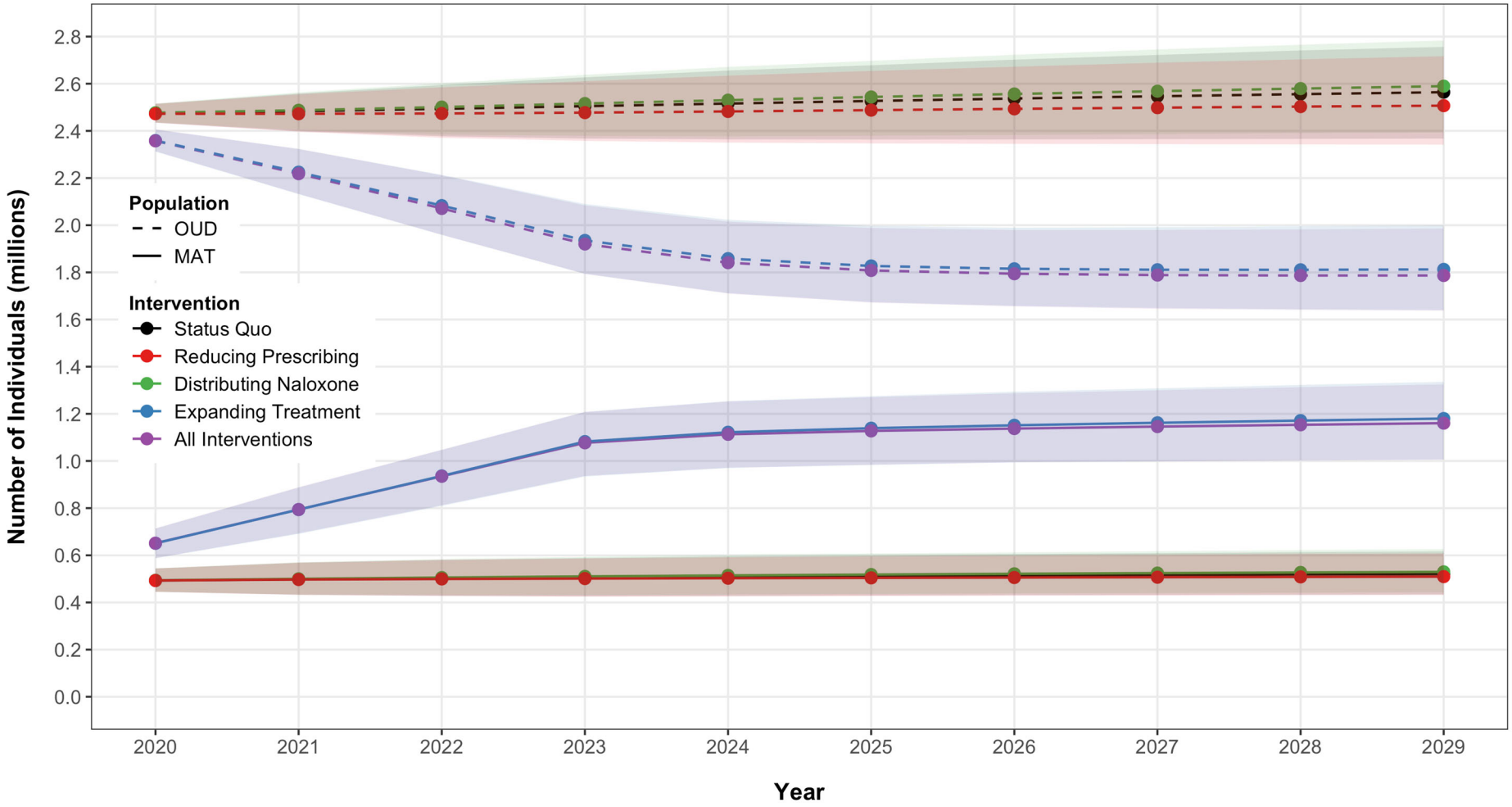
**eFigure 1.** Model of U.S. Opioid Epidemic (APOLLO) With Examples of Parameters



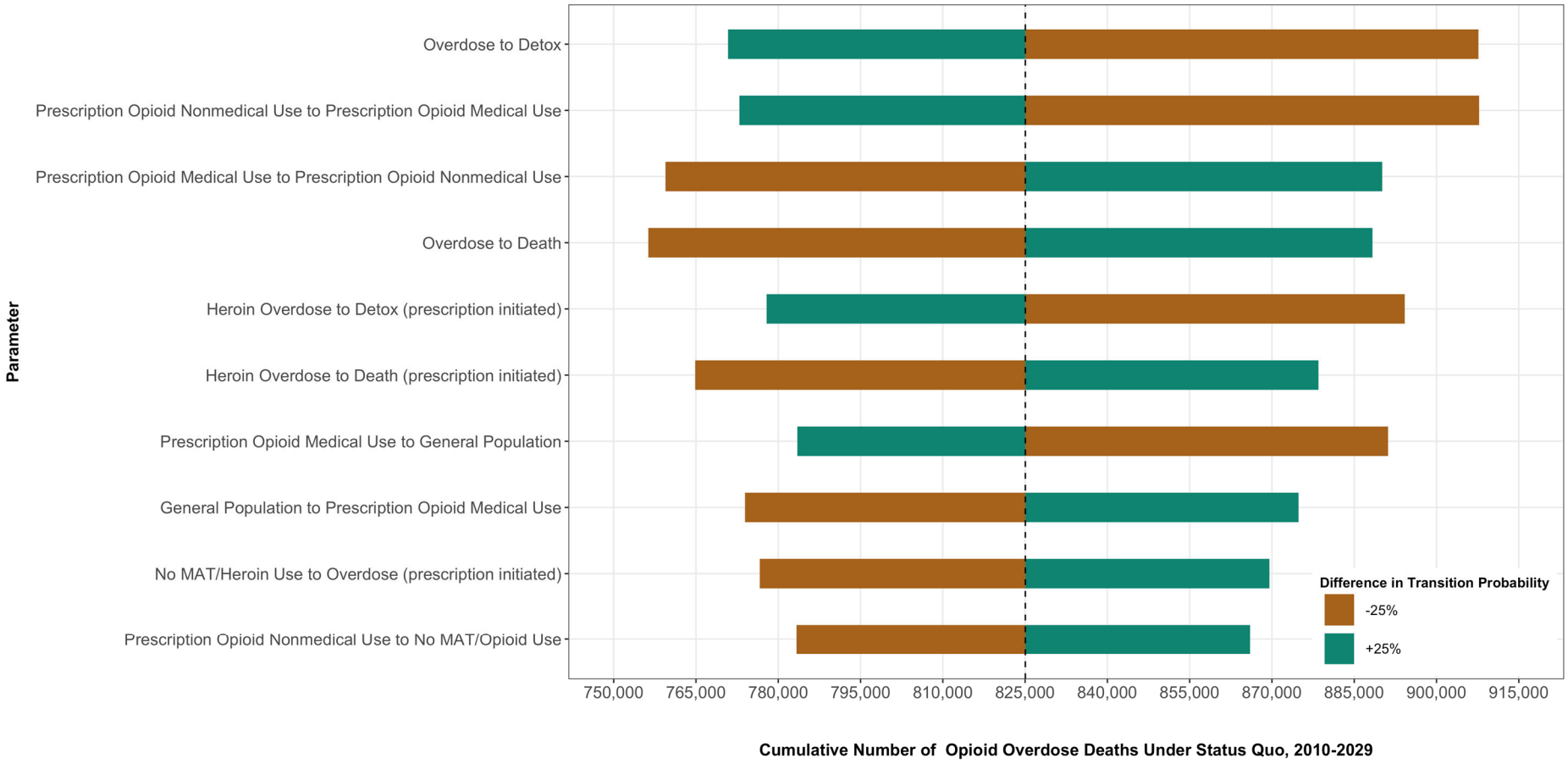

**eFigure 2.** Projected Number of Opioid Overdose Deaths Under Status Quo and Intervention Scenarios, 2020-2029



**eFigure 3.** Projected Number of Individuals with Opioid Use Disorder (OUD) and Number of Individuals Receiving Medications for Addiction Treatment (MAT) Under Status Quo and Intervention Scenarios, 2020-2029



**eFigure 4.** Univariate Sensitivity Analysis of ±25% Change in Top 10 Parameters Influencing Cumulative Number of Opioid Overdose Deaths Under Status Quo, 2010-2029



**eAppendix. Technical Information**

OVERVIEW

US-APOLLO model is a dynamic Markov model that describes the movement of populations in the U.S. through different phases of the opioid epidemic over time. This document provides the values, sources and notes for each parameter used in the model. Parameters were obtained from peer-reviewed publications, scientific reports from federal and state agencies, and expert opinion. Additionally, data used to populate US-APOLLO are derived from major national databases including: National Survey of Drug Use and Health (NSDUH), National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), CDC Wide-ranging ONline Data for Epidemiologic Research (WONDER) and National Health and Nutrition Examination Survey (NHANES). The choice of each parameter's value was driven by the strength of evidence and appropriateness of the parameter for the setting of the model. Final values for some parameters were adjusted during model calibration.

US-APOLLO starts on January 2010 and utilizes monthly time steps until December 2029. The model consists of 32 health states that reflect various states related to the opioid epidemic (e.g., prescription opioid medical use, prescription opioid use disorder, overdose death). A description of these 32 states can be found in the *Input Populations* section of the appendix. The model is an open model since populations can enter and exit the model; in other words, the model cohort is not fixed throughout time. We modeled the U.S. population age 12 years and older to maintain consistency with NSDUH, which focuses on this population in their "top-line" estimates, some of which are used to support model inputs.

US-APOLLO differentiates between heroin use disorder (HUD) that was initiated after prescription opioid use and heroin use disorder that was not initiated after prescription opioid use. For prescription- and non-prescription initiated HUD, the model has symmetrical treatment pathways and transition probabilities, although these two populations have different numbers of individuals at a given time point. For example, in 2010, the total prescription-initiated HUD population had 168,730 individuals, while the non-prescription initiated HUD population had 190,270 individuals.

While the model tracks the opioid epidemic through 2029, the years from 2010 to 2018 are used to calibrate the model. The process of calibration refers to the adjustment of parameters such that key model populations (e.g., overdose deaths) reflect the observed rates during the calibration period using actual data. US-APOLLO is calibrated based on the following populations and statistics: prescription opioid medical use, prescription opioid nonmedical use, heroin use, past year prescription opioid use disorder, past year heroin use disorder, overall opioid overdose deaths, prescription opioid overdose deaths, and heroin opioid overdose deaths. The sources of these data are identified below. In all cases, populations of heroin users in US-APOLLO include those using illicit synthetic opioids such as fentanyl.

**KEY DEFINITIONS**

The following is a list of key terms and their definitions used in US-APOLLO.

| TERM | DEFINITION |
|---|---|
| *Data Sources* | |
| **SAMSHA** | Substance Abuse and Mental Health Services Administration |
| **NSDUH** | National Survey on Drug Use and Health |
| **NESARC** | National Epidemiologic Survey on Alcohol and Related Conditions |
| **CDC WONDER** | CDC Wide-ranging ONline Data for Epidemiologic Research |
| **NHANES** | National Health and Nutrition Examination Survey |
| **TEDS** | Treatment Episode Data Set |
| | |
| *Data Terms* | |
| **POMU** | Prescription Opioid Medical Use |
| **PONU** | Prescription Opioid Nonmedical Use |
| **MAT** | Medication-Assisted Treatment (methadone, buprenorphine or naltrexone) |
| **MMEs** | Morphine Milligram Equivalents |
| **HUD** | Heroin Use Disorder |
| **ED** | Emergency Department |
| **BCBS** | Blue Cross Blue Shield |
| | |
| *Model Terms* | |
| **B_*** | B_* represents model boxes that are not heroin related. |
| **BH_*** | BH_* represents model boxes that are heroin related with prior prescription opioid use, with one exception; BH_3 represents heroin use with or without prior prescription opioid use. |
| **BHN_*** | BHN_* represents model boxes that are heroin related without prior prescription opioid use. |
| **P_*** | P_* represents transition probabilities that do not originate from heroin related boxes. |
| **PH_*** | PH_* represents transition probabilities that originate from heroin related boxes with prior prescription opioid use. |
| **PHN_*** | PHN_* represents transition probabilities that originate from heroin related boxes without prior prescription opioid use. |
| **OD_*** | OD_* represents transition probabilities to overdose state (fatal and non-fatal) that do not originate from heroin related boxes. |
| **ODH_*** | ODH_* represents transition probabilities to overdose state that originate from heroin related boxes with prior prescription opioid use. |
| **ODHN_*** | ODHN_* represents transition probabilities to overdose state that originate from heroin related boxes without prior prescription opioid use. |

| TERM | DEFINITION |
|---|---|
| **D_*** | D_* represents transition probabilities to the death state that do not originate from heroin related boxes. |
| **DH_*** | DH_* represents transition probabilities to the death state that do originate from heroin related boxes with prior prescription opioid use. |
| **DHN_*** | DHN_* represents transition probabilities to the death state that do originate from heroin related boxes without prior prescription opioid use. |

**INITIAL POPULATION PARAMETERS**

The following table lists the initial populations for the model's 32 health states. These populations reflect monthly snapshots. For example, the "Prescription Opioid Medical Use" population represents the number of people taking prescription opioids in January 2010. The initial populations are modeled with the variables B_x, BH_x, or BHN_x, where "B" represents "Box", "H" represents "Heroin with prior prescription opioid use", "HN" represents "Heroin without prior prescription opioid use", and "x" represents a specific health state number.

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| GENERAL POPULATION<br>*U.S. population aged 12 years or older* | B_1 | 235,453,885 | [1] | To calculate B_1, we started with the population of individuals, 12 years and older, as reported by the 2010 U.S. Census, and subtracted all downstream populations which include boxes B_2 through B_12, BH_3 through BH_12, and BHN_4 through BHN_12. We removed these downstream populations to prevent double counting. |
| PRESCRIPTION OPIOID MEDICAL USE POPULATION<br>*U.S. population prescribed prescription opioids* | B_2 | 15,840,011 | [2,3,4] | Mojtabai et al. reported a 6.8% monthly prevalence of prescription opioid use based on 2013-2014 NHANES, though notably, this estimate may include individuals with nonmedical use of prescription opioids or those who have POUD.<br><br>Furthermore, Guy et al. report that prescribing rates did not change between 2010 and 2012, and thus, we made the assumption that monthly prevalence regarding prescription opioid use in 2010-2012 was also 6.8%. |
| PRESCRIPTION OPIOID NONMEDICAL USE<br>*U.S. population actively engaged in nonmedical use of prescription opioids* | B_3 | 5,093,000 | [5] | We calculated B_3 using 2010 estimates of the number of individuals age 12 and over who misused prescription opioids reported in NSDUH. |
| PRESCRIPTION OPIOID USE DISORDER POPULATION (POUD)<br>*U.S. population who meet DSM V criteria for POUD in past year* | B_4 | 1,766,630 | [5,6] | The 2010 NSDUH reports that there were 1,921,000 individuals with past year dependence on pain relievers (i.e., POUD) and 359,000 individuals with past year dependence on heroin (i.e., HUD) nationally. Using NSDUH estimates of total OUD, POUD, and HUD populations, we estimate that approximately 43% of the current HUD population also have concurrent POUD, and we |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | remove this proportion of individuals with HUD from the POUD population to avoid double-counting. |
| NO MAT/OPIOID USE<br>*U.S. population who have POUD but are not in treatment and are not considered hard to treat* | B_5 | 1,201,520 | Calculation | This population represents individuals who had POUD in the past year but who were not receiving MAT nor were they in detox. We calculate B_5 by subtracting B_6 through B_10 from B_4 (POUD POPULATION).<br><br>B_6 through B_10 refer to populations who had past year POUD and were at various stages of treatment (further defined below in B_7 to B_10) or who did not receive treatment (see B_6). |
| NO MAT/OPIOID USE (COMPLEX CARE)*U.S. population who have POUD but are not in treatment and are considered hard to treat* | B_6 | 353,326 | Expert opinion | Based on expert opinion, we estimated that one-fifth of the POUD POPULATION would be difficult to treat. |
| DETOX<br>*U.S. population who have POUD and are enrolled in medical detoxification* | B_7 | 17,666 | [7] | In Pitts et al.'s economic model, 1% of the POUD POPULATION enters detox each month. In US-APOLLO, because we model detox to last for 1 month, we estimate the DETOX POPULATION to be 1% of the POUD POPULATION. |
| MAT SUPERVISION/NO OPIOID USE<br>*U.S. population who have POUD and are in intensive MAT treatment and are not using opioid* | B_8 | 38,823 | [8,9] | B_8 through B_10 reflect different populations of individuals receiving MAT:<br>• B_8 captures individuals who were in supervised MAT and had no concurrent opioid use;<br>• B_9 captures individuals who were in supervised MAT and had concurrent opioid use; and<br>• B_10 captures individuals who were in stable MAT and had no concurrent opioid use.<br><br>Though there is no formal definition of supervised and stable MAT, we refer to supervised MAT as programs with relatively more intensive oversight (e.g., residential programs or intensive outpatient programs [IOP]) compared to stable MAT wherein there is less oversight on the individual (e.g., ambulatory, community-based treatment).<br><br>To calculate B_8 through B_10, we utilize estimates from Krebs et al.'s economic model. Krebs et al. estimate that 16.4% of POUD |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | are in MAT. We propose that the rate of POUD in MAT was a third lower in 2010 compared to the Krebs et al. estimate (i.e., only 67% of the 16.4% are in MAT) and this estimate was corroborated with sensitivity analyses/calibration.<br><br>Using 2010 TEDS admissions data, we estimate the MAT distribution into three populations: 20% are allocated into MAT supervision without concurrent opioid use [B_8], 20% are allocated into MAT supervision with concurrent opioid use [B_9], and 60% are allocated into stable MAT without concurrent opioid use [B_10]. We categorize ambulatory outpatient as reported by TEDS as MAT stable, and categorize intensive outpatient, residential and rehabilitation as reported by TEDS as MAT supervised. We standardize the distributions to 100% which suggest 60% of individuals in MAT stable while 40% of individuals in MAT supervision. We divide the 40% equally between MAT supervision with and without concurrent opioid use. |
| MAT SUPERVISION/OPIOID USE<br>*U.S. population who have POUD and are in intensive MAT treatment yet are still using opioid* | B_9 | 38,823 | [8,9] | Please see explanation for derivation of B_8. |
| MAT STABLE/NO OPIOID USE<br>*U.S. population who have POUD and are in stable, outpatient MAT treatment and are not using opioid* | B_10 | 116,470 | [8,9] | Please see explanation for derivation of B_8. |
| NO MAT/NO OPIOID USE<br>*U.S. population who had POUD and are no longer active POUD. These are lifetime POUD individuals.* | B_11 | 2,021,367 | [10] | This box represents the inactive POUD population and is derived from the difference between lifetime POUD population (i.e., people who have a history of POUD) and past year POUD population.<br><br>Lifetime POUD is derived from the 2010 national estimate of lifetime POUD as calculated by Saha et al. using NESARC 3 data. We subtracted boxes B_5 through B_10 and B_12 from lifetime |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | POUD to remove the proportion of individuals with past year POUD. |
| OVERDOSE<br>*Monthly number of prescription opioid overdoses includes fatal and non-fatal overdoses* | B_12 | 7,738 | [2,3,11] | According to CDC, there were approximately 92,000 emergency department visits for opioid overdoses in 2014 nationally, of which approximately 54,000 visits were for heroin. We consider the remaining 38,000 visits as due to prescription opioid overdoses in 2014.<br><br>We propose that only half of overdoses go to the emergency department (i.e., multiply 38,000 by 2), and adjust for higher opioid sales volumes in 2010 than 2015 (i.e., Guy et al. report 782 vs 640 MMEs in 2010 and 2015, respectively), resulting in 7,738 monthly fatal and nonfatal overdoses due to prescription opioids nationwide in 2010. |
| HEROIN USE DISORDER POPULATION (PRESCRIPTION INITIATED)<br>*U.S. population who have HUD and used prescription opioids prior to developing HUD* | BH_4 | 168,730 | [5,6] | The 2010 NSDUH reports that there were 359,000 individuals with past year dependence on heroin (i.e., HUD) nationally. Based on a study by Martins et al., we estimate that 47% of the 2010 HUD population had prior prescription opioid use. |
| NO MAT/HEROIN USE<br>*U.S. population who have HUD and used prescription opioids prior to HUD and are not in treatment and are not considered hard to treat* | BH_5 | 94,489 | Calculation | This box represents individuals who had HUD in the past year but who were not receiving MAT nor were they in detox. We calculate BH_5 by subtracting BH_6 through BH_10 from BH_4.<br><br>BH_6 through BH_10 refer to populations who had past year HUD (PRESCRIPTION INITIATED) and were at various stages of treatment (further defined below in BH_7 to BH_10) or who did not receive treatment (see BH_6). |
| NO MAT/HEROIN USE (COMPLEX CARE)*U.S. population who have HUD and used prescription opioids prior to HUD and are not in treatment and are considered hard to treat* | BH_6 | 33,746 | Expert opinion | Based on expert opinion, we estimated that one-fifth of the HUD (PRESCRIPTION INITIATED) POPULATION would be difficult to treat. |
| DETOX HEROIN | BH_7 | 6,749 | [7] | In Pitts et al.'s economic model, 4% of the HUD POPULATION enters detox each month. In US-APOLLO, because we model |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| *U.S. population who have HUD and used prescription opioids prior to HUD and are in detox* | | | | detox to last for 1 month, we also estimate the DETOX POPULATION to be 4% of the HUD (PRESCRIPTION INITIATED) POPULATION. |
| MAT SUPERVISION/NO HEROIN USE<br>*U.S. population who have HUD and used prescription opioids prior to HUD and are in intensive MAT treatment and are not using opioid* | BH_8 | 6,749 | [8,9] | Calculations for BH_8 to BH_10 are analogous to B_8 to B_10. See above for description of each MAT population.<br><br>To calculate BH_8 through BH_10, we utilize estimates from Krebs et al.'s economic model. Krebs et al. estimate that 10.4% to 31.5% of HUD are in MAT and we utilize the median at 20%.<br><br>Using 2010 TEDS admissions data, we then segment the MAT population into three populations: 20% are allocated into MAT supervision without concurrent opioid use (BH_8), 20% are allocated into MAT supervision with concurrent opioid use (BH_9), and 60% are allocated into stable MAT without concurrent opioid use (BH_10). |
| MAT SUPERVISION/HEROIN USE<br>*U.S. population who have HUD and used prescription opioids prior to HUD and are in intensive MAT treatment and are using opioid* | BH_9 | 6,749 | [8,9] | Please see explanation for derivation of BH_8. |
| MAT STABLE/NO HEROIN USE<br>*U.S. population who have HUD and used prescription opioids prior to HUD and are in stable, outpatient MAT treatment and are not using opioid* | BH_10 | 20,248 | [8,9] | Please see explanation for derivation of BH_8. |
| NO MAT/NO HEROIN USE (HUD PRESCRIPTION INITIATED)<br>*U.S. population who have HUD and used prescription opioids prior to HUD and are no longer active HUD. These are lifetime HUD individuals.* | BH_11 | 511,687 | [6] | Analogous to B_11, this box represents the inactive HUD population and is derived from the difference between lifetime HUD population (i.e., people who have a history of HUD but may not fulfill criteria for past year POUD) and past year HUD population.<br><br>Lifetime HUD is derived from the 2010 national estimate of lifetime HUD as calculated by Martins et al. using NESARC 3 data. |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | Furthermore, 47% of lifetime HUD is estimated to be due to prescription opioids. We subtracted boxes BH_5 through BH_10 and BH_12 from lifetime HUD to remove the proportion of individuals with past year HUD. |
| OVERDOSE HEROIN<br>*Monthly number of heroin overdoses of people who used prescription opioids prior to heroin. Includes fatal and non-fatal overdoses* | BH_12 | 4,230 | [6,11] | According to CDC, 54,000 emergency department visits were for heroin nationally in 2014.<br><br>We propose that only half of overdoses go to the emergency department (i.e., multiply 54,000 by 2), and that 47% of individuals using heroin had prior prescription opioid use. |
| HEROIN USE POPULATION<br>*U.S. population who use heroin but do not fulfill criteria for Heroin Use Disorder (HUD)* | BHN_3 | 179,250 | [5] | The 2010 NSDUH national estimate for average past month heroin use was 239,000. In calibration, we lowered the initial month's starting population (BHN_3) by 25% so that estimates regarding monthly heroin use for 2011 and onwards are closer to the actual monthly heroin use as derived from NSDUH. |
| HEROIN USE DISORDER POPULATION (NON-PRESCRIPTION INITIATED)<br>*U.S. population who have HUD and did not use prescription opioids prior to developing HUD* | BHN_4 | 190,270 | [5,6] | The 2010 NSDUH reports there were 359,000 individuals with past year dependence on heroin (i.e., HUD) nationally. As discussed in BH_4, we estimate that 53% of individuals with HUD did not have prior prescription opioid nonmedical use. |
| NO MAT/HEROIN USE<br>*U.S. population who have HUD and did not use prescription opioids prior to HUD and are not in treatment and are not considered hard to treat* | BHN_5 | 106,551 | Calculation | Analogous to BH_5. This box represents individuals who had HUD in the past year and did not have prior prescription opioid use but who were not receiving MAT nor were they in detox. We calculate BHN_5 by subtracting BHN_6 through BHN_10 from BHN_4.<br><br>BHN_6 through BHN_10 refer to populations who had past year HUD (non-prescription initiated) and were at various stages of treatment (further defined below in BHN_7 to BHN_10) or who did not receive treatment (see BHN_6). |
| NO MAT/HEROIN USE (COMPLEX CARE)*U.S. population who have HUD and did not use prescription opioids prior to HUD and are not in treatment and are considered hard to treat* | BHN_6 | 38,054 | Expert opinion | Based on expert opinion, we estimated that one-fifth of the HUD (NON-PRESCRIPTION INITIATED) POPULATION would be difficult to treat. |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| DETOX HEROIN (HUD NON-RX)<br>*U.S. population who have HUD and did not use prescription opioids prior to HUD and are in detox* | BHN_7 | 7,611 | [7] | Analogous to BH_7. In Pitts et al.'s economic model, 4% of the HUD population enters detox each month. In US-APOLLO, because we model detox to last for 1 month, we also estimate the detox population to be 4% of the HUD (NON-PRESCRIPTION INITIATED) POPULATION. We use 4% for both prescription and non-prescription initiated heroin cohorts. |
| MAT SUPERVISION/NO HEROIN USE<br>*U.S. population who have HUD and did not use prescription opioids prior to HUD and are in intensive MAT treatment and are not using illicit opioid* | BHN_8 | 7,611 | [8,9] | Calculations for BHN_8 to BHN_10 are analogous to BH_8 to BH_10. See above for description of each MAT population.<br><br>To calculate BHN_8 through BHN_10, we utilize estimates from Krebs et al.'s economic model. Krebs et al. estimate that 10.4% to 31.5% of HUD are in MAT and we utilize the median at 20%.<br><br>We then segment the MAT population into three populations: 20% are allocated into MAT supervision without concurrent opioid use (BHN_8), 20% are allocated into MAT supervision with concurrent opioid use (BHN_9), and 60% are allocated into stable MAT without concurrent opioid use (BHN_10). |
| MAT SUPERVISION/ HEROIN USE<br>*U.S. population who have HUD and did not use prescription opioids prior to HUD and are in intensive MAT treatment and are actively using illicit opioid* | BHN_9 | 7,611 | [8,9] | Please see explanation for derivation of BHN_8. |
| MAT STABLE/NO HEROIN USE<br>*U.S. population who have HUD and did not use prescription opioids prior to HUD and are in stable, outpatient MAT treatment and are not using illicit opioid* | BHN_10 | 22,832 | [8,9] | Please see explanation for derivation of BHN_8. |
| NO MAT/NO HEROIN USE (HUD NON-PRESCRIPTION INITIATED)<br>*U.S. population who have HUD and did not use prescription* | BHN_11 | 577,009 | [6] | Analogous to BH_11, this box represents the inactive HUD population and is derived from the difference between lifetime HUD population (i.e., people who have a history of HUD but may |

| DESCRIPTION | VARIABLE | VALUE | SOURCES | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| *opioids prior to HUD and are no longer active HUD. These are lifetime HUD individuals.* | | | | not fulfill criteria for past year POUD) and past year HUD population.<br><br>Lifetime HUD is derived from the 2010 national estimate of lifetime HUD as calculated by Martins et al. using NESARC 3 data. 47% of lifetime HUD is estimated to be due to prescription opioids. We subtracted boxes BHN_5 through BHN_10 and BH_12 from lifetime HUD to remove the proportion of individuals with past year HUD. |
| OVERDOSE HEROIN (HUD NON-PRESCRIPTION INITIATED)<br>*Monthly number of heroin overdoses of people who used prescription opioids prior to heroin. Includes fatal and non-fatal overdoses* | BHN_12 | 4,770 | [6,11] | According to CDC, 54,000 emergency department visits were for heroin nationally in 2014. We propose that only half of overdoses go to the emergency department (i.e., multiply 54,000 by 2), and that 53% of individuals using heroin did not have prior prescription opioid nonmedical use. |
| DEATH | B_13 | 0 | | Starts at 0 on 1/1/2010 |

**MONTHLY POPULATION ADDITION PARAMETERS**

The following table lists the monthly population additions into the model, which allow the model to reflect the underlying population growth in the U.S. These population additions represent the sum of projected net births and net migration in the population from the U.S. Census Bureau.[1]

| DESCRIPTION | VARIABLE | VALUE |
|---|---|---|
| MONTHLY POPULATION INFLOW IN 2010 | POP_2010 | 450,906 |
| MONTHLY POPULATION INFLOW IN 2011 | POP_2011 | 451,664 |
| MONTHLY POPULATION INFLOW IN 2012 | POP_2012 | 402,438 |
| MONTHLY POPULATION INFLOW IN 2013 | POP_2013 | 406,489 |
| MONTHLY POPULATION INFLOW IN 2014 | POP_2014 | 419,743 |
| MONTHLY POPULATION INFLOW IN 2015 | POP_2015 | 422,775 |
| MONTHLY POPULATION INFLOW IN 2016 | POP_2016 | 425,737 |
| MONTHLY POPULATION INFLOW IN 2017 | POP_2017 | 408,170 |
| MONTHLY POPULATION INFLOW IN 2018 | POP_2018 | 410,178 |
| MONTHLY POPULATION INFLOW IN 2019 | POP_2019 | 412,034 |
| MONTHLY POPULATION INFLOW IN 2020 | POP_2020 | 413,689 |
| MONTHLY POPULATION INFLOW IN 2021 | POP_2021 | 415,093 |
| MONTHLY POPULATION INFLOW IN 2022 | POP_2022 | 416,232 |
| MONTHLY POPULATION INFLOW IN 2023 | POP_2023 | 417,156 |
| MONTHLY POPULATION INFLOW IN 2024 | POP_2024 | 417,891 |
| MONTHLY POPULATION INFLOW IN 2025 | POP_2025 | 418,605 |
| MONTHLY POPULATION INFLOW IN 2026 | POP_2026 | 419,712 |

| DESCRIPTION | VARIABLE | VALUE |
|---|---|---|
| MONTHLY POPULATION INFLOW IN 2027 | POP_2027 | 420,339 |
| MONTHLY POPULATION INFLOW IN 2028 | POP_2028 | 420,812 |
| MONTHLY POPULATION INFLOW IN 2029 | POP_2029 | 421,159 |

**TRANSITION PROBABILITIES**

The following table lists the probabilities that a member of a given population will stay in that population or transition to another given population.

Many transitions in US-APOLLO are calculated using the differences between past year and past month estimates derived from NSDUH. The principle behind this calculation is that the difference between past year and past month represents the population that is engaged in a given behavior (e.g., prescription opioid medical use, prescription opioid nonmedical use) over one year. For example, if the number of individuals with prescription opioid nonmedical use during the past year is 12 times the average number of individuals with prescription opioid nonmedical use during past month, it would suggest that the prescription opioid nonmedical use population turns over each month, and thus implies an equal transition in and out of the population box.

For transition parameters denoted as D_*, DH_* and DHN_*, these transition parameters represent mortality rates excluding overdose mortality for individuals within this health state.

Variables annotated as placeholders are set to 0 and do not contribute to the output of the model. Rather, they are in place to facilitate potential future updates to the model.

| DESCRIPTION | VARIABLE | VALUE | SOURCE(S) | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| GENERAL POPULATION stay in GENERAL POPULATION | P_10 | [ 1 - rest ] | - | For this variable and for all other variables below, "rest" refers to all probabilities exiting each box.<br><br>For example, for GENERAL POPULATION, "rest" refers to P_11_*YEAR* and P_12. |
| GENERAL POPULATION to PRESCRIPTION OPIOID MEDICAL USE | P_11_*Year* | Ranges from 0.0210 to 0.0100 | [3,5] | We used the difference between past year and past month prescription opioid medical use (POMU) to estimate additional users over one year. This difference was divided by 12 months to estimate additional users per month. We divide by the starting population (i.e., GENERAL POPULATION in this scenario) to calculate the estimate as a percentage of the starting population that transitions away from this health state.<br><br>We estimate that 80% of additional users came from the GENERAL POPULATION, and 20% came |

| DESCRIPTION | VARIABLE | VALUE | SOURCE(S) | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | from the PRESCRIPTION OPIOID NONMEDICAL USE POPULATION, though this final estimate was eventually adjusted during calibration (proportion decreased by 20%). We applied a 3% annual decrease in prescribing rate, which is based on the change in national opioid prescribing rates as reported by Guy et al. from 2012 to 2015 (decrease from 81.2 to 70.6. which translates to a 3.1% annual decrease). |
| GENERAL POPULATION to HEROIN USE | P_12 | 0.0001 | 5 | We used the difference between past year and past month heroin use to estimate additional users over one year. This difference was divided by 12 months to estimate additional users per month, before dividing by the GENERAL POPULATION. |
| GENERAL POPULATION to PRESCRIPTION OPIOID NONMEDICAL USE | P_13 | 0.0005 | 12 | McCabe et al. reported that 80% of high school students had a history of prescription opioid nonmedical use. Hence, we applied a 4:1 ratio to the population flow from B_2 to B_3 (P_22, see below for definition) to determine P_13. This was further calibrated down by 25%. |
| PRESCRIPTION OPIOID MEDICAL USE stay in PRESCRIPTION OPIOID MEDICAL USE | P_20 | [ 1 - rest ] | - | [ 1 - rest ] |
| PRESCRIPTION OPIOID MEDICAL USE to GENERAL POPULATION | P_21 | 0.4000 | 5 | Using data from the 2010 NSDUH, we subtracted the monthly increase in PONU from the monthly increase in POMU. The difference was divided by B_2. This was calibrated to a final value of 0.4. |
| PRESCRIPTION OPIOID MEDICAL USE to PRESCRIPTION OPIOID NONMEDICAL USE | P_22 | 0.0385 | 5 | We used the difference between past year and past month PONU of prescription opioid use to estimate additional users over one year. This difference was divided by 12 months to estimate additional users per month, before dividing by |

| DESCRIPTION | VARIABLE | VALUE | SOURCE(S) | NOTES AND CALCULATIONS |
|---|---|---|---|---|
| | | | | the POMU POPULATION. We applied a calibration adjustment of 70%. |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| PRESCRIPTION OPIOID NONMEDICAL USE stay in PRESCRIPTION OPIOID NONMEDICAL USE | P_30 | [ 1 - rest ] | - | [ 1 - rest ] |
| PRESCRIPTION OPIOID NONMEDICAL USE to PRESCRIPTION OPIOID MEDICAL USE | P_31 | 0.1439 | [5] | We used the difference between past year and past month POMU to estimate additional users over one year. This difference was divided by 12 months to estimate additional users per month, before dividing by the PONU POPULATION (B_3). We model that 20% of the POMU POPULATION came from PONU POPULATION. |
| PRESCRIPTION OPIOID NONMEDICAL USE to NO MAT/OPIOID USE | P_32 | 0.0056 | [10] | P_32 and P_33 equal the annual POUD population growth from Saha et al. From 2002 to 2013, lifetime prevalence of POUD grew from 1.4% to 2.9%.<br><br>*(2.9% - 1.4%) * Base Population* represents the growth of POUD over 11 years. We divided by 11 years to get annual growth, adding back a 1% estimate of mortality population during the period, and divided by PONU POPULATION since this is where population originates. We applied a calibration adjustment of 80% to the calculated value. |
| PRESCRIPTION OPIOID NONMEDICAL USE to GENERAL POPULATION | P_35 | 0.0288 | Expert opinion | We set the 2010 value of P_35 equal to 20% of P_31, such that for every 4 people going from prescription opioid nonmedical use to medical use, 1 person goes from prescription opioid nonmedical use to the general population. |
| NO MAT/OPIOID USE stay in NO MAT/OPIOID USE | P_50 | [ 1 - rest ] | - | [ 1 - rest ] |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| NO MAT/OPIOID USE to DETOX | P_51_*Year* | Ranges from 0.0100 to 0.0996 | 7 | Pitt et al. suggests 1% monthly transition into detox from POUD. We set the initial parameter at 1%, but increase it over time to reflect the increase in MAT uptake. |
| NO MAT/OPIOID USE to NO MAT EVER/OPIOID USE | P_52 | 0.0043 | Expert opinion | 5% of POUD without treatment transition annually into the hard to treat population, NO MAT EVER/OPIOID USE. 5% annual estimate converts to a 0.4% monthly estimate. |
| NO MAT/OPIOID USE to NO MAT/NO OPIOID USE | P_53 | 0.0184 | Calibration | P_53 represents the transition of individuals going from POUD to abstinent POUD without the assistance of MAT treatment.<br>Final value based on calibration. |
| NO MAT/OPIOID USE to NO MAT/HEROIN USE | P_54_*Year* | Ranges from 0.0060 to 0.0082 | 4, 13 | P_54 represents the transition of individuals from PRESCRIPTION OPIOID USE DISORDER [B_5] TO HEROIN USE DISORDER [BH_4].<br><br>2016 NSDUH reported 170,000 new heroin users. We estimate that 80% came from POUD (80% * 170,000). We then divided by the population in B_4 which equals to 7.6%.<br><br>We set the 2010 transition rate slightly lower than 7.6% then increase this estimate over time to reflect the inverse relationship between prescription opioid prescribing rates (which are decreasing over time) to heroin use (which is thought to increase as the former decreases). |
| NO MAT EVER/OPIOID USE stay in NO MAT EVER/OPIOID USE | P_60 | [ 1 - rest ] | - | [ 1 - rest ] |
| NO MAT EVER/OPIOID USE to NO MAT/OPIOID USE | P_61 | 0.0021 | Calibration | Represents individuals transitioning from the "hard to treat" population to NO MAT/OPIOID USE. Final value based on calibration. |
| NO MAT EVER/OPIOID USE to NO MAT/NO OPIOID USE | P_62 | 0.0043 | Calibration | Represents individuals transitioning from the "hard to treat" population to abstinence without the aid of MAT. Final value based on calibration. |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| DETOX stay in DETOX | P_70 | 0 | Expert opinion | Individuals in detox will only stay in detox for up to 1 month before either relapsing, dying, overdosing, or transitioning into MAT. |
| DETOX to MAT SUPERVISION/NO OPIOID USE | P_71 | 0.5500 | [8, 14] | Jackson et al. suggested a 0.62% daily dropout rate of methadone, which suggests a 30-day retention of 83%. However, Krebs et al. suggests an annual 74% acute relapse from medical withdrawal, which suggests a 26% retention. We took the average between the two at 55%. |
| DETOX to NO MAT/OPIOID USE | P_72 | [ 1 - rest ] | - | Individuals who relapse during detox.<br>[ 1 - rest ] |
| MAT SUPERVISION/NO OPIOID USE stay in MAT SUPERVISION/NO OPIOID USE | P_80 | [ 1 - rest ] | [7,8,14] | Individuals in MAT SUPERVISION/NO OPIOID USE who do not dropout after 1 month have roughly equal chance of transitioning into one of the following 3 MAT pathways:<br><br>(a) stay in MAT supervision with no opioid use (MAT SUPERVISION/NO OPIOID USE, P_80);<br><br>(b) transition to MAT supervision with opioid use (MAT SUPERVISION/OPIOID USE, P_81); or<br><br>(c) transition into a stable MAT program with no opioid use (MAT STABLE/NO OPIOID USE, P_82).<br><br>According to Krebs et al., 60% remain in opioid agonist treatment each month. However, Pitt et al.'s model has a 95% retention in MAT. Jackson et al. suggests a 79% retention rate across MAT. We utilize Jackson et al.'s estimate, given that 79% is close to the average of all three estimates. We allocate proportions of the 79% to P_80, P_81, or P_82 based on expert opinion and model calibration: |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| | | | | • with 25% going to MAT SUPERVISION/OPIOID USE [B_9];<br>• 40% going to MAT STABLE/NO OPIOID USE [B_10];<br>• 14% remaining in MAT SUPERVISION/NO OPIOID USE [B_8]. |
| MAT SUPERVISION/NO OPIOID USE to MAT SUPERVISION/OPIOID USE | P_81 | 0.2500 | 7,8,14 | Please see explanation for P_80. |
| MAT SUPERVISION/NO OPIOID USE to MAT STABLE/NO OPIOID USE | P_82 | 0.4000 | 7,8,14 | Please see explanation for P_80. |
| MAT SUPERVISION/NO OPIOID USE to NO MAT EVER/OPIOID USE | P_83 | Ranges from 0.1550 to 0.0775 | 7,8,14, Expert opinion | As noted in P_81, Jackson et al. estimate a retention rate of 79%, implying a 21% dropout rate. We estimate that 75% of those who drop out will relapse into the hard to treat population (B_6 NO MAT EVER/OPIOID USE) and 25% will relapse into B_11 (NO MAT/NO OPIOID USE).<br><br>We decrease this estimate by half by 2020 to reflect the impact of MAT churn, which is defined by a 50% decrease in MAT relapse sustained for 10 years.<br><br>*21% (proportion who dropout from MAT) * 75% (proportion that relapses into B_6)* |
| MAT SUPERVISION/NO OPIOID USE to NO MAT/NO OPIOID USE | P_84 | 0.0550 | 7,8,14, Expert opinion | Please see explanation for P_83.<br><br>*21% (proportion who dropout from MAT) * 25% (proportion that relapses into B_11)* |
| MAT SUPERVISION/OPIOID USE stay in MAT SUPERVISION/OPIOID USE | P_90 | [ 1 - rest ] | - | [ 1 - rest ] |
| MAT SUPERVISION/OPIOID USE to MAT SUPERVISION/NO OPIOID USE | P_91 | 0.2000 | Calibration | Represents the transition of individuals in MAT supervised treatment who discontinue concurrent opioid use while in treatment.<br>Final value based on calibration. |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| MAT SUPERVISION/OPIOID USE to NO MAT/OPIOID USE | P_92 | Ranges from 0.0500 to 0.0250 | 7, Expert opinion | Pitt et al. use a MAT dropout rate of 5%, which we use for populations B_9 (MAT SUPERVISION/OPIOID USE) and B_10 (MAT STABLE/NO OPIOID USE) who transition out of MAT.<br><br>Dropout from MAT is most likely to occur at the earliest stage of MAT (i.e., during B_8 when individuals transition into MAT supervised from detox) or after the individual has spent a long time in MAT. Since B_9 and B_10 represent MAT treatment pathways that are at least one month after detox, we use a lower estimate for MAT dropout for B_9 and B_10 compared to the estimate used in P_81 (21% dropout for B_8 MAT SUPERVISION/NO OPIOID USE).<br><br>We decrease this estimate by half by 2020 to reflect the impact of MAT churn, which is defined by a 50% decrease in MAT relapse sustained for 10 years. |
| MAT STABLE/NO OPIOID USE stay in MAT STABLE/NO OPIOID USE | P_100 | [ 1 - rest ] | - | [1 - rest] |
| MAT STABLE/NO OPIOID USE to NO MAT/NO OPIOID USE | P_101 | 0.0250 | 7 | Please see explanation for P_92.<br><br>We apply Pitt et al.'s estimate of 5% MAT dropout for the MAT STABLE/NO OPIOID USE POPULATION. However, since this transition represents the transition to abstinence, we reduce this by 50% representing that individuals are more likely to relapse than move to abstinence. |
| MAT STABLE/NO OPIOID USE to NO MAT/OPIOID USE | P_102 | Ranges from 0.0250 to 0.0125 | 7, 15 | Please see explanation for P_92. We started with Pitt et al.'s estimate of 5% MAT dropout for the MAT STABLE/NO OPIOID USE POPULATION and |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| | | | | decreased this estimate by 50% to reflect the dropout to abstinence.<br><br>We decrease this estimate by half by 2020 to reflect the impact of MAT churn, which is defined by a 50% decrease in MAT relapse sustained for 10 years. |
| NO MAT/NO OPIOID USE stay in NO MAT/NO OPIOID USE | P_110 | [ 1 - rest ] | - | [ 1 - rest ] |
| NO MAT/NO OPIOID USE to NO MAT/OPIOID USE | P_111 | 0.0100 | 7, Scientific assumption | We assume that this estimate is one-fifth as likely to relapse as P_92. B_11 represents the stable health state of dormant POUD population.<br><br>*20% * P_92* |
| GENERAL POPULATION to DEATH | D_1 | 0.0008 | 1 | Average monthly death rate from U.S. Census.<br><br>For D_2 to D_11, hazard ratios were adjusted based on model calibration and tested against total deaths and fatal opioid overdoses. |
| PRESCRIPTION OPIOID MEDICAL USE to DEATH | D_2 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| PRESCRIPTION OPIOID NONMEDICAL USE to DEATH | D_3 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| NO MAT/OPIOID USE to DEATH | D_5 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| NO MAT EVER/OPIOID USE to DEATH | D_6 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| DETOX to DEATH | D_7 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| MAT SUPERVISION/NO OPIOID USE to DEATH | D_8 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| MAT SUPERVISION/OPIOID USE to DEATH | D_9 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| MAT STABLE/NO OPIOID USE to DEATH | D_10 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| NO MAT/NO OPIOID USE to DEATH | D_11 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| OVERDOSE to DEATH | D_12_*Year* | Ranges from 0.1500 to 0.1222 | 11 | In 2014, there were 38,000 emergency department visits presumed to be due to prescription opioids, and 14,838 of these visits were fatal overdoses nationally. We estimate that only half of fatal and non-fatal overdoses are captured by the emergency department. This suggests a 19% mortality rate (i.e., 14,383 / [38,000 * 2]). The final value for D_12_2010 was lowered to 15% due to calibration. |
| PRESCRIPTION OPIOID MEDICAL USE to OVERDOSE | OD_2 | 0.00006 | Calibration | Calibrated to be 1% of OD_6 (transition probability of NO MAT EVER/OPIOID USE to OVERDOSE). |
| PRESCRIPTION OPIOID NONMEDICAL USE to OVERDOSE | OD_3 | 0.0009 | Calibration | Calibrated to be 15% of OD_6 (transition probability of NO MAT EVER/OPIOID USE to OVERDOSE). |
| NO MAT/OPIOID USE to OVERDOSE | OD_5_*Year* | Ranges from 0.0024 to 0.0030 | 11 | In 2014, CDC reported 92,000 emergency department visits due to opioid overdoses nationally, of which 38,000 were presumed to be prescription opioid overdoses. We propose that only half of overdoses are captured in the emergency department. We then divide by 12 months to estimate monthly overdoses.<br>We divided the number of prescription opioid overdoses (38,000 / 12 * 2) by B_5 (NO MAT/OPIOID USE POPULATION), presuming that 50% of these overdoses occurred without treatment. The final numbers were adjusted due to calibration.<br><br>*50% * 38,000 / 12 * 2 / B_5* |

| PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| NO MAT EVER/OPIOID USE to OVERDOSE | OD_6 | 0.0058 | Calibration | Calibrated to be 2 times the average of OD_5 from 2010 to 2029. |
| DETOX to OVERDOSE | OD_7 | 0.0058 | Calibration | Calibrated to be the same as OD_6. |
| MAT SUPERVISION/OPIOID USE to OVERDOSE | OD_9 | 0.0029 | Calibration | Calibrated to be 50% of OD_6 annual rate. |
| OVERDOSE to DETOX | OD_12_*Year* | Ranges from 0.8500 to 0.8778 | Calculation | Calculated as 1 - D12_*Year.* |

| HEROIN USE WITH OR WITHOUT PRIOR PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| HEROIN USE stay in HEROIN USE | PHN_30 | [ 1 - rest ] | - | [ 1 - rest ] |
| HEROIN USE to GENERAL POPULATION | PHN_31 | 0.0644 | Calibration | Final value based on calibration. |
| HEROIN USE to NO MAT/HEROIN USE | PHN_32 | 0.0017 | Calibration | Final value based on calibration. |
| NO MAT/HEROIN USE stay in NO MAT/HEROIN USE | PH_50, PHN_50 | [ 1 - rest ] | - | [ 1 - rest ] |
| NO MAT/HEROIN USE to DETOX | PH_51_*Year,* PHN_51_*Year* | Ranges from 0.0400 to 0.1768 | 7,8 | In Pitt et al.'s economic model, 4% of the heroin population transition monthly into treatment. We set the initial parameter at 0.04, but increase it over time to reflect the increase in MAT access.<br><br>A higher heroin to treatment rate was also observed by Krebs et al., though we chose to go with a more conservative estimate. |
| NO MAT/HEROIN USE to NO MAT EVER/HEROIN USE | PH_52, PHN_52 | 0.0043 | Expert opinion | Similar to P_52, 5% of HUD without treatment transition annually into the hard to treat NO MAT EVER/OPIOID USE POPULATION. 5% annual estimate converts to a 0.4% monthly estimate. |
| NO MAT/HEROIN USE to NO MAT/NO HEROIN USE | PH_53, PHN_53 | 0.0184 | Calibration | Final value based on calibration. |
| NO MAT EVER/HEROIN USE stay in NO MAT EVER/HEROIN USE | PH_60, PHN_60 | [ 1 - rest ] | - | [ 1 - rest ] |
| NO MAT EVER/HEROIN USE to NO MAT/HEROIN USE | PH_61, PHN_61 | 0.0021 | Calibration | Final value based on calibration. |

| HEROIN USE WITH OR WITHOUT PRIOR PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| NO MAT EVER/HEROIN USE to NO MAT/NO HEROIN USE | PH_62, PHN_62 | 0.0043 | Calibration | Final value based on calibration. |
| DETOX stay in DETOX | PH_70, PHN_70 | 0 | Expert opinion | People in detox will only stay in detox for up to 1 month before either relapsing, dying, overdosing, or transitioning into MAT. |
| DETOX to MAT SUPERVISION/NO HEROIN USE | PH_71, PHN_71 | 0.5500 | 8,14 | We utilize the same dropout rate as noted in P_71 (please see P_71 for explanation). |
| DETOX to NO MAT/HEROIN USE | PH_72, PHN_72 | [ 1 - rest ] | - | [ 1 - rest ] |
| MAT SUPERVISION/NO HEROIN USE stay in MAT SUPERVISION/NO HEROIN USE | PH_80, PHN_80 | [ 1 - rest ] | - | [ 1 - rest ] |
| MAT SUPERVISION/NO HEROIN USE to MAT SUPERVISION/HEROIN USE | PH_81, PHN_81 | 0.1400 | Scientific assumption | We assume this estimate is two times the average of PH_84. |
| MAT SUPERVISION/NO HEROIN USE to MAT STABLE/NO HEROIN USE | PH_82, PHN_82 | 0.2100 | Scientific assumption | We assume this estimate is three times the average of PH_84. |
| MAT SUPERVISION/NO HEROIN USE to NO MAT EVER/HEROIN USE | PH_83, PHN_83 | Ranges from 0.0700 to 0.0350 | 7 | Pitt et al. calculates a 14% dropout rate of MAT for severe HUD. We utilize equal dropout rates for MAT SUPERVISION/NO HEROIN USE to either (a) NO MAT/HEROIN USE (PH/PHN_83) or (b) NO MAT/NO HEROIN USE (PH/PHN_84).<br><br>We decrease this estimate by half by 2020 to reflect the impact of MAT churn, which is defined by a 50% decrease in MAT relapse sustained for 10 years. |
| MAT SUPERVISION/NO HEROIN USE to NO MAT/NO HEROIN USE | PH_84, PHN_84 | 0.0700 | 7 | Please see PH_83/PHN_83 for explanation. |
| MAT SUPERVISION/HEROIN USE stay in MAT SUPERVISION/HEROIN USE | PH_90, PHN_90 | [ 1 - rest ] | - | [ 1 - rest ] |
| MAT SUPERVISION/HEROIN USE to MAT SUPERVISION/NO HEROIN USE | PH_91, PHN_91 | 0.2000 | Calibration | Final value based on calibration. |
| MAT SUPERVISION/HEROIN USE to NO MAT/HEROIN USE | PH_92, PHN_92 | Ranges from 0.1400 to 0.0700 | 7 | Pitt et al. calculates a 14% dropout rate of MAT for severe HUD. We decrease this estimate by half by 2020 to reflect the impact of MAT churn, |

| HEROIN USE WITH OR WITHOUT PRIOR PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| | | | | which is defined by a 50% decrease in MAT relapse sustained for 10 years. |
| MAT STABLE/NO HEROIN USE stay in MAT STABLE/NO HEROIN USE | PH_100, PHN_100 | [ 1 - rest ] | - | [ 1 - rest ] |
| MAT STABLE/NO HEROIN USE to NO MAT/NO HEROIN USE | PH_101, PHN_101 | 0.1000 | [7] | Please see P_101 for explanation. Final value adjusted based on calibration. |
| MAT STABLE/NO HEROIN USE to NO MAT/HEROIN USE | PH_102, PHN_102 | Ranges from 0.0250 to 0.0125 | [7,15] | Analogous to P_102. We started with Pitt et al.'s estimate of 5% MAT dropout and decreased this estimate by 50% to reflect the dropout to abstinence.<br><br>We decrease this estimate by half by 2020 to reflect the impact of MAT churn, which is defined by a 50% decrease in MAT relapse sustained for 10 years. |
| NO MAT/NO HEROIN USE stay in NO MAT/NO HEROIN USE | PH_110, PHN_110 | [ 1 - rest ] | - | [ 1 - rest ] |
| NO MAT/NO HEROIN USE to NO MAT/HEROIN USE | PH_111, PHN_111 | 0.0100 | Scientific assumption | B_11 represents the stable health state of dormant HUD population. |
| HEROIN USE to DEATH | DHN_3 | 0.0016 | Scientific assumption | Assume hazard ratio is 2 to D_1<br><br>For DHN_3, DH/DHN_5 to DH/DHN_11, hazard ratios were adjusted based on model calibration and tested against total deaths and fatal opioid overdoses. |
| NO MAT/HEROIN USE to DEATH | DH_5, DHN_5 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| NO MAT EVER/HEROIN USE to DEATH | DH_6, DHN_6 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| DETOX TO DEATH | DH_7, DHN_7 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| MAT SUPERVISION/NO HEROIN USE to DEATH | DH_8, DHN_8 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |

| HEROIN USE WITH OR WITHOUT PRIOR PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| MAT SUPERVISION/HEROIN USE to DEATH | DH_9, DHN_9 | 0.0016 | Scientific assumption | Assumed hazard ratio is 2 to D_1. |
| MAT STABLE/NO HEROIN USE to DEATH | DH_10, DHN_10 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| NO MAT/NO HEROIN USE to DEATH | DH_11, DHN_11 | 0.0012 | Scientific assumption | Assumed hazard ratio is 1.5 to D_1. |
| OVERDOSE to DEATH | DH_12_*Year*, DHN_12_*Year* | Ranges from 0.0600 to 0.1481 | 11, Expert opinion | In 2014, there were 92,000 emergency department visits for opioid overdoses nationally, of which 54,000 were heroin overdoses. We propose that only half of overdoses are captured in the emergency department.<br><br>There were 6,506 opioid overdose deaths that were not due to prescription opioids, suggesting a 6% mortality rate. We set the 2010 value for DH_12 to approximately 6% and increased it slightly over time. We start decreasing this estimate at 2020 to demonstrate the impact of naloxone, which reflects a 5% annual decrease of overdose mortality for 4 years that is sustained for 6 years.<br><br>*6,506 / (54,000 * 2)* |
| HEROIN USE to OVERDOSE | ODHN_3 | 0.0043 | Calibration | Calibrated to be 25% of ODH_5. |
| NO MAT/HEROIN USE to OVERDOSE | ODH_5_*Year,* ODHN_5_*Year* | Ranges from 0.0135 to 0.0185 | 11 | In 2014, there were 92,000 emergency department visits for opioid overdoses nationally, of which 54,000 were heroin overdoses. We propose that only half of overdoses are captured in the emergency department.<br><br>The total number of heroin users is 538,250 (BH_3 + BH_4 + BHN_4). |

| HEROIN USE WITH OR WITHOUT PRIOR PRESCRIPTION OPIOID USE | | | | |
|---|---|---|---|---|
| **TRANSITION PROBABILITIES** | **VARIABLE** | **VALUE** | **SOURCE(S)** | **NOTES AND CALCULATIONS** |
| | | | | 54,000 * 2 / 538,250 = annual overdose rate of approximately 20%. The final value that was utilized is slightly lower due to calibration. |
| NO MAT EVER/HEROIN USE to OVERDOSE | ODH_6, ODHN_6 | 0.0387 | Calibration | 2 times the average of ODH_5 from 2010 to 2029. |
| DETOX to OVERDOSE | ODH_7, ODHN_7 | 0.0184 | Calibration | Calibrated to have 2% annual rate. |
| MAT SUPERVISION/HEROIN USE to OVERDOSE | ODH_9, ODHN_9 | 0.0173 | Calibration | Calibrated to be 50% of ODH_6. |
| OVERDOSE to DETOX | ODH_12_*Year,* ODHN_12_*Year* | Ranges from 0.9400 to 0.8519 | Calculation | Calculated as 1 - DH_12_*Year.* |

**SENSITIVITY ANALYSES**

We performed univariate and multivariate (probabilistic) sensitivity analyses; the univariate analyses tested the sensitivity of model outcomes to a change in each individual state transition variable. Such sensitivity analyses serve two main purposes. First, by clarifying the robustness and key components of our model, these analyses allowed us to identify transitions driving model outcomes and to quantify the impact of variation in these parameters on our primary outcomes. Second, from a public health perspective, sensitivity analyses help to identify key policy levers and intervention points of greatest value in preventing harmful outcomes. Analyses were done using using @Risk® (Palisade Software).

Results are presented as tornado diagrams in **eFigure 1**. For the multivariate probabilistic analysis, we identified key transitions and used a mix of published evidence and expert opinion to create probability distributions for these transitions. Correlations between transition probability distributions were defined as low (<0.6), medium (0.6 to 0.8), or high (>0.8) based on expert opinion, and were used in our probabilistic analyses. Results of the multivariate probabilistic sensitivity analysis are provided as a 95% uncertainty range, defined as the $2.5^{th}$ and $97.5^{th}$ percentiles across 1,000 probabilistic simulations.

From the univariate sensitivity analysis, the probability of surviving an opioid overdose and the case fatality of prescription overdose to be most influential on cumulative overdose deaths from 2010-2029. Rates of transition from medical to nonmedical prescription opioid use, heroin overdose to detoxification and heroin overdose to death were nearly as influential. Parameters that had small influences on overdose deaths notably included non-opioid related mortality rates across all populations.

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