Modeling Health Benefits and Harms of Public Policy Responses to the US Opioid Epidemic

SUPPLEMENT

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S1. Supplemental Methods

S1.1 Model Overview

We developed a dynamic compartmental model of pain, opioid prescribing, and opioid addiction in the US. We accounted for prescription of opioids that results in addiction—either for the patient or for others to whom the pills may be diverted—and for opioid pill addiction that leads to heroin addiction. We used this model to assess the health effects of different interventions that aim to curb opioid addiction and overdose deaths, accounting for morbidity and mortality. We modeled the five-year period from 2016 through 2020 and the ten-year period from 2016 through 2025 using one-month time increments. We implemented the model in Microsoft Excel and instantiated it with parameters derived from the literature wherever available, otherwise relying on approximation and expert opinion. Values and sources for model parameters are shown in Appendix Table 1.

S1.2 Model Compartments

We modeled 12 mutually exclusive and collectively exhaustive compartments representing the population of the US aged 12 and older (Figure 1):

- Pain-free nonuser: individuals with neither acute nor chronic pain who do not use opioids.
- Acute pain nonuser: individuals recovering from a surgery or procedure that produces moderate to severe pain, as well as those having experienced trauma resulting in physical pain, but who are not being treated with opioids for their pain during their up to one month period of acute pain.
- Acute pain with Rx (prescription): same as "acute pain nonuser," except these individuals are being treated with opioids.
- Chronic pain nonuser: individuals suffering from longer-term moderately to severely painful conditions (i.e., extending beyond the typical period of tissue healing), who are not being treated with opioids for their pain and are not suffering from severe opioid use disorder (SOUD).
- Chronic pain with Rx: same as "chronic pain nonuser", except these individuals are being treated with opioids.
- Chronic pain SOUD with Rx: same as "chronic pain with Rx", except these individuals are suffering from SOUD. We assumed that individuals with SOUD misuse prescription opioids but do not have SHUD.
- Pain-free SOUD with Rx: individuals with neither acute nor chronic pain who have SOUD and are being prescribed opioids.
- SOUD without Rx: individuals with SOUD without a current prescription for opioids who thus must get opioids through diversion from those with a prescription. These individuals may or may not have chronic pain.
- SHUD: individuals with severe heroin use disorder (SHUD). These individuals may also misuse prescription pills.
- SOUD in MAT: individuals being treated for SOUD by medication-assisted therapy (MAT).
- SHUD in MAT: individuals being treated for SHUD by medication-assisted therapy (MAT).
- Dead.

We did not model SHUD for individuals who initiate heroin use directly without first having addiction to prescription opioids because they are less likely to be impacted by opioid prescribing practices. We instead only included individuals with SHUD who progressed from

SOUD. We also did not model prescription of opioids to the terminally ill, as the pain states we accounted for in our model are limited to acute pain, chronic pain, and pain-free.

S1.3 Initial Compartment Sizes

Here we describe how we estimated the number of individuals in each compartment at the start of the modeled time horizon. We set the total initial model population size to the size of the US population aged 12 and older in 2015.[1] We estimated acute pain prevalence among the population without chronic pain or addiction, based on the percentage of the population undergoing inpatient or outpatient surgery per month.[2,3] We also included the percentage of the population treated for trauma in an emergency department,[4] excluding the few who are hospitalized[5] to avoid double counting, and excluding an estimated 20% who are probable doctor shoppers.[6] We accounted only for moderate to severe pain as assessed by a survey of post-operative pain using a verbal categorical scale.[7] We distinguished "Acute pain nonuser" from "Acute pain with Rx" in accordance with approximately 50% percent receiving an opioid prescription at discharge.[8-10]

We approximated the size of the population with opioid prescriptions for chronic pain ("Chronic pain with Rx", "Chronic pain SOUD with Rx", and "Pain-free SOUD with Rx") by subtracting the percent prescribed opioids for acute pain from the reported percentage of the population on opioids they have been prescribed.[11] We estimated the percent of this population holding opioid prescriptions for chronic pain who have SOUD ("Chronic pain SOUD with Rx" and "Pain-free SOUD with Rx") compared to the population without ("Chronic pain with Rx").[12] We used a published estimate of chronic pain prevalence among people with opioid use disorder[13] to approximate the breakdown of prescription holders with chronic pain with SOUD versus without chronic pain ("Chronic pain SOUD with Rx" versus "Pain-free SOUD with Rx").

The National Survey on Drug Use and Health (NSDUH)[14] tends to underreport opioid use disorder due to omission of some key populations (e.g., homeless, incarcerated) that are known to have high rates of illicit drug use, so we used estimates from RAND Corporation[15] to estimate SHUD prevalence. Based on the RAND data, we estimated that 1 million people had SHUD in 2010 (this is the number of individuals with 21+ days of use per month). Because the RAND data ends with 2010, we projected to 2016 prevalence using the 64% growth in heroin use disorder reported by NSDUH from 2010 to 2015.[14] This yielded an estimate of 1.7 million people with SHUD in 2016. We adjusted this total to have the model reflect only the ~80% of individuals with SHUD who first had SOUD,[16,17]. Though the monthly prevalence of MAT among individuals with SHUD is not reported, studies indicate that rates of MAT are low relative to the population with abuse and/or dependence.[18-20] We approximated the percentage of individuals with SHUD who are enrolled in MAT ("SHUD in MAT") based on expert opinion (K. Humphreys).

NSDUH and the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III)[21] report rates of prescription opioid dependence and use trends; however, prevalence of severe opioid use disorder is not reported. Additionally, these surveys suffer from underreporting in key populations of relevance to the epidemic. We therefore estimated SOUD prevalence based on reported prescription opioid overdose deaths, adjusted for underreporting, and the estimated likelihood of overdose death. We performed the adjustment for underreporting by assuming that the actual number of prescription opioid-related deaths was 24% greater[22] than the total opioid deaths minus deaths from illicit opioids (heroin and synthetic opioids other than methadone) reported by the Centers for Disease Control and Prevention.[23] Because there is no

reliable data on the risk of overdose death from SOUD, we estimated it assuming a 0.5 relative risk of overdose mortality for SOUD relative to SHUD. (We describe calculation of the SHUD overdose mortality rate in the Mortality subsection of S1.4). For individuals with SOUD in MAT, mortality risk is reduced by half.[24] We solved the equation below to obtain an estimate of the size of the total SOUD population ("Chronic pain SOUD with Rx", "Pain-free SOUD with Rx", "SOUD without Rx", "SOUD in MAT"). Based on expert opinion, we assumed that a lower percentage of individuals with SOUD than with SHUD enroll in MAT (K. Humphreys).

$$\frac{SOUD\ overdose\ deaths}{SOUD\ population\ size} = SOUD\ overdose\ mortality\ risk\ not\ in\ MAT * (1 - proportion\ SOUD\ enrolled\ in\ MAT) + SOUD\ overdose\ mortality\ risk\ not\ in\ MAT * risk\ reduction\ in\ MAT * proportion\ SOUD\ enrolled\ in\ MAT$$

where

$$SOUD\ overdose\ mortality\ risk\ not\ in\ MAT = SHUD\ overdose\ mortality\ risk\ not\ in\ MAT * relative\ risk\ of\ mortality\ in\ SOUD\ vs.\ SHUD$$

Given the total SOUD population, the percent in MAT, and the number of individuals in the "Chronic pain SOUD with Rx" and "Pain-free SOUD with Rx" compartments, we determined the size of the "SOUD in MAT" and "SOUD without Rx" populations.

We estimated the "Chronic pain nonuser" prevalence based on chronic pain prevalence for adults and children as reported in the literature[25-27], weighting for the breakdown between adults and children in our modeled population, to arrive at a chronic pain prevalence of 43%. However, we only model pain potentially severe enough for opioids to be considered as a treatment option, so we adjusted for approximately 20% percent of chronic pain qualifying as moderate to severe.[28] Our resulting estimation of moderate to severe chronic pain prevalence in the population is 5.9%. From this we subtracted those already accounted for in the "Chronic pain with Rx" and "Chronic pain SOUD with Rx" compartments. We also subtracted 45% of those accounted for in the "SOUD without Rx", "SHUD", "SOUD in MAT", and "SHUD in MAT" populations whom we assumed have moderate to severe chronic pain.[13] We assumed a somewhat lower prevalence of chronic pain among individuals with SOUD/SHUD who do not have an opioid prescription (45%)[29] than among those who do (65%).[30] The remainder represents the "Chronic pain nonuser" population.

We assumed that "Pain-free nonusers" accounted for the remainder of the over 12-year-old US population not included in the compartments described above.

S1.4 Transition Probabilities

Entry We assumed that entry into the model is constant and equal to the average mortality rate among individuals aged 12 and older in the US.[31] We assumed that individuals enter the population as either "Pain-free nonusers" or "Chronic pain nonusers" in proportion to the initial chronic pain prevalence.

Pain progression We modeled the possibility for "Pain-free nonusers" to transition into acute or chronic pain. We only modeled possible transition to acute pain for "Pain-free nonusers" because we are interested in tracking the potential for individuals to be exposed to opioid use, and individuals in chronic pain or opioid-addicted states have other channels by which they

would more likely be exposed. Since we assumed that acute pain can last for up to only one month, we calculated monthly incidence in the same manner as described above for calculating its prevalence. We assumed that acute pain that persists beyond one month will transition to chronic pain. The literature reports a wide range of probabilities for this occurrence[32]; we assumed there is a 15% chance of pain transitioning from acute to chronic. We approximated a slightly lower probability of transition to chronic pain for acute pain patients who received an opioid prescription ("Acute pain with Rx") compared with those who did not receive a prescription ("Acute pain nonuser") because when treated, acute pain is less likely to become chronic.[33] We also modeled potential for "Pain-free nonusers" to develop chronic pain. In light of limited data on the incidence of moderate/severe chronic pain, we approximated these rates using calibration—selecting it such that chronic pain prevalence is constant over the model time horizon,[19,34] given an estimate of chronic pain resolution that suggested that 27% of patients' pain had at least somewhat improved over three months.[35] For simplicity, we did not model the potential for individuals with SOUD or SHUD to experience a change in pain status. (We recognize that this is a simplification, particularly given the endogeneity between addiction and chronic pain.[13])

Opioid prescribing We approximated the likelihood of opioids being prescribed upon hospital discharge to patients with acute pain based on reports from the literature.[9,10] For "Acute pain with Rx" patients whose pain transitions to becoming chronic, we estimated that half of them continue in their use of opioids. (We estimated this given our assumption that 15% of patients with acute pain develop chronic pain, that the chronic pain opioid prescription renewal rate is high, and that 6% of individuals prescribed post-surgical opioids remain on them for at least 3 months.[8]) Opioid prescribing has declined slightly since its peak in 2012.[36] We assumed that this reduction in prescribing reflects decreased prescribing for chronic pain. Due to lack of recent data on rates of initiating opioid use for chronic pain, we used model calibration to approximate the probability of a "Chronic pain nonuser" beginning prescription opioid use assuming a steady prevalence of opioid prescription holders from 2016 onward.

In addition to "Chronic pain nonusers" beginning opioid treatment, individuals in the "SOUD without Rx" state may also seek an opioid prescription. We did not find data suggesting how successful such individuals are in securing an opioid prescription; we assumed that the likelihood that they are prescribed these drugs (in the absence of interventions) is related to the rate at which physicians prescribe drugs to the "Chronic pain nonusers." Given uncertainty about whether "SOUD without Rx" individuals are more or less likely to obtain opioid prescriptions than "Chronic pain nonusers", we assumed that they are prescribed opioids at the same rate. Because the "SOUD without Rx" state includes individuals with and without chronic pain, individuals who successfully receive an opioid prescription may transition to either the "Pain-free SOUD with Rx" or "Chronic pain SOUD with Rx" state. We assumed that the proportion of individuals going from "SOUD without Rx" to "Pain-free SOUD with Rx" versus "Chronic pain SOUD with Rx" is equal to the proportion of pain-free versus chronic pain individuals entering the four states for which we do not explicitly distinguish pain status ("SOUD without Rx", "SOUD in MAT", "SHUD", and "SHUD in MAT"). We used this same approach in calculating the transition from any of these four states ("SOUD without Rx", "SOUD in MAT", "SHUD", and "SHUD in MAT") to a state for which pain status is explicit.

Prescription renewal We assumed that each month there is a chance that individuals prescribed opioids for chronic pain do not get their prescription renewed, either because they do not wish to or their doctor decides not to approve a renewal. Several studies report rates of

discontinuation of opioid prescriptions for chronic pain[37-39]; however, the studies generally do not distinguish between whether discontinuation was due to pain resolution, whether discontinuation was at the patient or doctor's discretion, and whether rates of discontinuation were for individuals with versus without SOUD. Given limited data, we assumed that 99% of non-addicted people with an opioid prescription for chronic pain ("Chronic pain with Rx") whose pain has not subsided want to continue their prescription each month instead of seeking another pain management method. Furthermore, we assumed that "Chronic pain with Rx" individuals are typically able to get their prescription renewed if they wish, and that approximately 90% remain in that state from one month to the next. We assumed that all "Chronic pain SOUD with Rx" and "Pain-free SOUD with Rx" individuals who do not desist or seek treatment wish to renew their prescription. Given uncertainty about whether addicted individuals are more or less successful than non-addicted individuals in getting their prescription renewed, we assumed that individuals with addiction are only slightly less likely (0.99 monthly relative risk) to have their prescription renewed. We assumed that those who are not able to get their prescription renewed transition to the "SOUD without Rx" state.

Addiction We modeled the potential for SOUD to develop either through iatrogenic addiction or through diversion of opioids from those to whom they are prescribed to those for whom they are not intended. Some interventions that we analyzed impact both of these channels by which addiction may occur (e.g., reducing prescribing rates), whereas other interventions largely act on only one (e.g., excess opioid disposal reduces drug diversion, but does not reduce access for the prescribed population).

We assumed that the likelihood of iatrogenic addiction depends on the duration of opioid treatment (i.e., constant monthly risk of iatrogenic addition that is consistent between acute and chronic pain treatment). We used the prevalence of addiction and average duration of exposure to prescription opioids reported in a systematic review to determine the monthly chance of iatrogenic addiction.[40] For the few "Acute pain with Rx" individuals who become iatrogenically addicted, we assumed that they are as likely to receive an opioid prescription as those whose acute pain transitions to chronic.

We modeled addiction through diversion of pills only to "Pain-free nonusers" because we assumed that nonusers with pain are able to obtain an opioid prescription directly. We employed a Susceptible-Infected epidemic model structure to model addiction that results from pill diversion: this is the transition from "Pain-free nonuser" to "SOUD without Rx." We assumed that the incidence of opioid pill addiction for "Pain-free nonusers" depends on the size of this population, the size of the prescription holding population, and the chance of diversion leading to addiction. We refer to "Pain-free nonusers" as the "susceptible" population (S), and the prescription-holding population ("Acute pain with Rx", "Chronic pain with Rx", "Chronic pain SOUD with Rx", "Pain-free SOUD with Rx") as "infected" (I)—this latter population is essentially carriers. We let N represent the size of the total model population. We let β represent the product of (1) the number of interactions per person per month, (2) the probability of interactions between the susceptible and infected population that result in diversion of opioids, and (3) the probability that diversion leads to addiction. With this notation, we have

$$Incidence\ of\ addiction\ through\ diversion = \beta * \frac{I*S}{N}.$$

We estimated the product of (1) and (2) as 0.01 interactions per month resulting in diversion of opioids to pain-free nonusers. We assumed that the probability of addiction for a nonuser who receives diverted opioids is 6.8%, given an 18.2% probability that a non-medical opioid user

becomes dependent[21] and an estimated 37% percent of the population with opioid dependence qualifying as having SOUD (ratio of SOUD to OUD prevalence).[41]

In addition to diversion of pills to pain-free nonusers, we modeled diversion of pills from the prescription-holding populations to the "SOUD without Rx" population. We assumed that in order to sustain their addiction, "SOUD without Rx" individuals must receive pills through diversion. We used the size of the prescription holding population as a proxy for the quantity of pills available to be diverted to the "SOUD without Rx" population and assumed a linear relationship between the quantity of pills available for diversion and the number of prescription holders.[42] We modeled a constant proportionally factor between the size of the prescription holding populations and the maximum number of individuals in the "SOUD without Rx" state. We did not model an instantaneous effect of changes in the quantity of pills prescribed on changes in the number "SOUD without Rx" individuals but instead assumed a one-year lag in the relationship between the size of the prescription-holding populations and the number of individuals able to be sustained as "SOUD without Rx." We did this because when the supply of prescribed pills drops there will still be excess pills that will not be immediately consumed. We assumed that the proportionality factor between the maximum possible size of the "SOUD without Rx" population and the size of the prescription-holding populations one year prior is constant for the duration of the modeled time horizon and equal to the ratio of the size of the "SOUD without Rx" population at the start of the time horizon to the size of the population of prescription holders one year before the model start year. We used IMS Health's reported 4.6% per year decline in opioid prescriptions from 2012 through 2015[36] and assumed a proportional decline in the number of prescription holders to approximate the number of prescription holders one year prior to the model start. If the number of individuals able to be sustained in the "SOUD without Rx" state is exceeded, the remainder must enroll in MAT ("SOUD in MAT"), desist use ("Pain-free nonuser" or "Chronic pain nonuser"), or escalate to heroin use ("SHUD"). We approximated the relative likelihood of each of these transitions using expert opinion (K. Humphreys). In addition to "forced" escalation to "SHUD", we assumed a baseline rate of escalation from the "SOUD without Rx" state independent of opioid pill availability. We approximated the baseline rate of escalation based on one study's reported 10% rate of heroin initiation over 30 months among prescription opioid-dependent individuals enrolled in MAT,[29] but assuming a higher rate of escalation among the total SOUD population and some degree of underreporting in the study. Since we assumed that only individuals in the "SOUD without Rx" compartment escalate to heroin use, we used model calibration to arrive at a monthly chance of escalation among the "SOUD without Rx" population to account for the overall approximated rate of escalation from SOUD to SHUD.

Desistance and treatment For simplicity, we modeled desistance as cessation of all opioid use. We found no consistent data on rates of desistance from opioid use among individuals with addiction, so we approximated these values assuming very low rates of recovery, given the relapsing nature of disease and limited successful recovery, especially for those who do not receive at least one year of MAT.[43-45] We assumed a 1% monthly desistance rate of individuals with SOUD in MAT.[29] MAT has been proven the most effective of available treatments (more than purely psychosocial treatment) for reducing illicit opioid use and mortality.[46] Individuals enrolled in MAT have a higher rate of desistance than their non-enrolled counterparts, so we assumed a 0.5 monthly relative risk of voluntary desistance for those not in MAT. [24] We assumed equal likelihood of voluntary desistance across all individuals with SOUD not receiving MAT, regardless of prescription status. We assumed 50% lower rates of desistance for

individuals with SHUD, in line with relative risk for retention in treatment for individuals with SHUD vs. SOUD.[47,48]

Given limited data on likelihood of enrollment in MAT and wide variation in reported rates of dropout,[49] we approximated these and used model calibration to select enrollment and dropout rates that yield increasing prevalence of MAT among the prescription opioid-addicted (reflecting recent efforts to curb illicit use) and constant treatment prevalence among heroin addicts under the status quo. One study reported rates of enrollment in MAT for individuals with SHUD who received an intervention designed to encourage treatment,[50]; we assumed a lower rate of enrollment in MAT for the general population of individuals with SHUD. We assumed this enrollment rate also applies to the "SOUD without Rx" population, but that individuals with opioid prescriptions ("Pain-free SOUD with Rx" and "Chronic pain SOUD with Rx") have lower rates of MAT enrollment. We approximated the rate of MAT dropout for the "SHUD in MAT" population given data reported in a systematic review.[51], and assumed a lower rate of dropout for individuals with SOUD.[47,48,52]

Mortality We assumed a baseline mortality rate equal to the current rate of death for the US population aged 12 and older.[53] We modeled an additional risk of death by overdose for individuals with SHUD based on the following equation:

$$\frac{heroin\ overdose\ deaths}{SHUD\ population\ size} = SHUD\ overdose\ mortality\ risk\ not\ in\ MAT * (1 - proportion\ of\ SHUD\ enrolled\ in\ MAT) + SHUD\ overdosemortality\ risk\ not\ in\ MAT * relative\ risk\ reduction\ in\ MAT * proportion\ enrolled\ in\ MAT$$

We estimated heroin overdose deaths in 2015 by adjusting rate of deaths from illicit opioids (heroin and synthetic opioids other than methadone) reported by the Centers for Disease Control and Prevention,[23] assuming that the actual number of heroin-related deaths was 24% greater than that reported.[22] We estimated the size of the SHUD population in 2015 by applying the 2010 to 2015 growth rate reported by NSDUH[14] to the 2010 prevalence reported by RAND[15] (detailed in section S1.3 above). We estimated the proportion of individuals with SHUD who were enrolled in MAT in 2015 using expert opinion (K. Humphries). We assumed a 50% reduction in addiction-related mortality for individuals enrolled in MAT.[24]

For individuals with SOUD, we assumed a 0.5 lower relative risk of mortality compared to individuals with SHUD. In addition to risk of overdose, individuals with SHUD incur mortality risk due to infection. For simplicity, we assumed that only individuals with SHUD are drug injectors. We estimated the risk of infection for "SHUD" individuals using a relative risk of death from infection compared to that for overdose among heroin users.[54] Our all-cause mortality risk for individuals with SHUD is consistent with that reported in a study of heroin addicts awaiting treatment.[55]

S1.5 Quality of Life

We assumed that the population of pain-free nonusers has a health utility of 1 and that pain and addiction are associated with health utility decrements.[56] We used a study reporting health utility values associated with various levels of pain on the Numeric Pain Rating Scale (NPRS)[56] in conjunction with reported rates of various levels of pain (moderate, severe, and extreme) during the two weeks post discharge from surgery[7] to assign utility values to the acute

pain states. We used the breakdown between moderate, severe, and extreme pain post discharge to arrive at an NPRS of 5 for acute pain patients. However, this report of pain is for acute pain patients with and without prescribed opioids. We assumed that half of acute pain patients receive opioids at discharge. We estimated 30% pain reduction from opioid treatment of acute pain, compared to treatment without opioids, given a 30% pain reduction reported by a literature review of opioid use for chronic pain.[57] We used the equation below to arrive at an approximation of the NPRS scores with and without opioids.

$$\begin{aligned} &NPRS\ for\ acute\ pain\ patients \\ &\quad = (1 - \ proportion\ of\ acute\ pain\ patients\ prescribed\ opioids) \\ &\quad * NPRS\ for\ acute\ pain\ without\ opioids \\ &\quad + proportion\ of\ acute\ pain\ patients\ prescribed\ opioids \\ &\quad * \ NPRS\ for\ acute\ pain\ with\ opioids \end{aligned}$$

where

$$\begin{aligned} &NPRS\ for\ acute\ pain\ with\ opioids = \ NPRS\ for\ acute\ pain\ without\ opioids \\ &* (1 - \ reduction\ in\ pain\ with\ opioid\ prescription) \end{aligned}$$

This results in an NPRS score of 4 for acute pain patients with opioids and 6 for patients without, which correspond to health utility decrements of 0.12 and 0.25, respectively.[56] We assumed that acute pain lasts an average of half a month, after which the patient returns to a pain-free state, so for acute pain, we averaged the resulting utility values with that for a pain-free nonuser.

We assumed that chronic pain incurs a utility decrement of 0.15. We assumed that treatment with opioids does not yield any benefit, in light of reports showing no evidence of reduction in pain from long-term use of opioids as well as uncertainty in the net effect of opioid use on quality of life, given undesirable side effects.[58-62]

We estimated health utility decrements associated with SHUD based on published literature:[63-65] we used a utility value of 0.8 for individuals with SHUD who are not in MAT. We assigned a 0.9 utility value for individuals with SHUD who are in MAT, because we assumed MAT mitigates utility loss.[66] We did not find studies estimating health utility associated with SOUD, so we assumed values similar to but higher than those for SHUD.

S1.6 Base Case Parameter Sets

We sought to model the US opioid epidemic "on average." However, there is substantial uncertainty around what value for each input parameter would truly represent the US on average. For this reason, we created ten base case parameter sets, described in Appendix Table 3, as potential representations of the status quo. The parameters described in sections S1.3 through S1.5 were used to arrive at initial compartment sizes, transition probabilities, and utility values, and form base case parameter set 1. We developed each of nine additional base case parameter sets by altering a small number of parameters from Set 1. We did not alter any parameters that impact the initial compartment sizes.

S1.7 Outcome Measures

We calculated the following outcome measures: discounted net present (2016) life years lived; discounted net present (2016) quality-adjusted life years (QALYs) lived; the number of prescription opioid deaths (due to overdose) and heroin addiction-related deaths (due to overdose and infection) monthly and aggregated over five and ten years; and monthly incidence and prevalence of SOUD and SHUD. We discounted all LYs and QALYs at 3%, annually.[67]

S1.8 Post-Time-Horizon Accounting

At the end of the modeled time horizon the distribution of individuals across compartmental states may differ between policies. These states are associated with various utility values and mortality rates. To account for this, we included the discounted net present value of LYs and QALYs for these individuals, assuming that they remain in their end-of-time horizon state until death (e.g., no additional transitions to other pain, opioid use, or addiction statuses). We implemented this as a simple alive-dead Markov model for each compartment that commences at the end of the modeled time horizon. Because we model a wide range of ages in the population, we assumed the post-time-horizon survival curve for individuals without addiction is consistent with that of a 44-year old (the average age in the aged 12+ US population).[68] (For simplicity, we assume no differences in the age distributions across compartments.) For individuals with addiction, we assumed an additional risk of death from overdose or infection consistent with rates described in section S1.4 and Appendix Table 1. For each compartment, we calculated discounted LYs and QALYs accrued post-time-horizon and added them to those accrued during the modeled time horizon.

S1.9 Intervention Descriptions

We assessed the effects of 11 interventions aimed at curbing the opioid epidemic (Appendix Table 2). All of these interventions have been implemented to some extent in certain regions of the country; we aim to project the effect of implementing each intervention on a broader scale. We assumed the mechanism by which each intervention would impact the dynamics of the system and the magnitude of the effects using expert opinion (K. Humphreys) and information from the literature when available. The interventions and our baseline assumptions about their effects are as follows:

- *Reduced prescribing for acute pain* We assumed that changes to guidelines for treatment of acute pain result in a 25% reduction in acute pain prescribing.
- *Reduced prescribing for transitioning pain* We assumed that changes to guidelines for managing pain that extends beyond one month results in a 25% reduction in prescribing for pain that is transitioning from acute to chronic.
- *Reduced prescribing for chronic pain* We assumed that changes to guidelines for treatment of chronic pain result in a 25% reduction in chronic pain prescribing. We recognize that 25% reduction in prescribing for the three interventions above is significant and that policies to reduce prescribing could take a variety of forms ranging from aggressive regulatory action to loose guidelines for providers. Given the dramatic rise in prescribing in the first decade of the 21st century, reversal of this trend, in somewhat similar dramatic fashion, does not seem implausible.
- *Drug rescheduling* More restrictive scheduling of opioids under the Controlled Substances Act puts additional barriers in place for refilling prescription (e.g., requiring that patients see their physician every 30 days in order to get monthly refills). The extent to which rescheduling might impact the chance of opioid prescription renewal depends on the set of drugs for which the rescheduling would apply. We assumed that a drug rescheduling policy would reduce by 10% the likelihood that a prescription holder desiring renewal is able to obtain a renewal.
- *Prescription monitoring program (PMP)* Individuals with SOUD attempting to misuse prescribed opioids often attempt to obtain multiple prescriptions from several doctors

("doctor shopping"). PMPs provide prescribers and dispensers with an up-to-date history of controlled substance dispensing to individual patients. Improvements to PMPs might include having the it cover a broader range of medications, making the PMP easier to access (e.g., by integrating it into the electronic health record), and increasing the proportion of providers who participate via incentives, a mandate, or both. The effects of these initiatives would likely be wide ranging, improving safety of prescribing beyond the opioid epidemic (e.g., identifying potentially dangerous combinations of drugs). However, as it pertains to the opioid epidemic, we assume that PMPs most notably prevent a small portion of patients with SOUD from doctor shopping, which we represent as a 2.5% reduction in the likelihood that an individual with SOUD is able to obtain a prescription renewal. We also assume a smaller (1%) reduction in the relative likelihood that an individual with SOUD is able to obtain a new opioid prescription, compared to a person with chronic pain who does not have SOUD, since aided with data from a PMP, a provider might observe a history of prescriptions that could suggest potential OUD. Additionally, we assume that opioid prescribing in general (for acute, transitioning, and chronic pain) will be slightly reduced (1%) given that use of the PMP will alert providers to a small subset of patients for whom opioid prescription is counterindicated given other medications that the patient is taking (e.g., benzodiazepines), thereby reducing prescribing.

- *Drug reformulation* Tamper-resistant/abuse-deterrent formulations of opioids reduce the likelihood that the drugs are misused. However, these formulations tend to be more expensive, so currently these reformulated drugs may be prescribed to individuals who are perceived to have heightened risk of misuse. We assumed that expanded use of tamper-resistant/abuse-deterrent formulations would reduce risk of iatrogenic addiction by 10%. Tamper-resistant pills are also less attractive for misuse purposes, as evidenced by a 36% reduction in the street price of OxyContin when reformulated.[69] Thus, for the drug reformulation policy we also modeled a 30% reduction in pill-seeking behavior for the "SOUD without Rx" population. We implemented this as a 30% reduction in the likelihood of "SOUD without Rx" individuals obtaining a prescription, as well as a 30% reduction in the proportionality factor between the number of individuals who can be in the "SOUD without Rx" state and the total number of prescription holders one year prior. However, because we modeled a one-year lag between the number of prescription holders and the number of individuals able to be sustained in the "SOUD without Rx" state, we also modeled a one-year lag before this intervention reaches its full effect on the proportionality factor between the number of individuals who can be in the "SOUD without Rx" state and the total number of prescription holders one year prior. (We assumed linear change in the proportionality factor over a one year period from when the intervention is initiated.)
- *Excess opioid disposal* Excess opioid disposal programs are intended to reduce diversion of drugs by providing receptacles for safe disposal of excess pills. Such programs have been found to have small effects.[70] We modeled the impact of expansion of such programs via a 10% reduction in diversion of pills to "Pain-free nonusers" as well as a 10% reduction in proportionality factor between the number of individuals permitted in the "SOUD without Rx" state and the total number of non-SOUD prescription holders one year prior. We assumed that individuals in the "Pain-free SOUD with Rx" and "Chronic pain SOUD with Rx" population groups will not participate in excess opioid

disposal programs. Similar to the implementation of the drug reformulation policy, we modeled a one-year lag before this intervention reaches its full effect on the proportionality factor between the number of individuals who can be in the "SOUD without Rx" state and the total number of prescription holders one year prior.

- *Increased naloxone availability* Approximately 11% of opioid overdoses are fatal if naloxone is not administered.[71] However, opioid overdose deaths are usually avoidable if naloxone is administered in time.[71] In order to administer naloxone, an overdose must be witnessed, which is the case in approximately 80% of overdoses.[72] We assumed that expanded naloxone access would result in a 5% reduction in overdose mortality rates among individuals with SOUD and SHUD. We chose this number conservatively in light of many barriers to use of naloxone even if it is made more widely available (e.g., reluctance to carry naloxone, witness's hesitation to use it for fear of "stealing someone's high", witness opts to steal the drugs and money of the person suffering from an overdose, etc.).
- *Expanded needle exchange programs.* Needle exchange programs reduce the infection-related morbidity and mortality associated with injection drug use (e.g., due to HIV, HCV, etc.). One study found a 33% reduction in HIV incidence among injection drug users participating in needle exchange.[73] We modeled the effect of expanded needle exchange as a 10% reduction in infection-related mortality from the "SHUD" state.
- *Expanded access to medication-assisted therapy (MAT*) We assumed that expansion of MAT would increase enrollment rates by 25% and that dropout rates would be unchanged.
- *Expanded access to psychosocial treatment* For simplicity, we did not model an explicit health state for enrollment in psychosocial interventions. Instead, we assumed that increasing access to such interventions would increase by 25% the likelihood of desistance from the non-MAT addiction states (i.e., "pain-free SOUD with Rx", "chronic pain SOUD with Rx", "SOUD without Rx", and "SHUD"). We assumed that psychosocial treatment is included in MAT programs and thus did not model increased desistance for individuals in MAT as a result of this policy.

S2. Supplemental Results

S2.1 Status Quo Results

Appendix Tables 4 and 5 show the status quo model outcomes (i.e., current trajectory without additional policies enacted) over five and ten years for each of the ten base case parameter sets. Appendix Figures 1 through 10 illustrate for each base case parameter set the number of people in each compartment or group of compartments by month (excluding pain-free non-users), the number of individuals with SHUD, and the number of SHUD-related and SOUD-related deaths by year.

S2.2 Single Intervention Results

We evaluated the impact of the 11 individual interventions on each of the ten model parameter sets over five and ten years. Appendix Table 6 and Appendix Table 8 summarize the mean, minimum, and maximum results relative to the status quo on change in LYs, QALYs, pill addiction-related deaths, heroin addiction-related deaths, opioid addiction-related deaths, and percent of total population holding a prescription over five and ten years, respectively. Appendix Figure 11 shows SOUD and SHUD incidence (top panel), prevalence (middle panel), and related deaths (bottom panel) over ten years for each individual policy (a-k), relative to the status quo.

Reduced prescribing for acute pain (Appendix Figure 11a) reduces incidence of pill addiction through reduced iatrogenic addiction. This further reduces SOUD prevalence relative to the status quo over time. Heroin addiction is reduced in the first year following the policy initiation because there are fewer individuals with SOUD to escalate to heroin use. However, the incidence of heroin addiction spikes after that year (we modeled a one-year lag in effect on pill supply) as individuals with SOUD and no prescription face a reduced supply of diverted pills and some shift to heroin addiction. By 2019 the reduction in heroin initiation stemming from reduced iatrogenic addiction exceeds the increase in heroin initiation resulting from reduced pill supply. By 2020, SHUD prevalence under this policy is projected to be consistently lower than under the status quo. SOUD and SHUD deaths mirror the prevalence trajectories and the net effect is a steady decline in deaths relative to the status quo.

The reduced prescribing for transitioning pain policy (Appendix Figure 11b) has a similar but smaller effect on addiction incidence, prevalence, and deaths, because the transitioning pain population is smaller than the population with acute pain. However, reduced prescribing for transitioning pain prompts an immediate increase in SHUD incidence as some individuals who become iatrogenically addicted during acute pain treatment are also unable to receive a prescription to continue opioid treatment and thus join the “SOUD without Rx” population—a population at risk of escalation to heroin use. It takes ten years for the monthly net opioid addiction deaths to decline to a level below that of the status quo.

The reduced prescribing for chronic pain policy (Figure 2) is similar to the reduced prescribing for transitioning pain policy but the effects are far greater due to the size of the population with chronic pain. Notably, although the reduced prescribing for chronic pain policy still reduces SOUD prevalence to a greater extent than it increases SHUD prevalence, the greater deadliness of SHUD compared to SOUD results in a net increase in total opioid addiction deaths.

Drug rescheduling (Appendix Figure 11c) decreases SOUD incidence relative to the status quo, but increases SHUD incidence as some individuals with SOUD escalate to heroin addiction in response to reduced pill availability. The incidence of SHUD attenuates over time as a result of reduced SOUD prevalence. However, although SOUD prevalence under this strategy

decreases relative to the status quo, relative SHUD prevalence is greater for the entire time horizon as are total addiction-related deaths. (Although the SOUD prevalence reduction is greater than the increase in SHUD prevalence, the greater deadliness of SHUD compared to SOUD results in a net increase in total opioid addiction deaths.) The gap between status quo opioid addiction-related deaths and deaths under this policy declines over time, but after ten years this policy still results in a higher number of monthly opioid deaths. Over a longer time horizon, annual addiction-related deaths decrease relative to the status quo: 570 fewer deaths under the drug rescheduling policy are projected during the year 2030 compared to the status quo.

The PMP policy (Appendix Figure 11d) has an effect similar to the drug rescheduling policy, but with far less impact on SOUD incidence, because the PMP policy largely prevents SOUD addiction through diversion to nonusers and does little to prevent iatrogenic addiction. SHUD incidence under the PMP policy compared to the status quo remains higher as many individuals addicted to prescription pills are denied refills and escalate to heroin use. As a result, SHUD prevalence relative to the status quo does not approach zero over time and total opioid deaths relative to the status quo continue to increase.

The drug reformulation policy (Appendix Figure 11e) causes an immediate drop in SOUD incidence, prevalence, and deaths as iatrogenic addiction is reduced. SHUD incidence initially spikes as prescription pills are less attractive for abuse and more of the SOUD population escalates to heroin use. (SHUD incidence reaches its highest level one year after the intervention is implemented, because we modeled a one-year period for the policy to reach its full effect on the proportionality factor between the number of individuals who can be in the "SOUD without Rx" state and the total number of prescription holders one year prior.) However, SHUD incidence then decreases over time, as there are fewer individuals with SOUD to escalate to heroin use, and falls to a level below that of the status quo by 2024. The net effect is a short-term increase in deaths per month, but after five years, deaths per month under this policy become lower than the status quo.

The excess opioid disposal policy (Appendix Figure 11f) causes an immediate reduction in monthly SOUD incidence, prevalence, and deaths relative to the status quo. However, a spike in SHUD incidence occurs as there are fewer pills available for diversion to the "SOUD without Rx" population. (Similar to the drug rescheduling policy, we modeled a one-year period before the policy reaches its full effect on the proportionality factor between the number of individuals who can be in the "SOUD without Rx" state and the total number of prescription holders one year prior. Thus, SHUD incidence takes one year to reach its highest level.) SHUD incidence then decreases, falling to a level below that of the status quo by 2022. Similarly, SHUD prevalence and deaths initially increase relative to the status quo, but this gap diminishes over time. Net monthly opioid deaths are initially equal to status quo, but become lower after two years.

The increased naloxone availability policy (Appendix Figure 11g) has a negligible impact on SOUD incidence, but increases SOUD prevalence relative to the status quo as fewer individuals with SOUD die from overdose. Because SOUD prevalence is higher, SHUD incidence and prevalence are higher than under the status quo. This policy reduces both SOUD and SHUD deaths.

The needle exchange policy (Appendix Figure 11h) does not impact SOUD incidence, prevalence, or deaths. It has no effect on SHUD incidence, but decreases heroin deaths and increases SHUD prevalence because fewer individuals with SHUD die.

The increased MAT availability policy (Appendix Figure 11i) has a negligible effect on SOUD incidence, but reduces SHUD incidence relative to the status quo as individuals opt for MAT—first dramatically, but the gap between the MAT policy and status quo attenuates as individuals with SHUD enrolled in MAT avoid death, then increases again as some desist heroin use. Since MAT reduces risk of death but also increases chance of recovery, SOUD prevalence relative to the status quo initially increases but then decreases. SHUD prevalence is consistently lower than the status quo and the gap continues to decrease. The net impact of this policy on deaths is consistent reduction relative to the status quo.

The psychosocial intervention policy (Appendix Figure 11j) has a negligible effect on SOUD incidence but decreases SOUD prevalence and deaths as desistance increases among individuals with SOUD. SHUD incidence, prevalence, and deaths are lowered relative to the status quo because SOUD prevalence decreases.

S2.3 Variation in Policy Effects across Base Case Models

Appendix Figure 12 details for each policy the distribution of effects over ten years across the ten base case parameter sets. The top row shows incidence of SOUD (left) and SHUD (right). The middle row shows prevalence of SOUD (left) and SHUD (right). The bottom row shows addiction-related deaths from SOUD (left), SHUD (middle), and in total (right). Overall, the SOUD and SHUD trends across the ten base case models are in the same direction. However, the overall net effect of a policy on opioid deaths may be positive or negative, depending on the parameter set. For example, Appendix Figure 12d illustrates the effect of the drug rescheduling policy. The panel in the bottom right shows monthly opioid-related deaths relative to the status quo. For base case model 4, we assume lower probability of escalating to SHUD when diverted pills are scarce compared to base case model 1 (reference case). It is reasonable to expect that a policy that reduces the opioid supply would result in fewer deaths if the constrained supply were less likely to result in escalation to SHUD. Conversely, in base case model 2, we assumed a higher mortality risk for SHUD, compared to model 1; thus, a policy that reduces pill supply and prompts escalation to SHUD will cause greater opioid-related deaths for model 2 than for model 1.

S2.4 Combined Intervention Results

We evaluated the impact of several combined interventions on each of the ten model parameter sets over five and ten years. We tested the potential to mitigate harmful effects from the reduced prescribing, drug rescheduling, and PMP policies by combining them with the four uniformly beneficial policies (naloxone availability, needle exchange, MAT, and psychosocial treatment). Appendix Tables 7 and 9 summarize the mean, minimum, and maximum results relative to the status quo on change in LYs, QALYs, pill addiction-related deaths, heroin addiction-related deaths, opioid addiction-related deaths, and percent of total population holding a prescription over five and ten years, respectively.

For the drug rescheduling and PMP interventions, the addition of naloxone, MAT, needle exchange, or psychosocial treatment policies still results in more addiction-related deaths and fewer LYs over five years compared to the status quo. We considered an “all prescribing” policy in which the reduced acute pain, transitioning pain, and chronic pain prescribing policies are implemented simultaneously. Compared to the status quo, this combined policy leads to more LYs and fewer QALYs, but a negligible change in total deaths over five years. The individual addition of naloxone availability, needle exchange, MAT, and psychosocial treatment to the all

prescribing policy produces more LYs and averts more deaths than the all prescribing strategy alone, and the QALY gains generated by pairing with the expanded naloxone availability or MAT interventions are enough to counterbalance the QALY loss from the all prescribing intervention.

The combination of policies resulted in nearly additive LYs, QALYs, and total opioid deaths. The combination of policies resulted in fewer pill deaths avoided than that for the sum of the individual policies. This is because the same life cannot be saved twice (e.g., drug rescheduling reduces pill addiction, which means there are fewer addicts to be saved by the naloxone strategy). Conversely, combining a policy that mitigates mortality impact (e.g., naloxone availability) with a policy that increases heroin usage, at least in the short term (e.g., drug rescheduling), results in more deaths averted than the sum of the individual policies, because a policy that reduces drug mortality impact can additionally benefit the larger number people escalating to heroin use.

S2.5 Threshold Analysis Results

We determined the magnitude each individual intervention would need to be implemented at to achieve a 10% reduction in mean addiction-related deaths over five years and ten years. Three interventions impact more than one model parameter: drug reformulation, excess opioid disposal, and PMP. For each of these cases we had to decide which parameters to vary in order to achieve a 10% reduction in addiction deaths. For the drug reformulation intervention, we only varied only the magnitude of reduction in iatrogenic addiction. We did not assess the impact of the policy under alternative magnitudes for the reduction in addiction through diversion of pills to "pain-free nonusers" or the reduction in prescription pill seeking behavior for "SOUD without Rx". (We assume that people who intend to abuse the drugs will find ways to do so, and thus intensifying the intervention would not likely be as impactful on the channels of diversion as it would be on iatrogenic addiction.) For the excess opioid disposal intervention, we varied, together and to the same degree, the magnitude of both the reduction in diversion to pain-free nonusers and the reduction in the number of individuals with SOUD and no prescriptions who are able to be sustained by prescription holders who do not have SOUD. For the PMP intervention, we varied only the reduction in the ability of an individual with SOUD to get opioid prescriptions renewed, as this is the most impactful element of the PMP intervention as it pertains to our model.

In Appendix Tables 10 and 11, we report the mean, minimum, and maximum results relative to status quo on change in LYs, QALYs, pill addiction-related deaths, heroin addiction-related deaths, and opioid addiction-related deaths at the effect magnitude needed to reduce deaths by 10% if possible (i.e., "-10% deaths achieved" is "Yes"). For the individual policies for which that level of death reduction is not possible (i.e., "-10% deaths achieved" is "No"), we report these metrics for the most extreme effect size that minimizes deaths (reported under "Policy Change Description").

For the drug rescheduling policy, the relationship between the percent reduction in likelihood of prescription renewal (i.e., the effect of the policy) and total addiction-related deaths is highly nonlinear, as shown in Appendix Figure 13. Over the five-year time horizon, no degree of likelihood of reduction in renewal is expected to reduce total addiction-related deaths. Over the ten-year time horizon, a 7% reduction in the likelihood of renewal leads to the greatest number of deaths over ten years relative to the status quo; at least a 55% reduction in likelihood

of renewal is required to reduce total deaths; and complete elimination of prescription renewals results in the largest number of lives saved.

S2.6 Sensitivity Analyses

We performed sensitivity analyses to test the robustness of our results to changes in key model parameters: likelihood of escalation to SHUD for the "SOUD without Rx" population when there are insufficient pills available through diversion; heroin overdose mortality; prescription pill overdose mortality; likelihood of diversion to "pain-free nonusers"; rate of enrollment in MAT; and quality-of-life impact of opioid treatment for chronic pain. Because some parameter values vary across the ten base case sets, we performed sensitivity analysis assuming a relative change in the value of a given parameter.

Escalation to SHUD when there are insufficient pills from diversion The number of individuals allowed in the "SOUD without Rx" state is determined by the size of the prescription-holding population. When the number of individuals in the "SOUD with Rx" population exceeds that able to be sustained by diverted prescription pills, these individuals are forced to either desist use, enroll in MAT, or escalate to SHUD. We evaluated how the effect of each individual policy differs under alternative assumptions about the likelihood that an individual in the "SOUD without Rx" population escalates to SHUD when there are not enough pills available from diversion. We explored the impact of a 25% (0.75x parameter level) and 50% (0.5x parameter level) reduction in the likelihood that these individuals escalate to heroin, compared to our base case assumption (1x parameter level), assuming that the additional individuals not turning to heroin desist use (i.e., the proportion enrolling in MAT is unaffected). Appendix Figure 14 shows the effects over five and ten years relative to status quo for each policy under the 1x, 0.75x, and 0.50x parameter levels for likelihood of escalation to SHUD. At lower likelihoods of escalation to SHUD, the reduced prescribing, drug rescheduling, PMP, drug reformulation, and excess opioid disposal polices result in fewer SHUD deaths as SHUD incidence and prevalence are decreased. Indeed, if the likelihood of escalation from "SOUD without Rx" to "SHUD" is 25% lower than in the base case (i.e., 0.75x), total monthly addiction deaths would be decreased relative to the status quo under the reduced prescribing for chronic pain, drug reformulation, and excess opioid disposal policies, even in the short term. If the likelihood of escalation from "SOUD without Rx" to "SHUD" is 50% lower, several policies would result in immediate reduction in monthly opioid addiction deaths. At lower likelihoods of escalation to SHUD, the naloxone availability, needle exchange, MAT, and psychosocial intervention policies save fewer lives because the SHUD incidence is not as high.

Heroin overdose mortality The increasing prevalence of fentanyl in the heroin supply has contributed to increased heroin overdose mortality.[74] In light of the possibility for further increase in the heroin overdose mortality risk, we assessed the impact of a 25% higher (1.25x parameter level) overdose mortality rate for SHUD individuals compared to our base case assumption (1x parameter level) for each policy. Because China recently acted to make fentanyl production illegal,[75] we also assessed the impact of 25% lower (0.75x parameter level) overdose mortality rate for SHUD individuals. Appendix Figure 15 shows that if SHUD overdose mortality is higher (lower) than the base case level, the impact of each policy (with the exception of the needle exchange policy) on SHUD deaths is amplified (reduced).

Prescription pill overdose mortality Our baseline analyses assumed that SOUD overdose mortality risk is 0.5 relative to the heroin mortality risk. Because substantial uncertainty exists regarding the relative deadliness of these prescription opioids versus heroin, we compared the

impact of a 25% lower (0.75x parameter level) and 25% higher (1.25x parameter level) overdose mortality rate for individuals with SOUD compared to our base case assumption (1x parameter level) for each policy. Appendix Figure 16 shows that if SOUD overdose mortality is higher (lower) than the base case level, each policy (with the exception of the needle exchange policy) would reduce SOUD deaths to a greater (lesser) extent. If the chance of SOUD overdose mortality is 25% greater, total addiction deaths over five years would be decreased relative to the status quo under the drug reformulation and excess opioid disposal policies.

Diversion to "pain-free nonusers" The rate of diversion of prescribed opioids to pain-free nonusers is uncertain. Therefore, we assessed the impact of each policy given 50% higher (1.5x parameter level) or 50% lower (0.5x parameter level) rate of diversion from prescription holders to pain-free nonusers, compared to our base case assumption (1x parameter level). The level of diversion primarily impacts the incidence of SOUD—specifically the transition from "pain-free nonusers" to "SOUD without Rx". Therefore, level of diversion impacts the size of the "SOUD without Rx"—which is limited by the number of prescription holders—and thus the rate at which individuals must leave the "SOUD without Rx" and potentially escalate to SUHD. Appendix Figure 17 shows that at higher rates of diversion, the benefit to policies that limit pill supply is greater. Such policies result in greater relative reduction in SOUD incidence at higher levels of diversion. However, the prevalence of SOUD is not similarly reduced by these policies at higher levels of diversion because the size of the "SOUD without Rx" is constrained by the number of prescription holders, so under the status quo, higher levels of diversion results in more individuals escalating to SHUD but little change in SOUD prevalence. Thus, there is little potential for polices that reduce pill supply to significantly impact SOUD prevalence and death rates under higher levels of diversion. Conversely, with respect to SHUD deaths, policies that reduce pill supply provide greater benefit under higher rates of diversion, because they reduce diversion, preventing "pain-free nonusers" from joining the constrained "SOUD without Rx" population. At higher rates of diversion, the potential to protect more individuals from escalating from "SOUD without Rx" to SHUD is greater.

If the rate of diversion to "pain-free nonusers" is lower than we assumed, the "SOUD without Rx" population is less likely to become larger than can be supported. At lower levels of diversion, policies that constrain the pill supply have less potential to prevent SOUD. These policies' impact on the prevalence of SOUD may be similarly reduced at lower levels of diversion to pain-free "nonusers" less diversion to pain-free nonusers. However, under a lower risk of diversion, the "SOUD without Rx" compartment is less likely to exceed its capacity, so fewer should escalate to SHUD in the status quo and SOUD prevalence may increase. This would increase the potential of pill supply reduction policies to reduce the SOUD prevalence relative to the status quo. With less diversion to pain-free nonusers, the impact of policies to reduce prescribing for pain have a less dramatic effect on SHUD death rates because with less diversion, the "SOUD without Rx" compartment is less likely to exceed its capacity so individuals are less likely to escalate to heroin use.

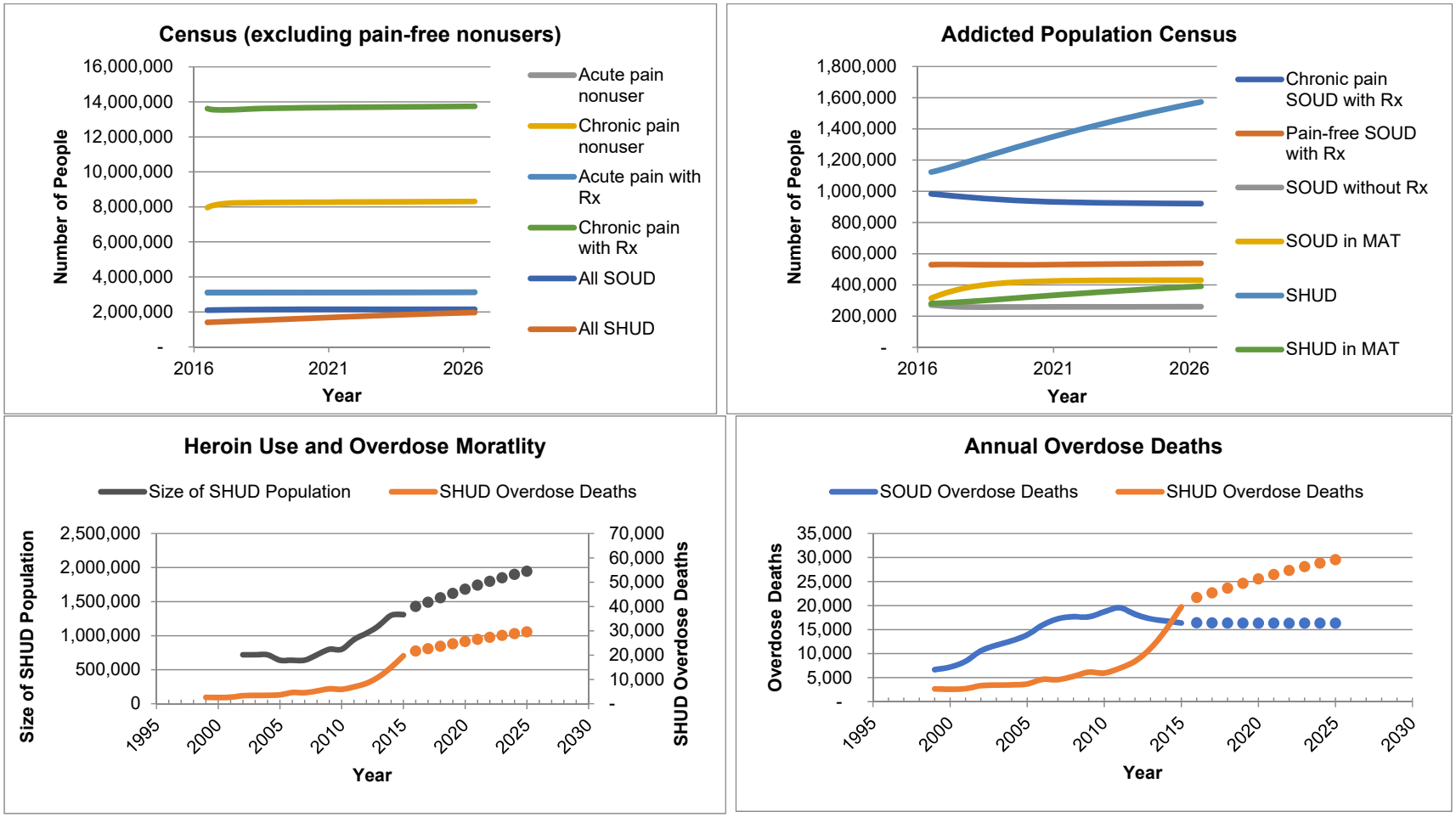
Rate of enrollment in MAT Medicaid pays for 25% of buprenorphine maintenance in the U.S.,[76] which is just one of several forms of MAT in light of recent and ongoing Congressional efforts to reduce funding to Medicaid, we modeled the impact of each intervention under lower levels of status quo enrollment in MAT: 25% reduction (0.75x parameter level) and 50% reduction (0.5x parameter level) in likelihood of enrollment relative to the status quo (1x parameter level). Appendix Figure 18 shows that the effect of the policies on deaths relative to the status quo is generally not substantially changed under assumptions of lower MAT

enrollment rates. The policies that cause the largest increases in SHUD incidence (i.e., drug rescheduling and PMP) result in somewhat higher monthly rates of SHUD deaths relative to the status quo if the MAT enrollment rate is lower than we assumed. The only policy that is substantially affected by alternate rates of MAT enrollment is the MAT policy: it is not surprising that lower status quo enrollment rates cause notably lower projected reduction in deaths.

Quality of life impact of opioid treatment for chronic pain Controversy exists regarding the impact of opioid treatment on chronic pain.[59,62] In light of this, in our base case assumptions, we assigned no quality-of-life benefit or harm for opioid treatment of chronic pain, allocating both the "Chronic pain nonuser" and "Chronic pain with Rx" states a utility of 0.85. We tested the impact of select policies under alternate utility levels for "Chronic pain with Rx": 0.83 (equivalent to SOUD), 0.84, 0.85 (base case assumption), 0.93, 1.00 (equivalent to "Pain-free nonuser"). We focused this analysis on the policies that directly impact chronic pain treatment (i.e., reduced prescribing for chronic pain, reduced prescribing for transitioning pain, and drug rescheduling), and for comparison also assessed the impact on reduced prescribing for acute pain. Appendix Figure 19 shows the QALY impact of these policies under each of these alternative utility values for "Chronic pain with Rx." The reduced prescribing for acute pain policy results in a substantial QALY loss regardless of these assumptions about utility value associated with opioid treatment for chronic pain. Reduced prescribing for transitioning pain results in a QALY loss if the utility for the "Chronic pain with Rx" state is greater than approximately 0.87 (i.e., assuming a 0.02 utility improvement for opioid treatment of chronic pain) or 0.88, for the five- and ten-year time horizons, respectively. Reduced prescribing for chronic pain results in a QALY loss if the utility for the "Chronic pain with Rx" state is greater than approximately 0.86 or 0.87, for the five- and ten-year time horizons, respectively. Drug rescheduling results in a QALY loss if the utility for the "Chronic pain with Rx" state is at least approximately 0.85 or 0.86, for the five- and ten-year time horizons, respectively. These findings suggest that QALYs gained from policies that directly impact chronic pain treatment are highly sensitive to assumptions about the effectiveness of opioid treatment of chronic pain.

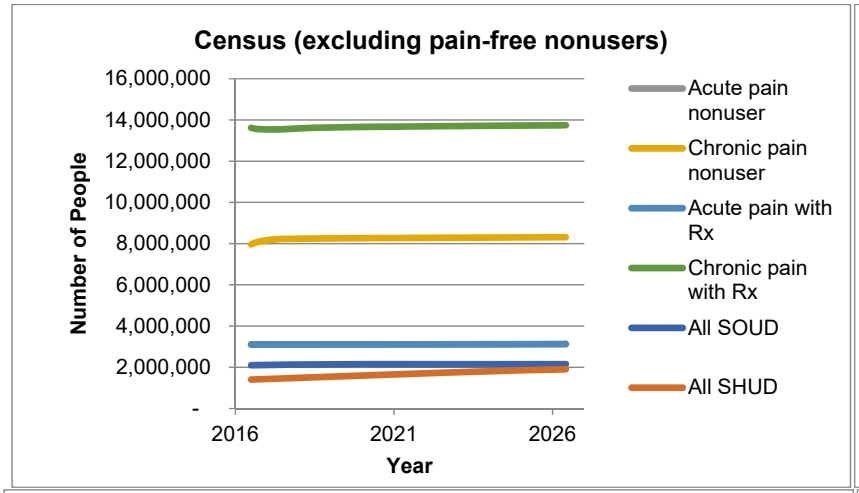
Appendix Figure 1. Status quo results for parameter set 1.

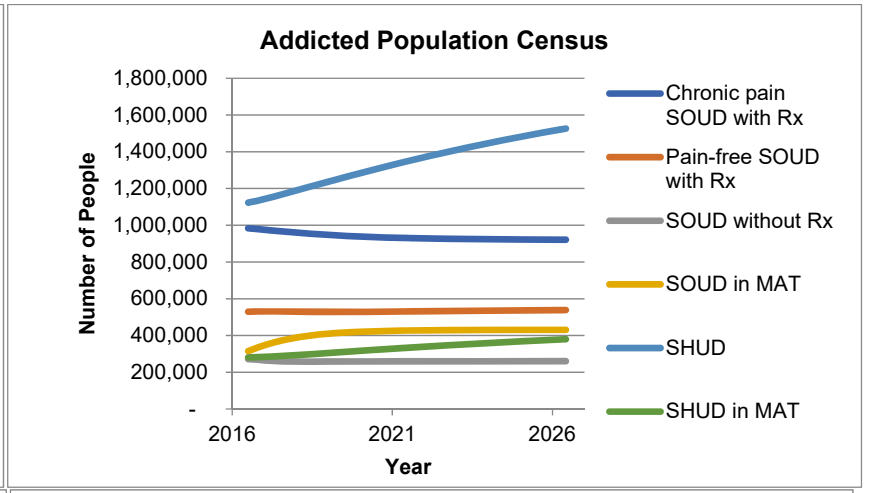
Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

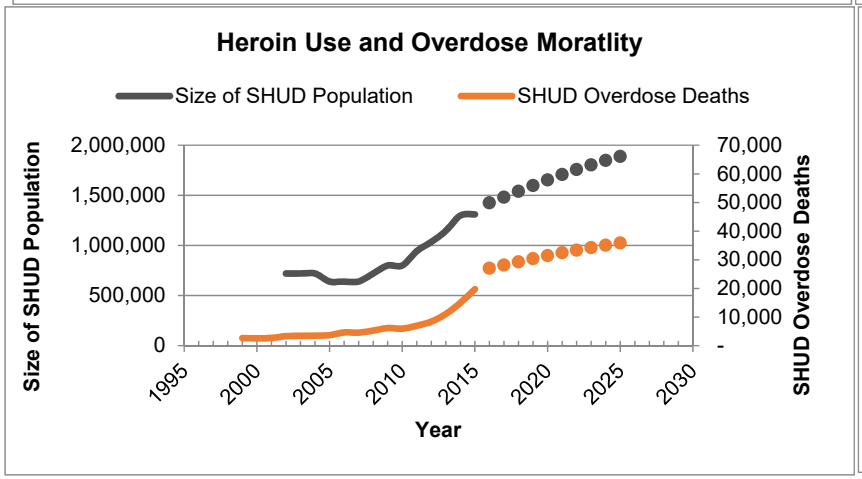


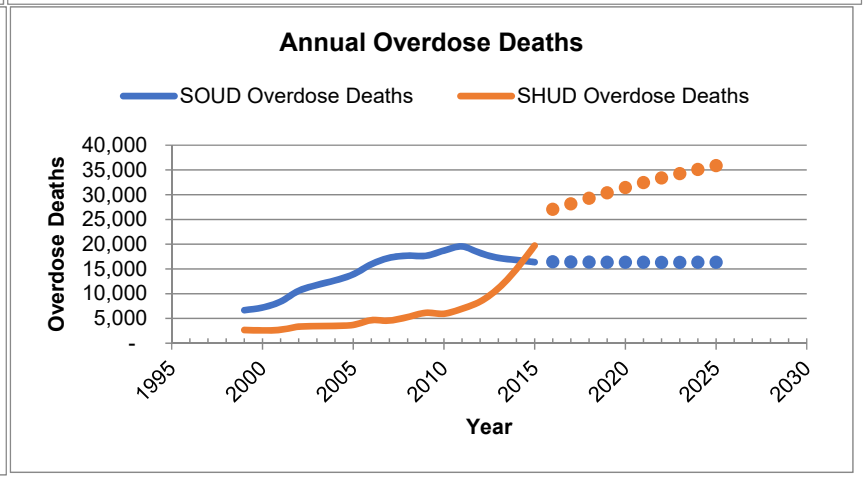
Appendix Figure 2. Status quo results for parameter set 2

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



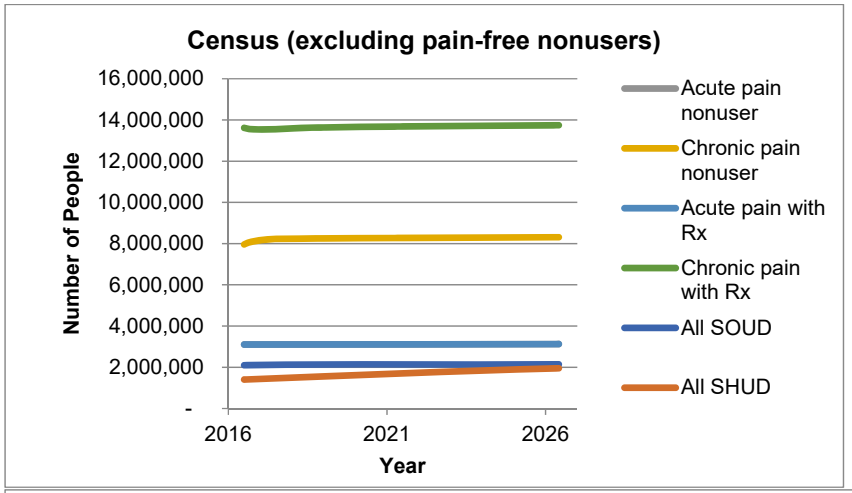


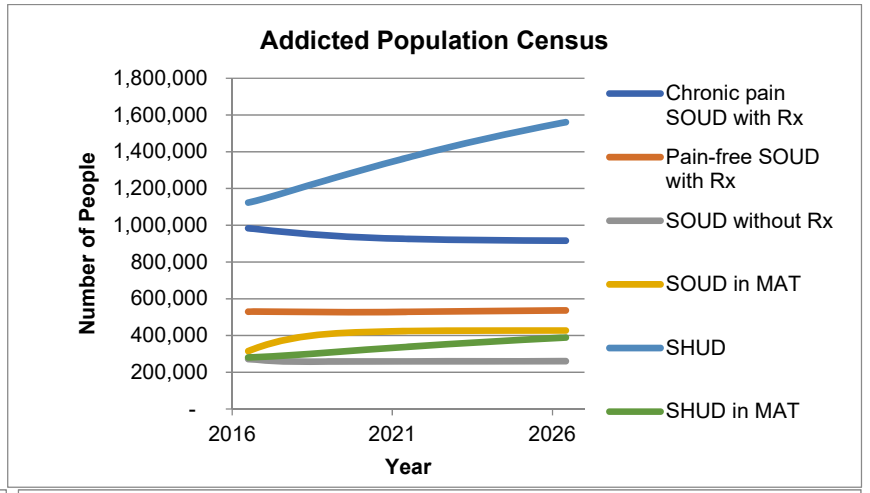


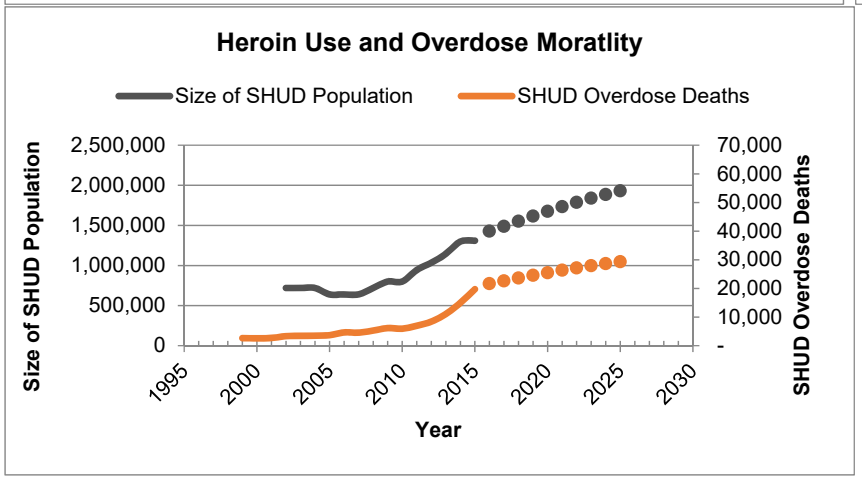


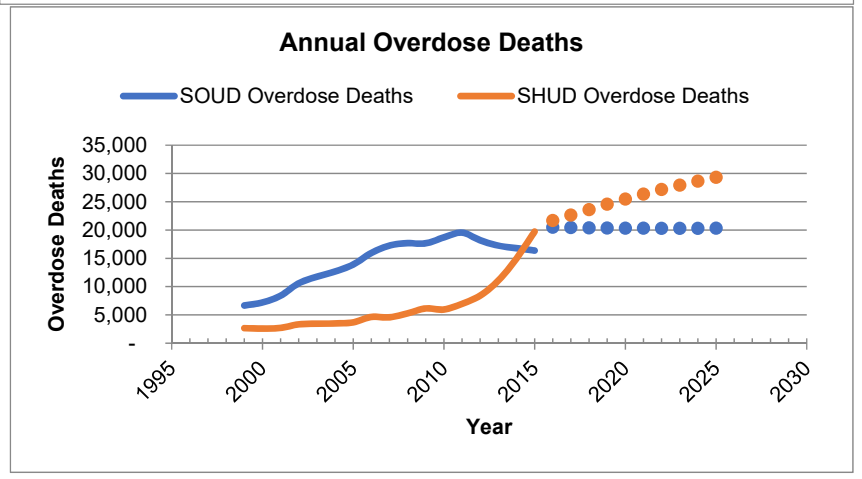
Appendix Figure 3. Status quo results for parameter set 3

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



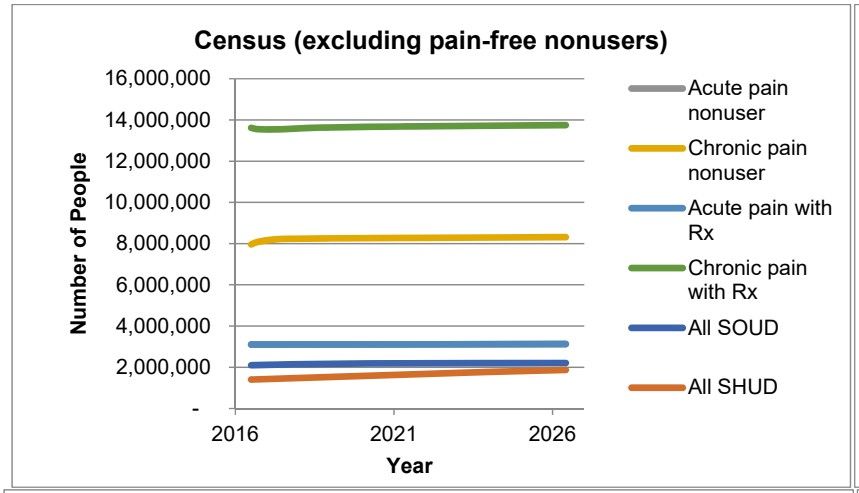


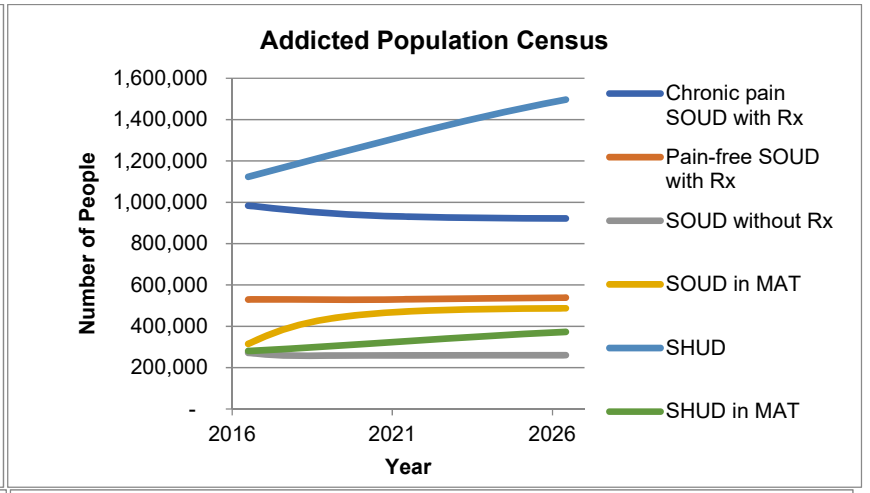


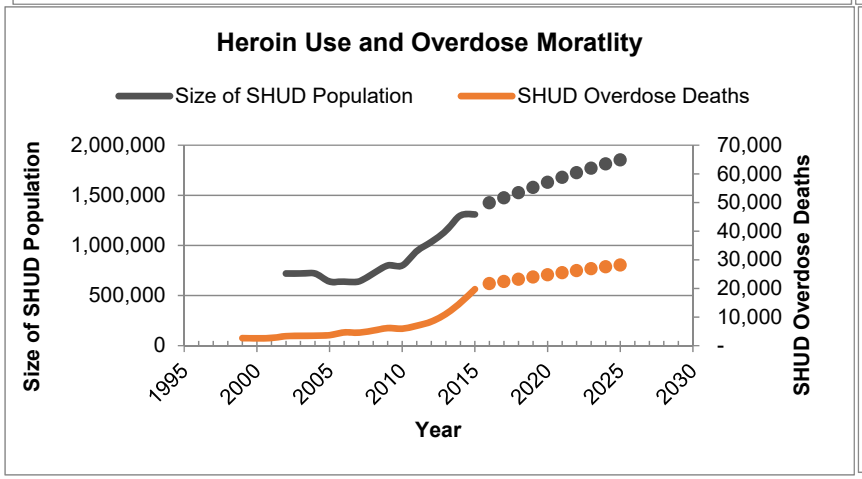


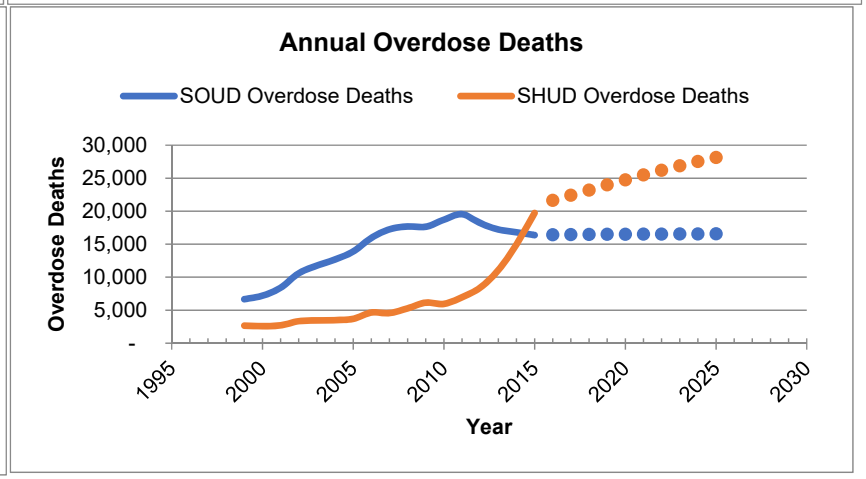
Appendix Figure 4. Status quo results for parameter set 4

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



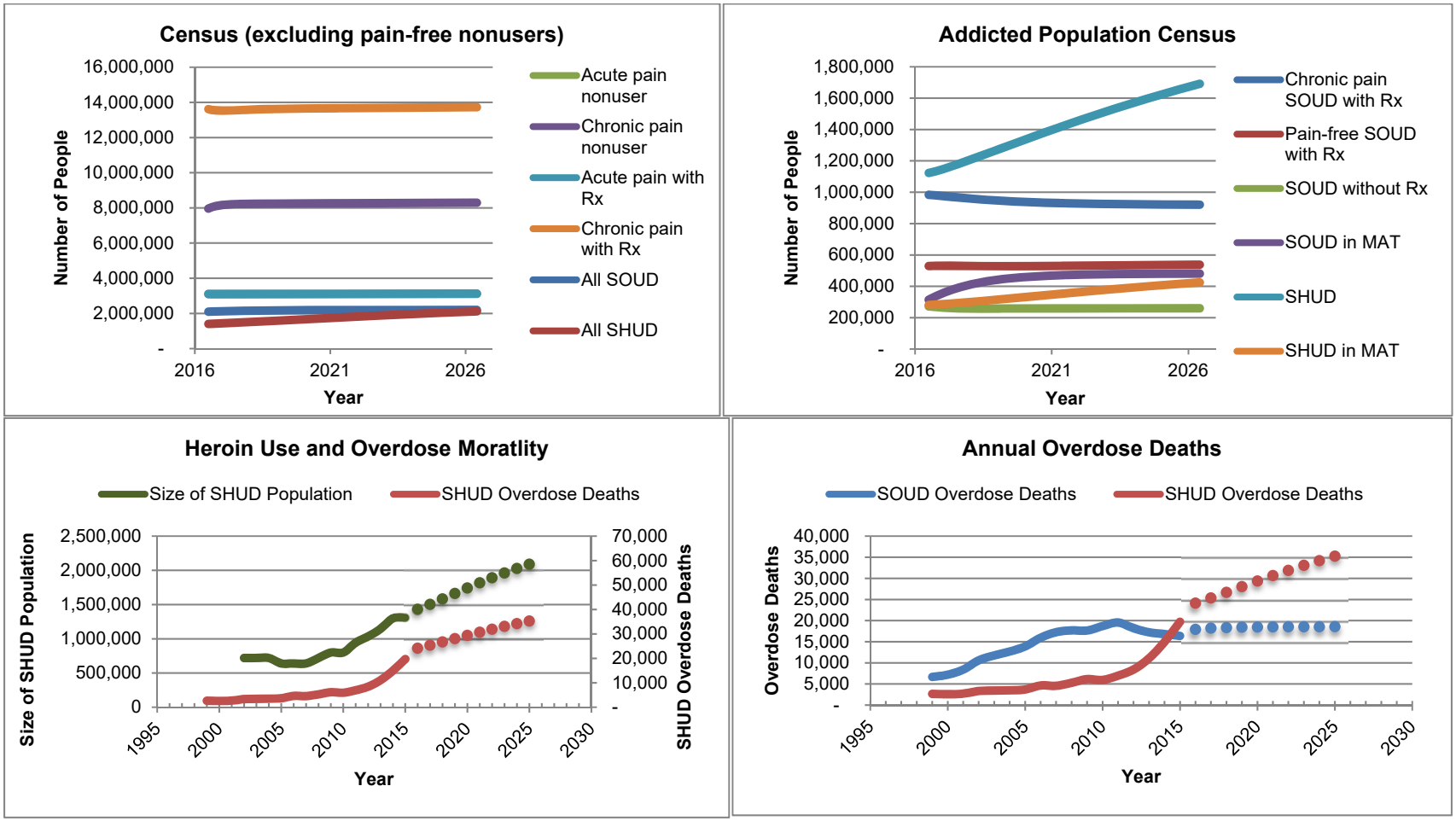






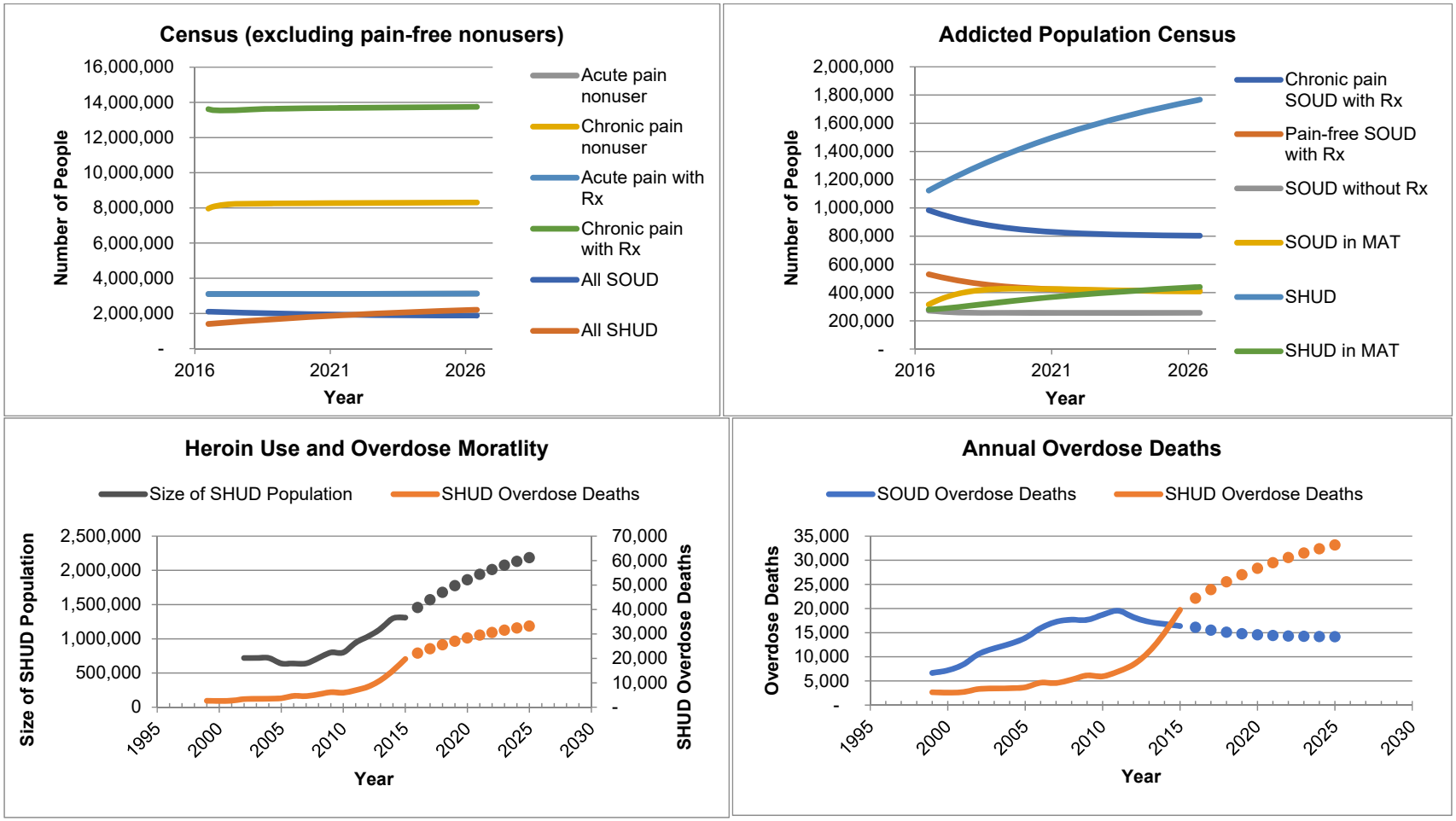
Appendix Figure 5. Status quo results for parameter set 5

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



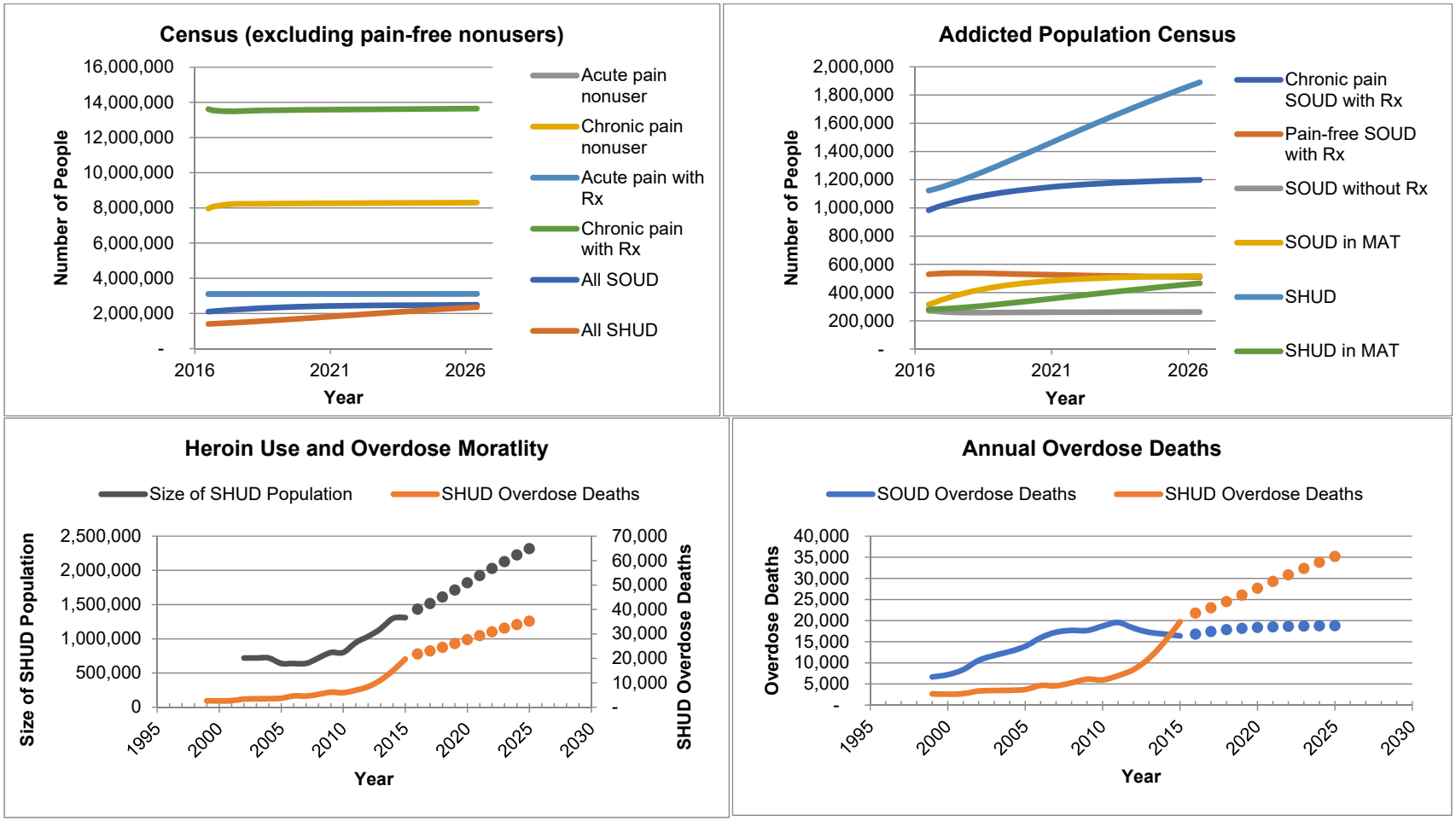
Appendix Figure 6. Status quo results for parameter set 6

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



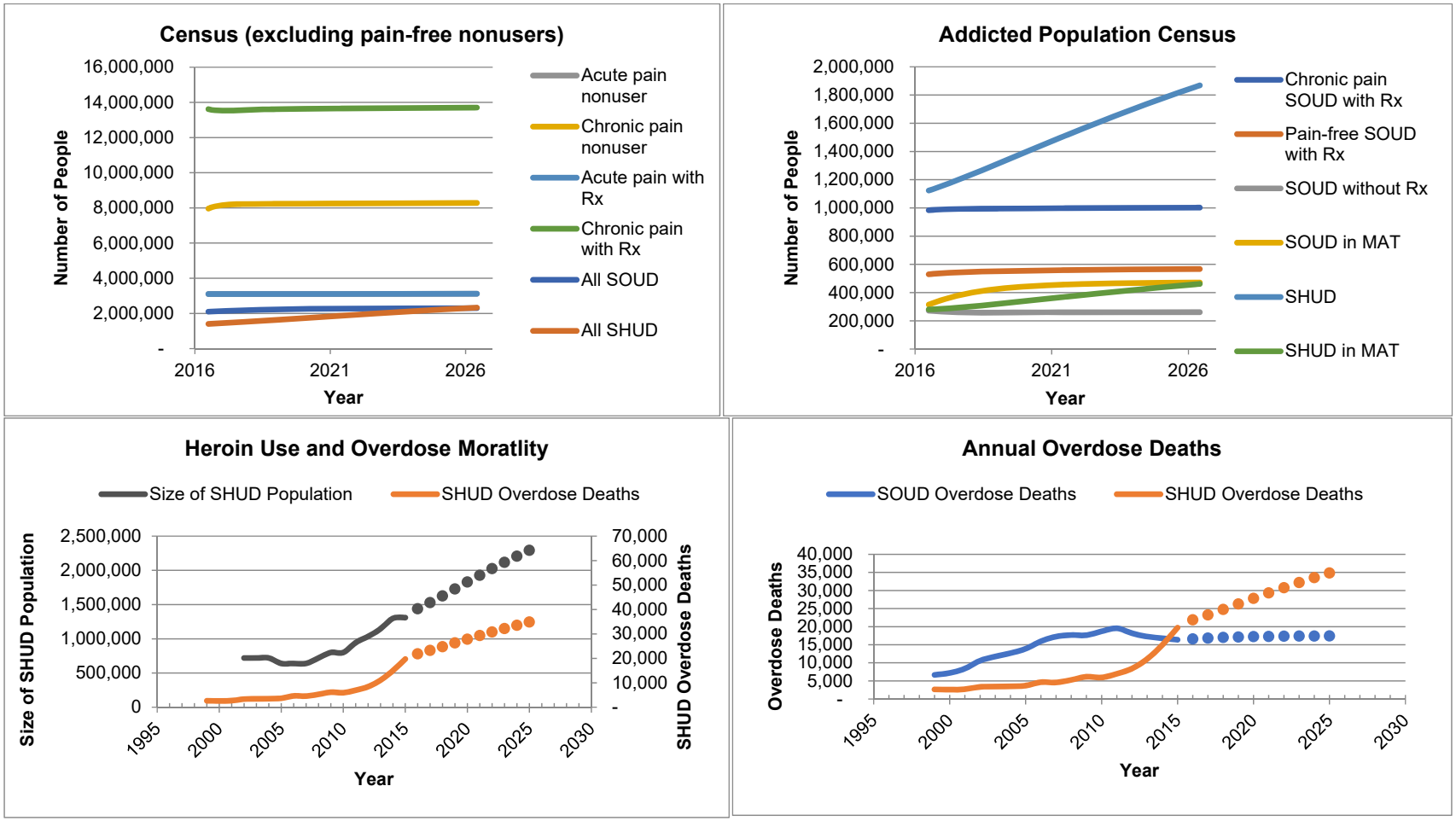
Appendix Figure 7. Status quo results for parameter set 7

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



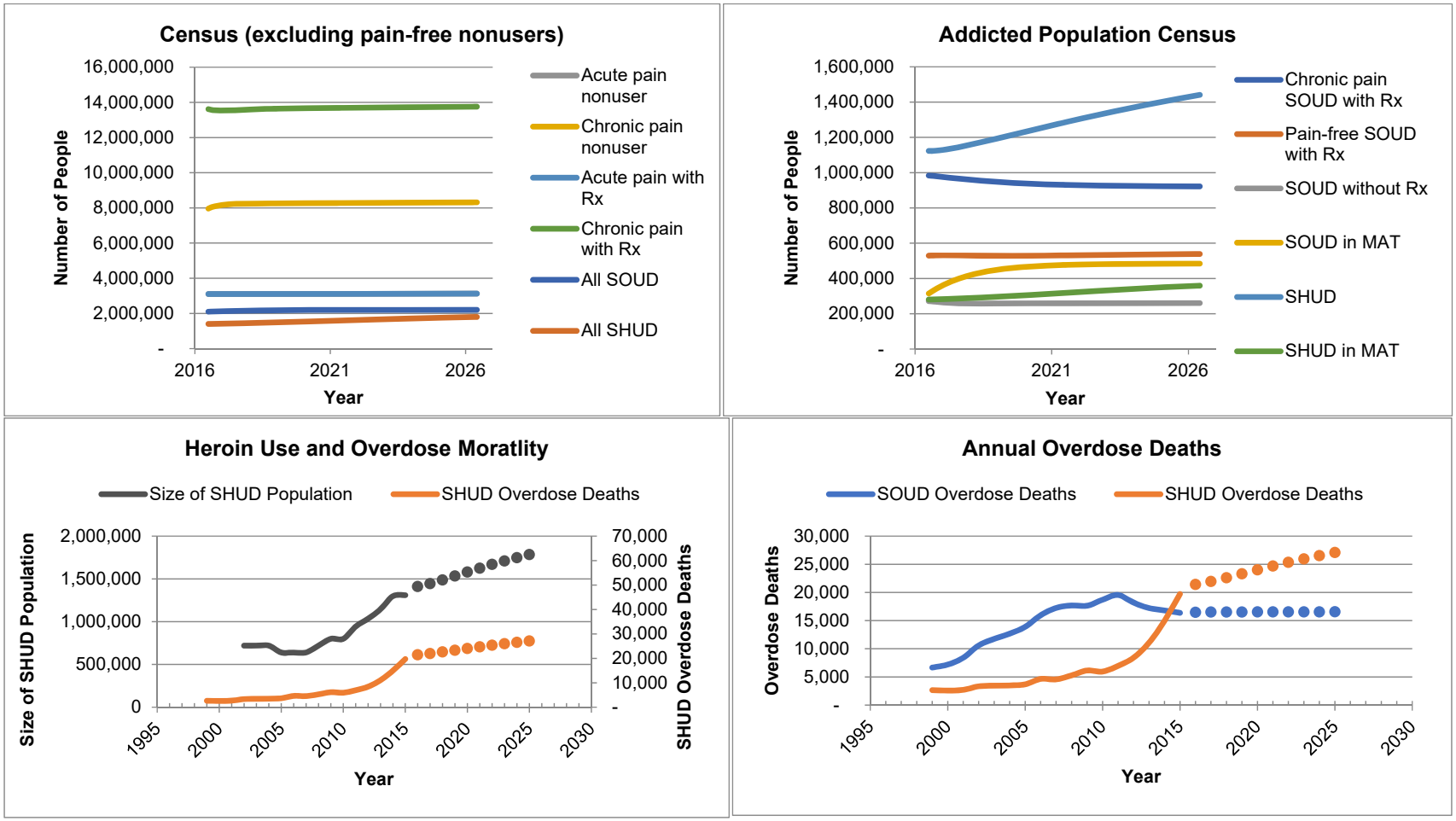
Appendix Figure 8. Status quo results for parameter set 8

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



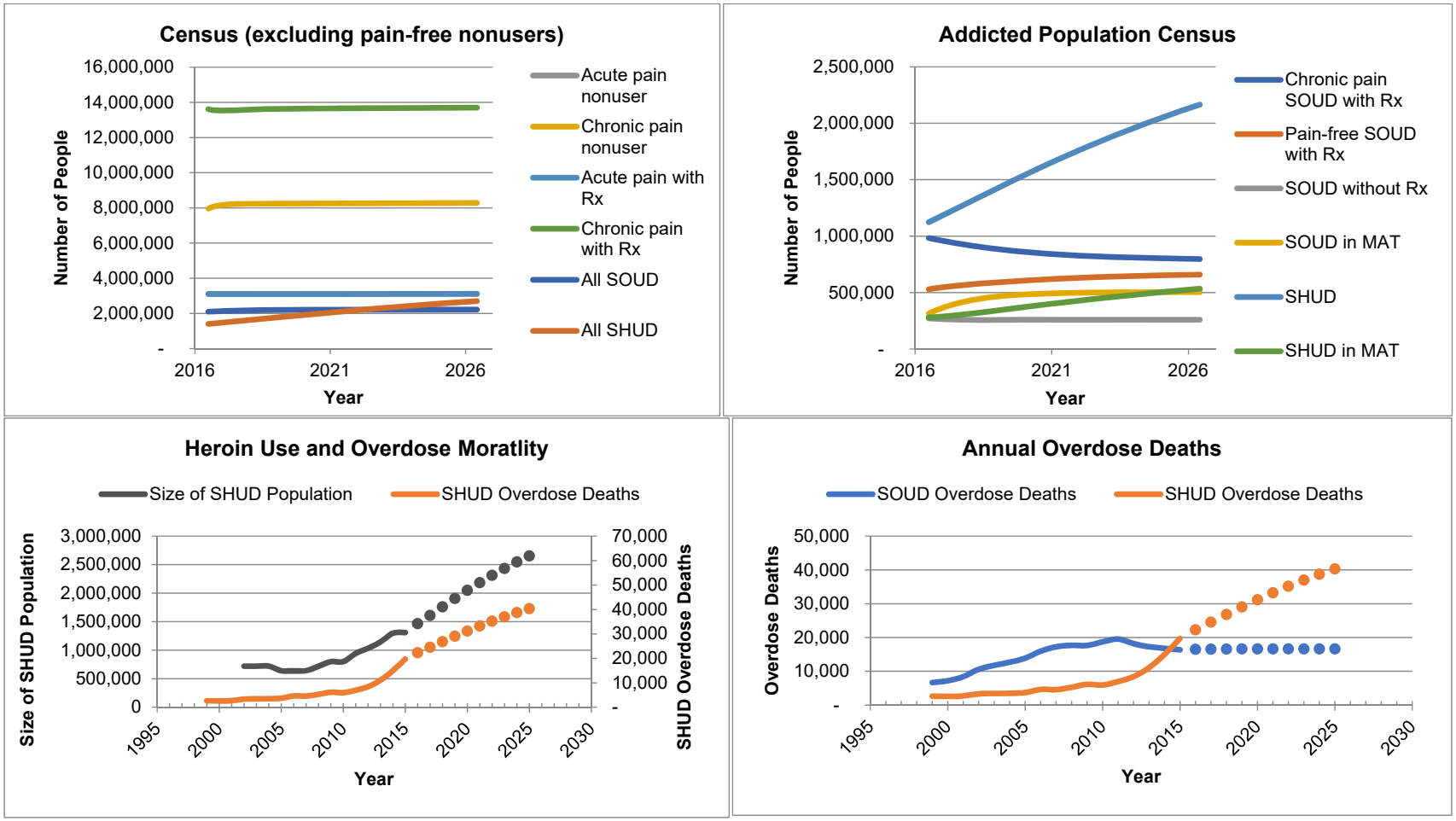
Appendix Figure 9. Status quo results for parameter set 9

Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.



Appendix Figure 10. Status quo results for parameter set 10

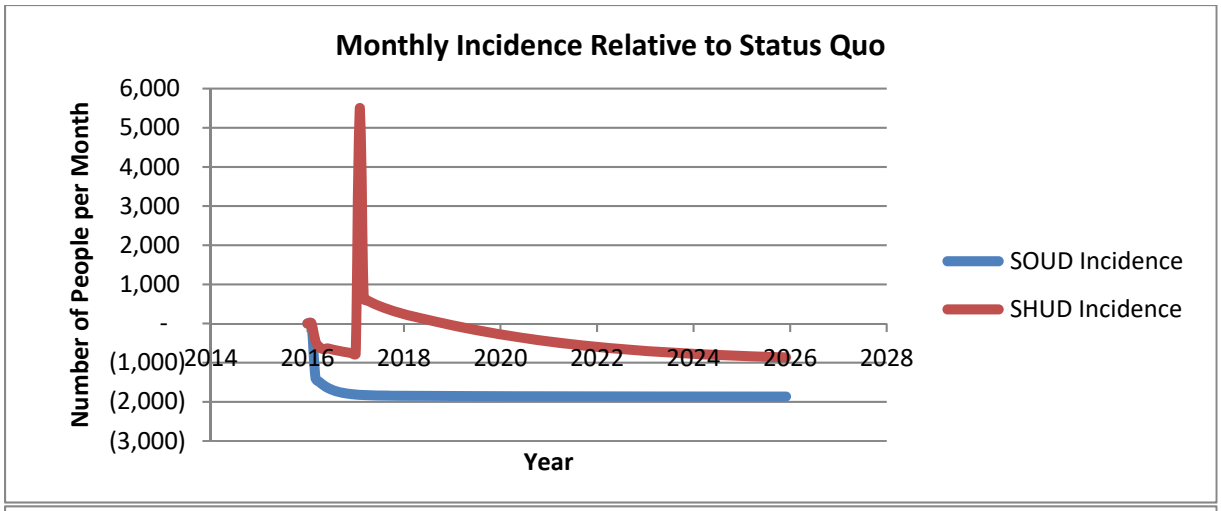
Top left: number of individuals in the “acute pain nonuser”, “chronic pain nonuser”, “acute pain with Rx”, “chronic pain with Rx”, any SOUD state (pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT), and any SHUD state (SHUD, SHUD in MAT) over ten years without any intervention. Top right: number of individuals in the pain-free SOUD with Rx, chronic pain SOUD with Rx, SOUD without Rx, SOUD in MAT, SHUD, and SHUD in MAT states over ten years without any intervention. Bottom left: number of individuals with SHUD and annual deaths from heroin overdose over the historical (solid) and modeled (dotted) periods. Bottom right: annual overdose deaths from SOUD and SHUD over the historical (solid) and modeled (dotted) periods. MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

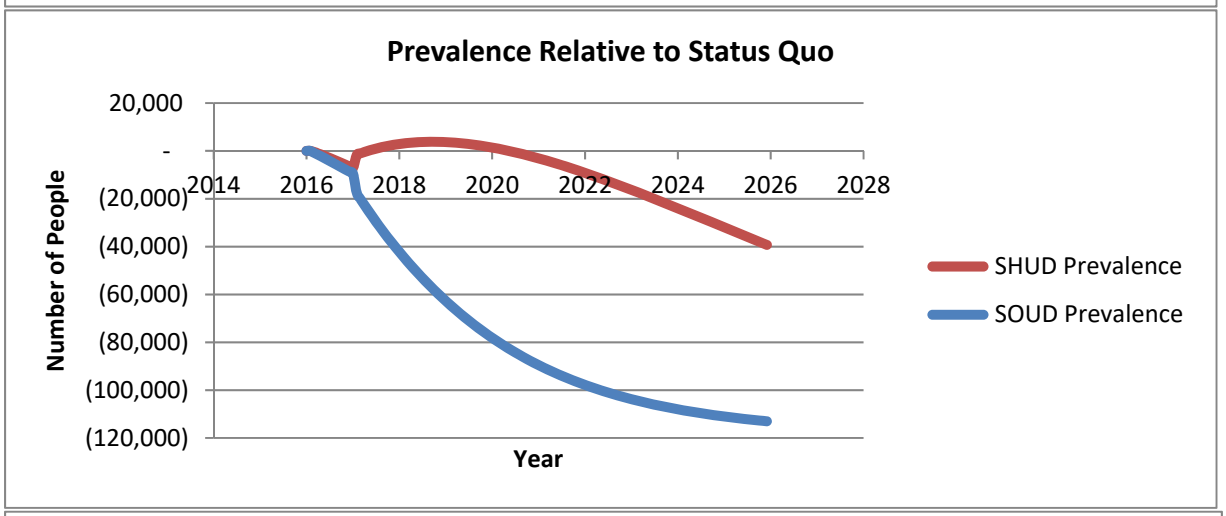


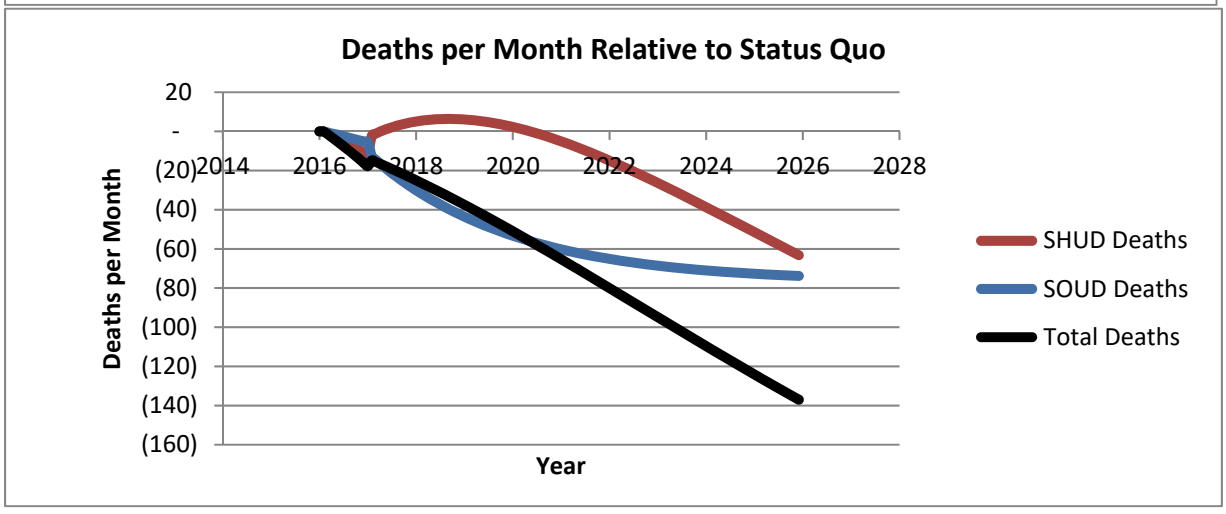
Appendix Figure 11. Effects of each intervention over time.

Mean effects of each policy on monthly incidence (top), prevalence (middle), and deaths (bottom), relative to without intervention, of/from severe [prescription] opioid use disorder (SOUD) and severe heroin use disorder (SHUD).

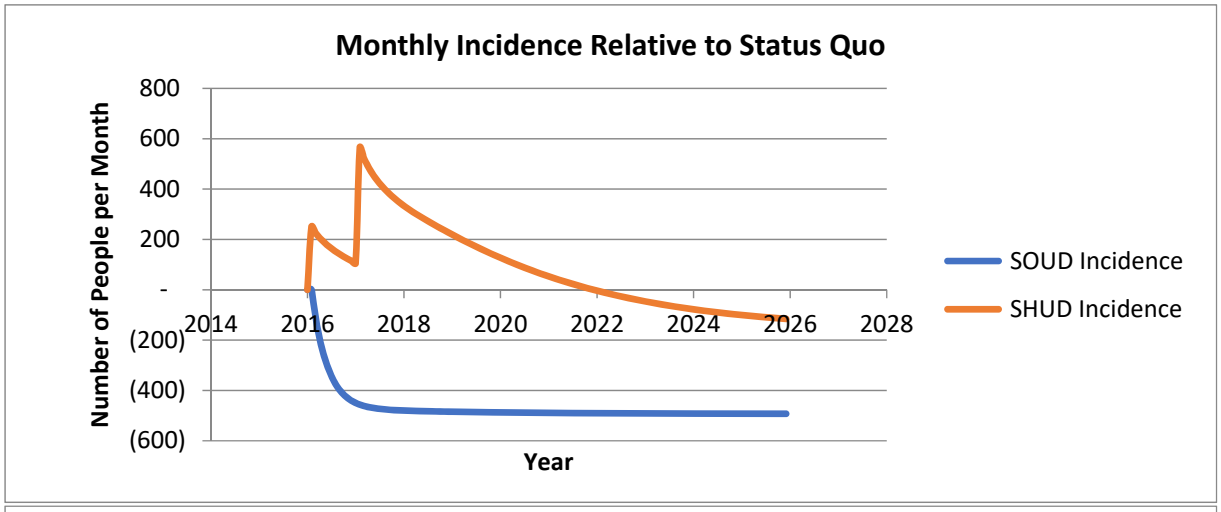
a) Reduced prescribing for acute pain

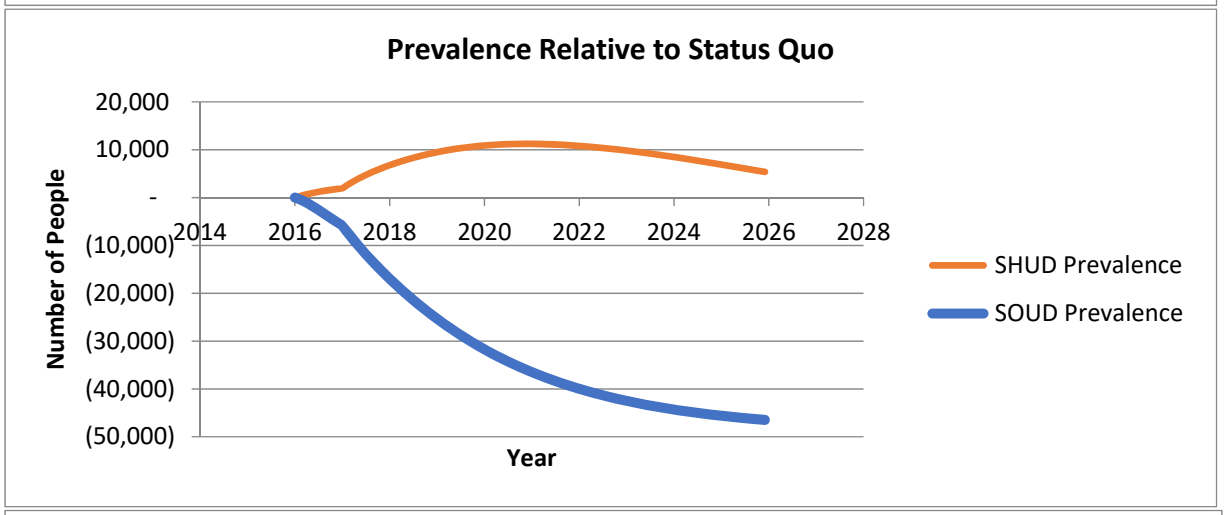


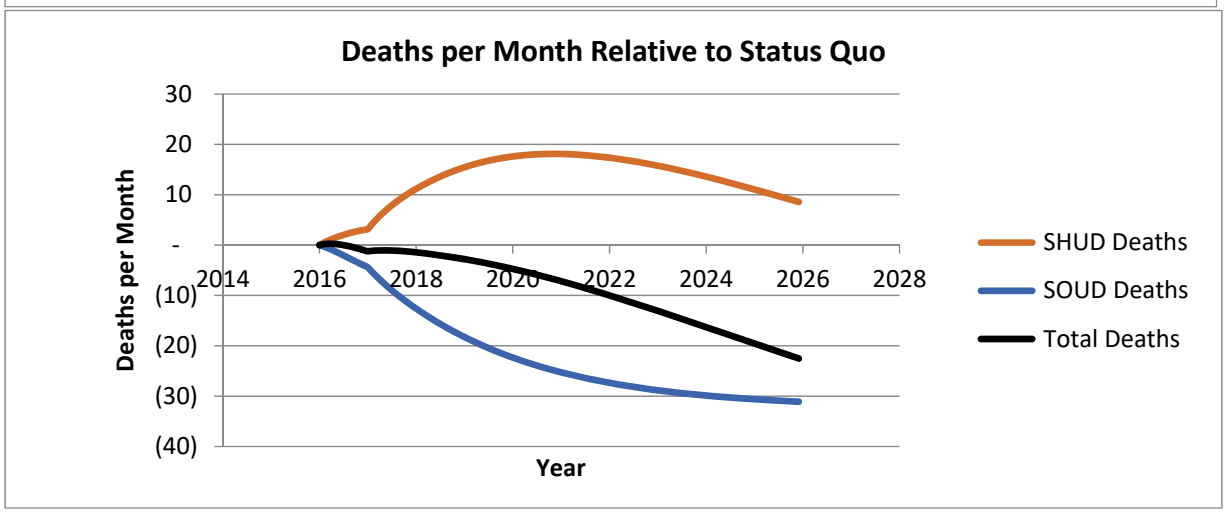




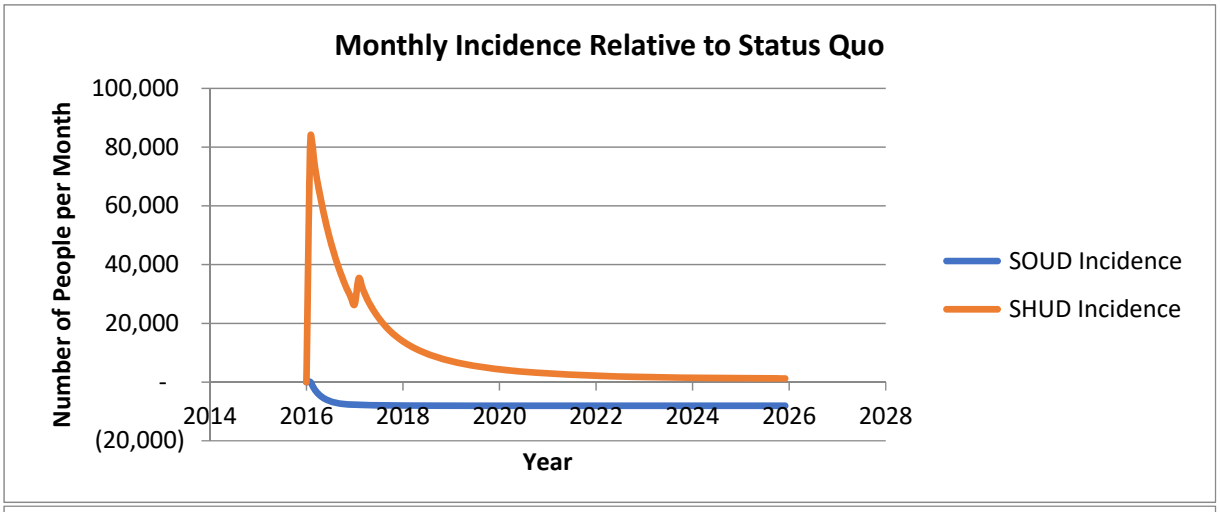
b) Reduced prescribing for transitioning pain

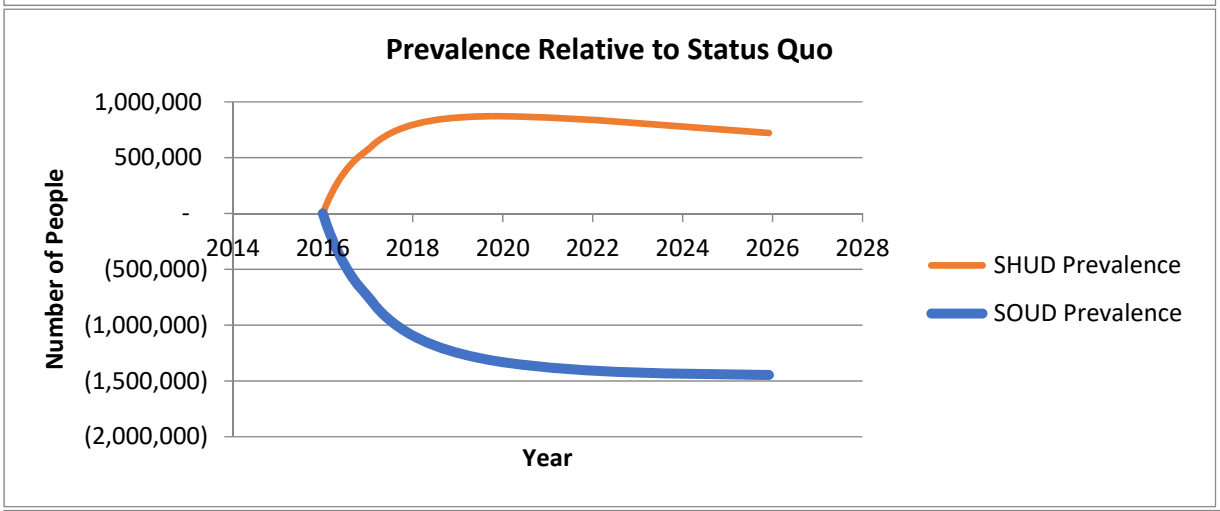


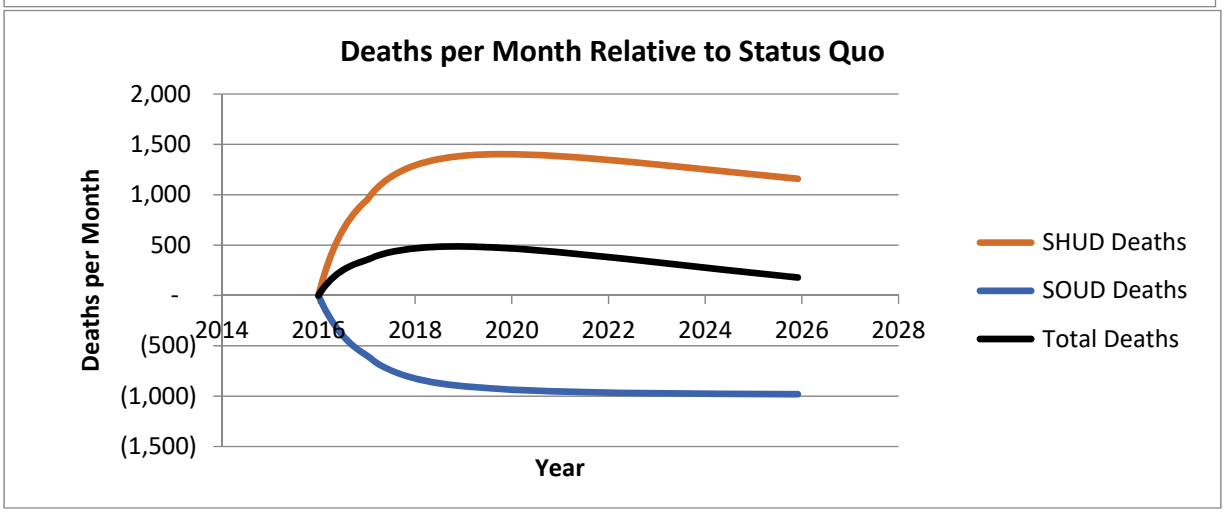




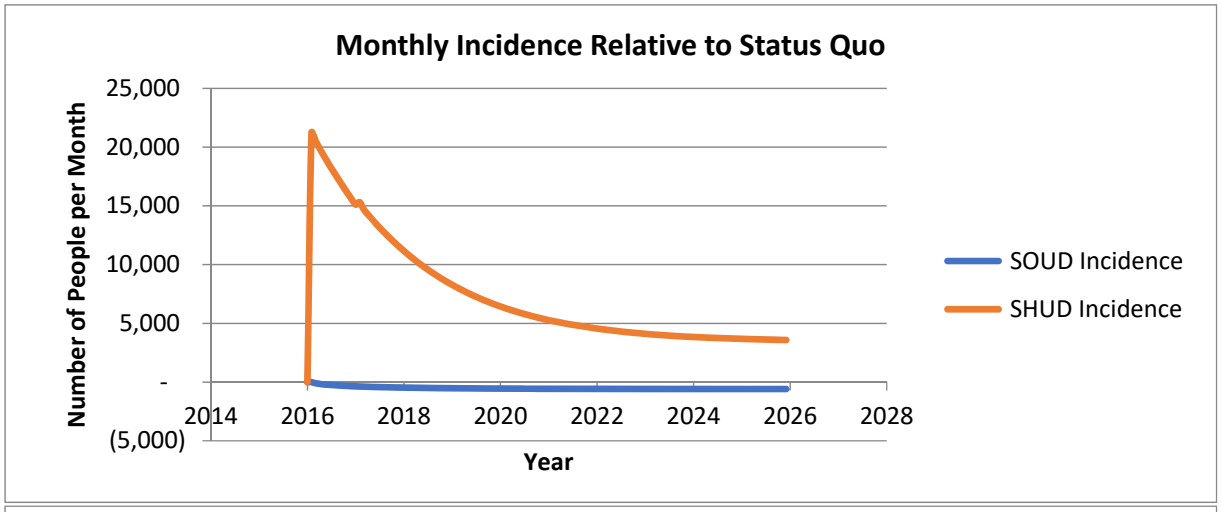
c) Drug rescheduling

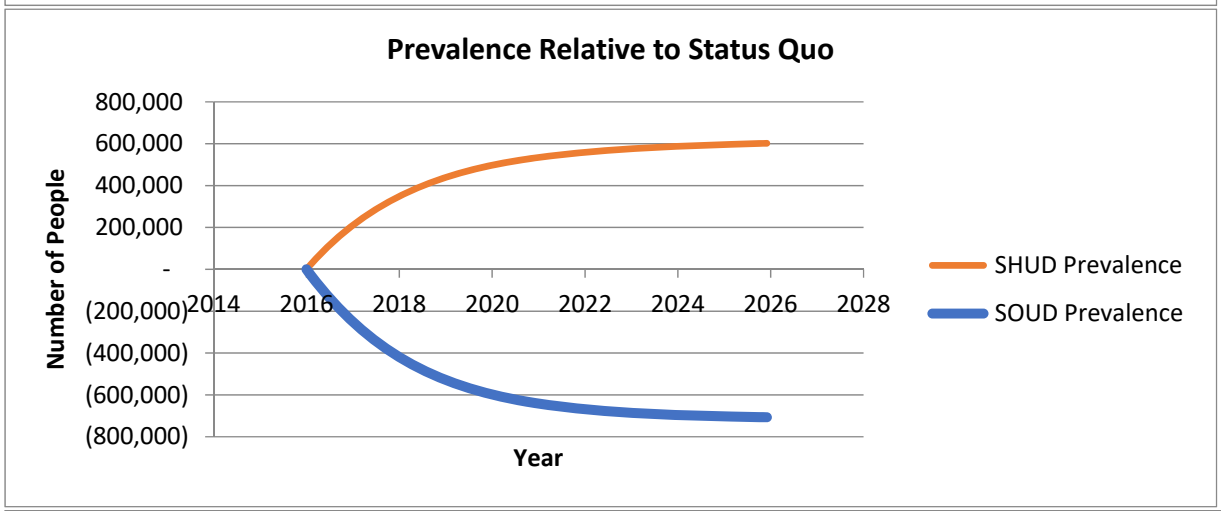


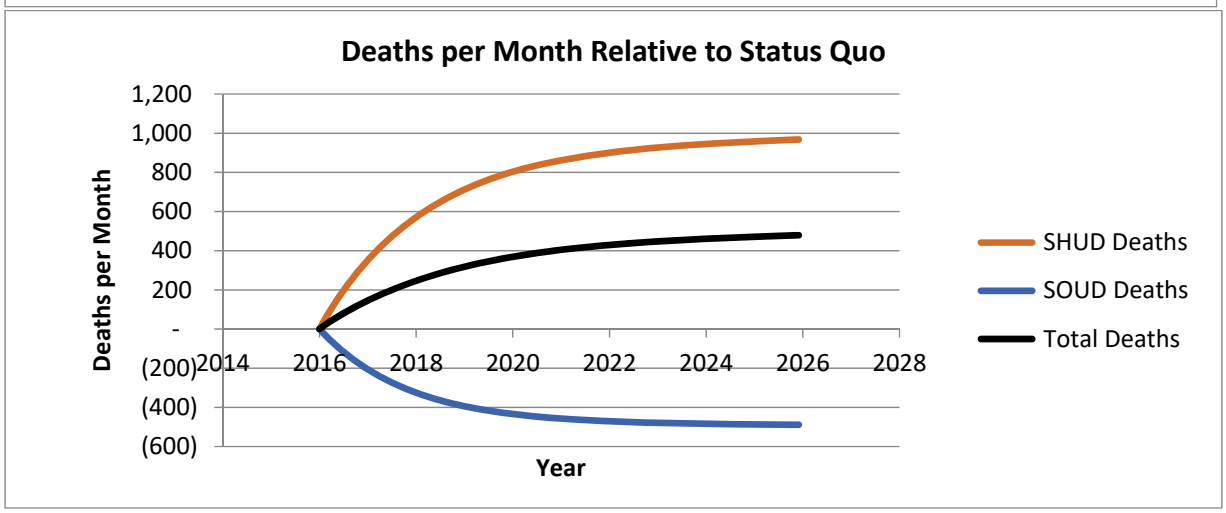




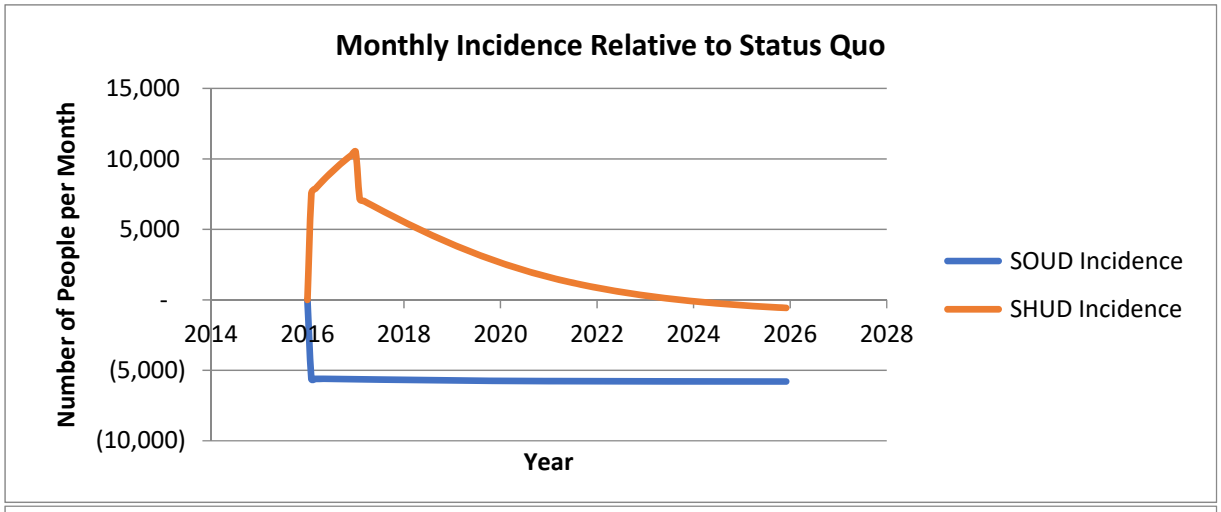
d) Prescription Monitoring Program

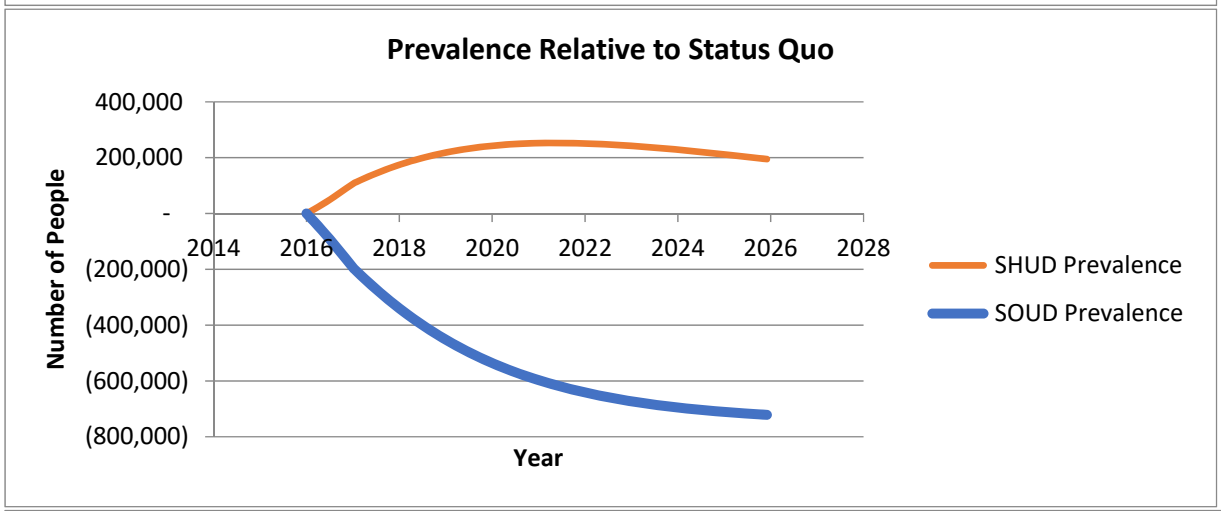


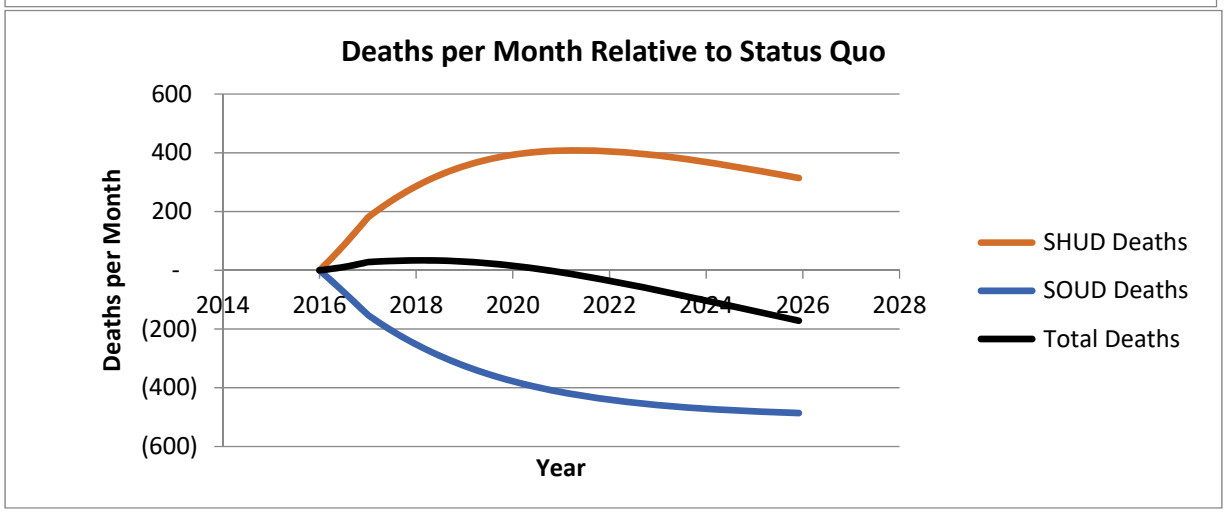




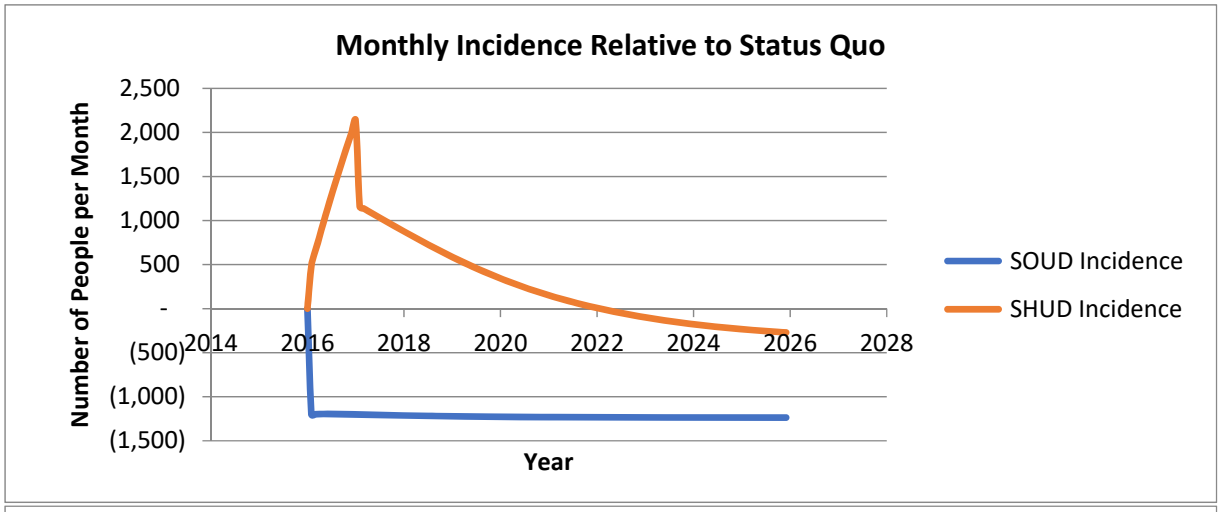
e) Drug reformulation policy

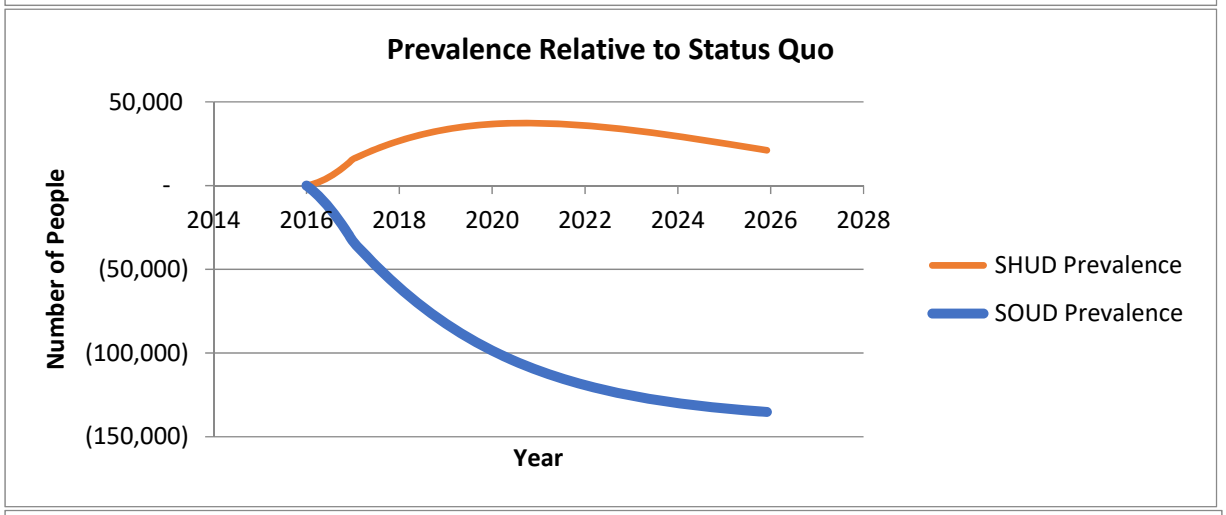


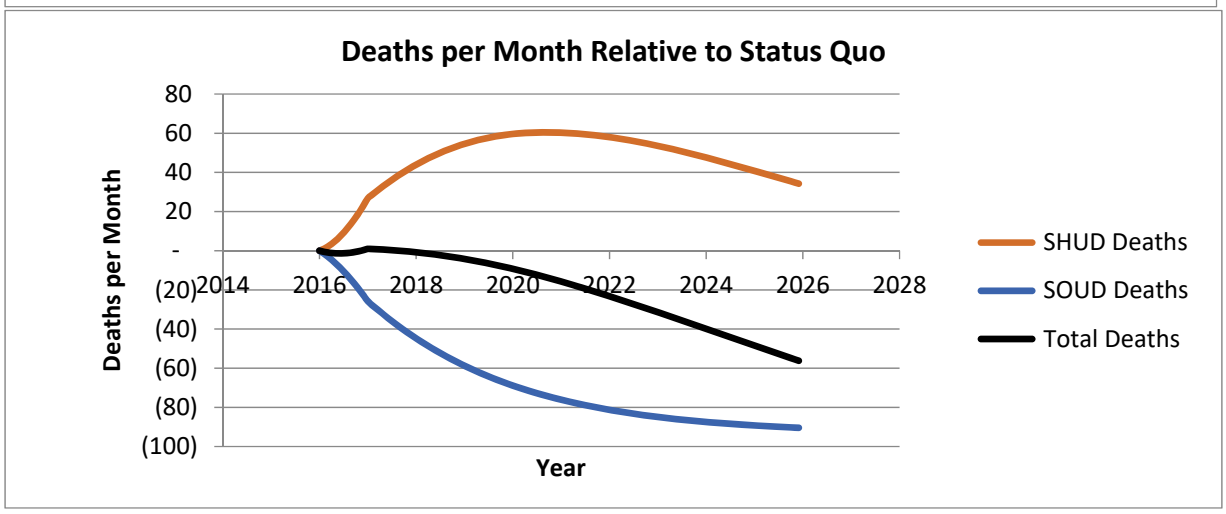




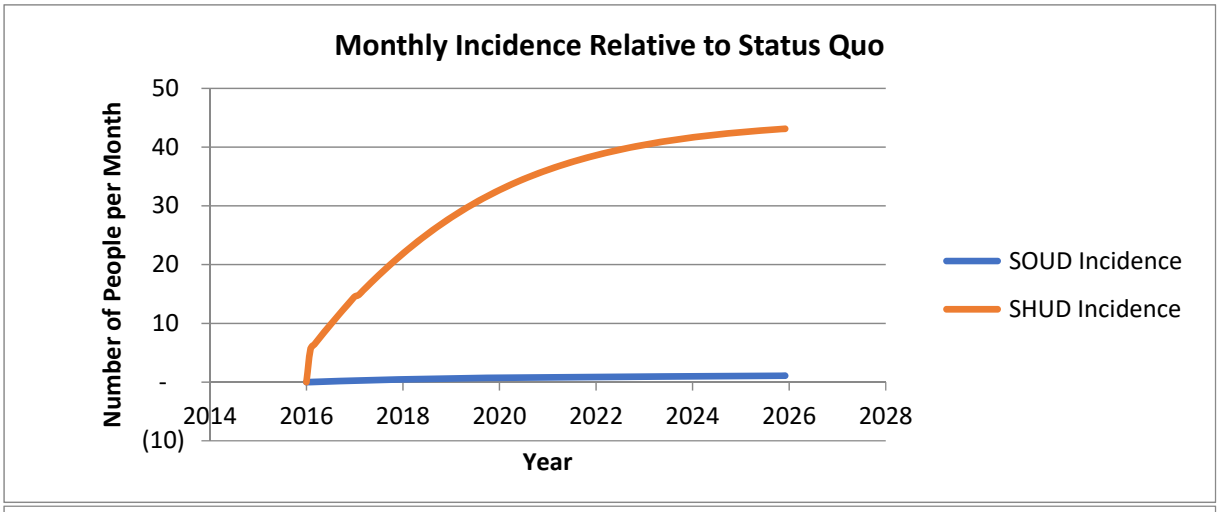
f) Excess opioid disposal

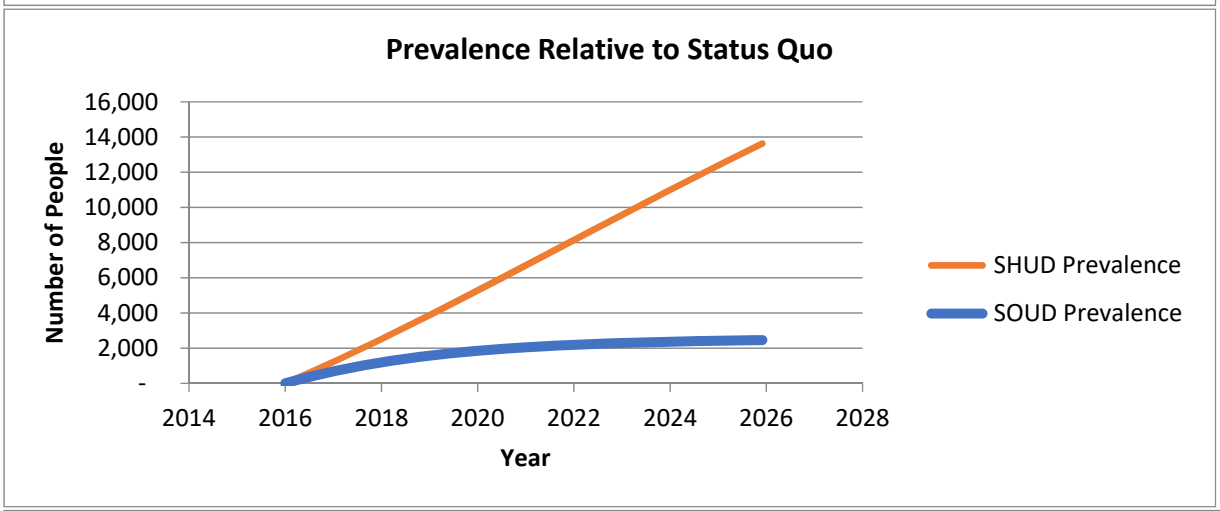


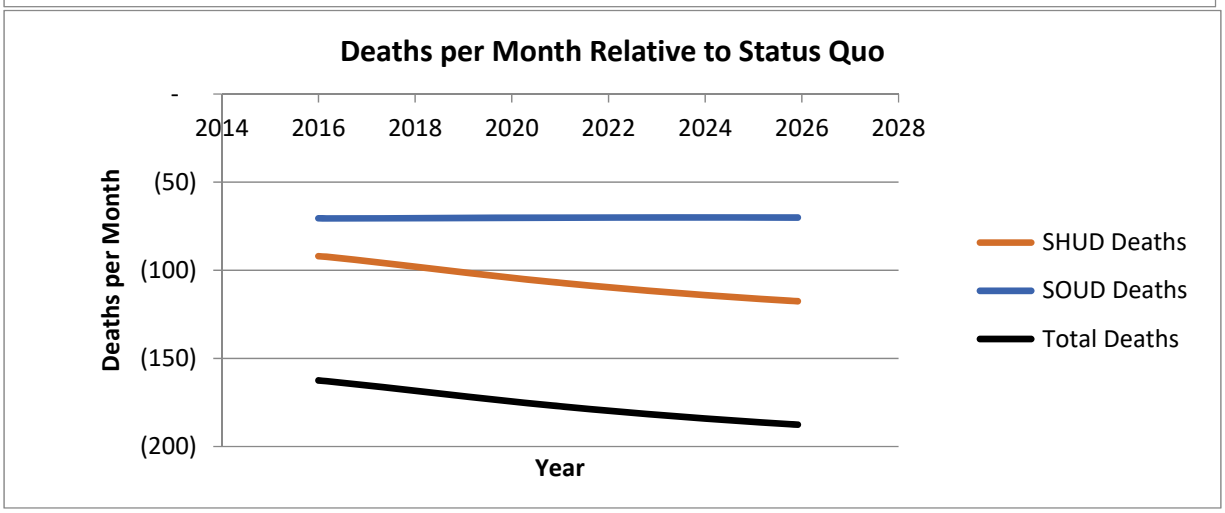




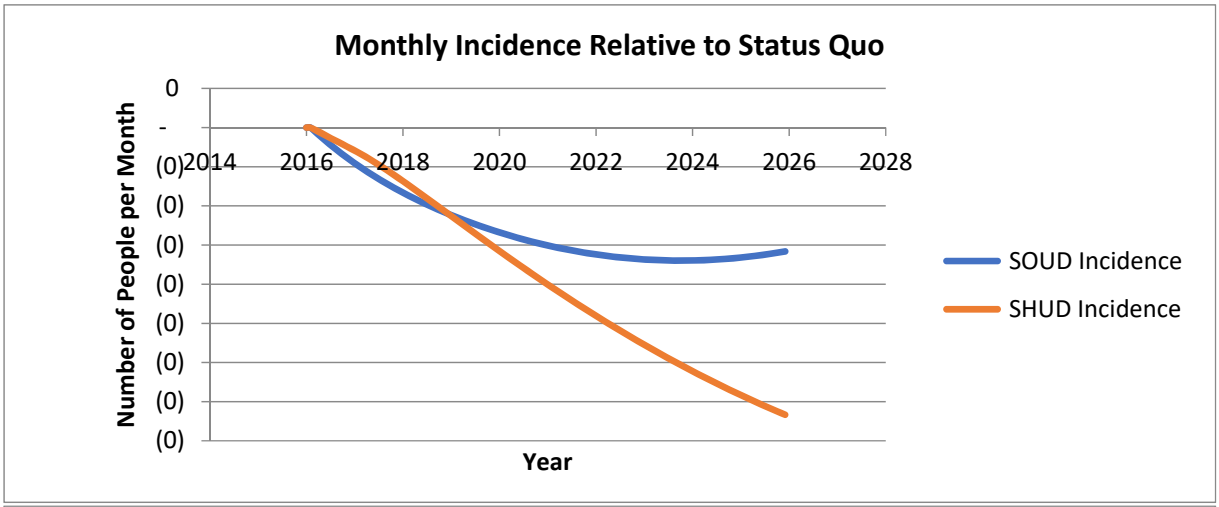
g) Increased naloxone availability

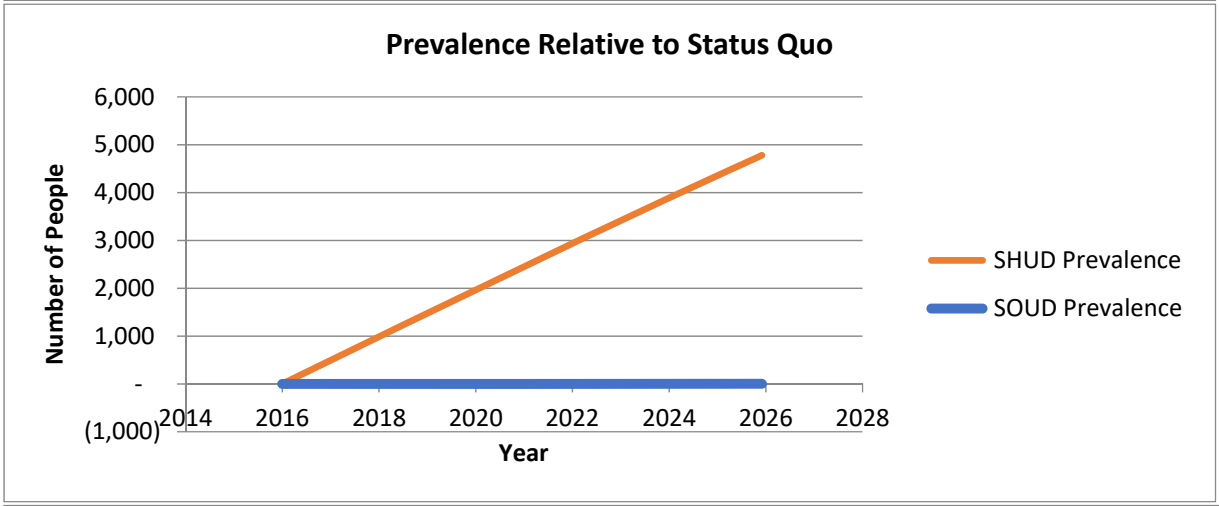


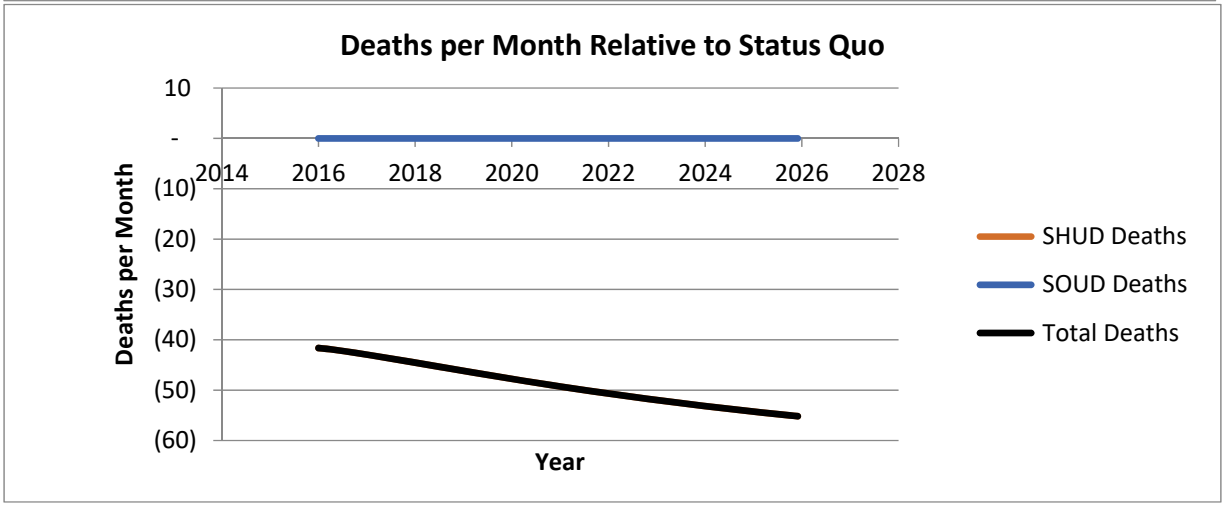




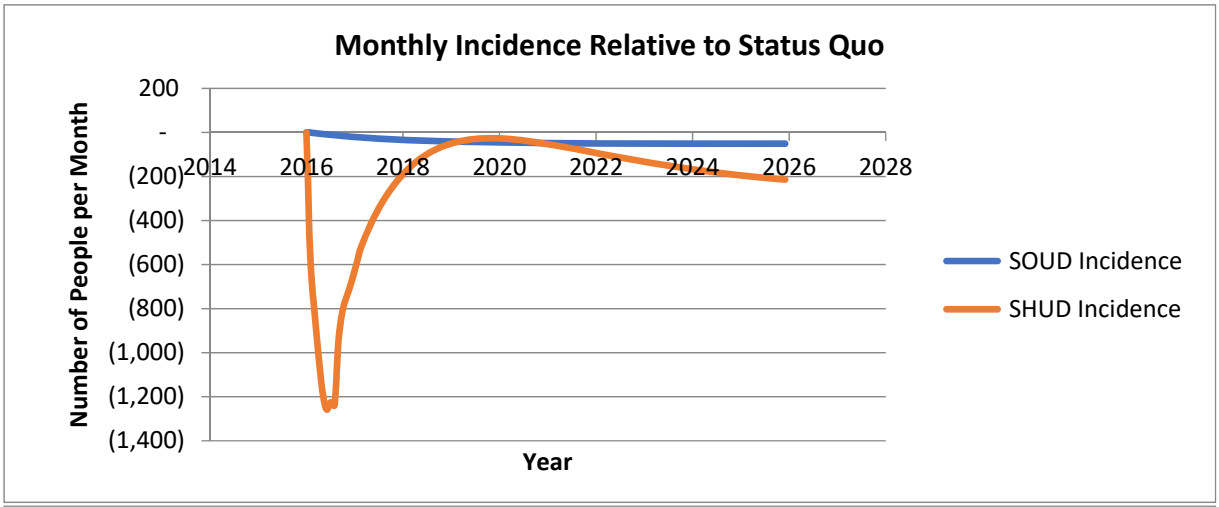
h) Needle exchange

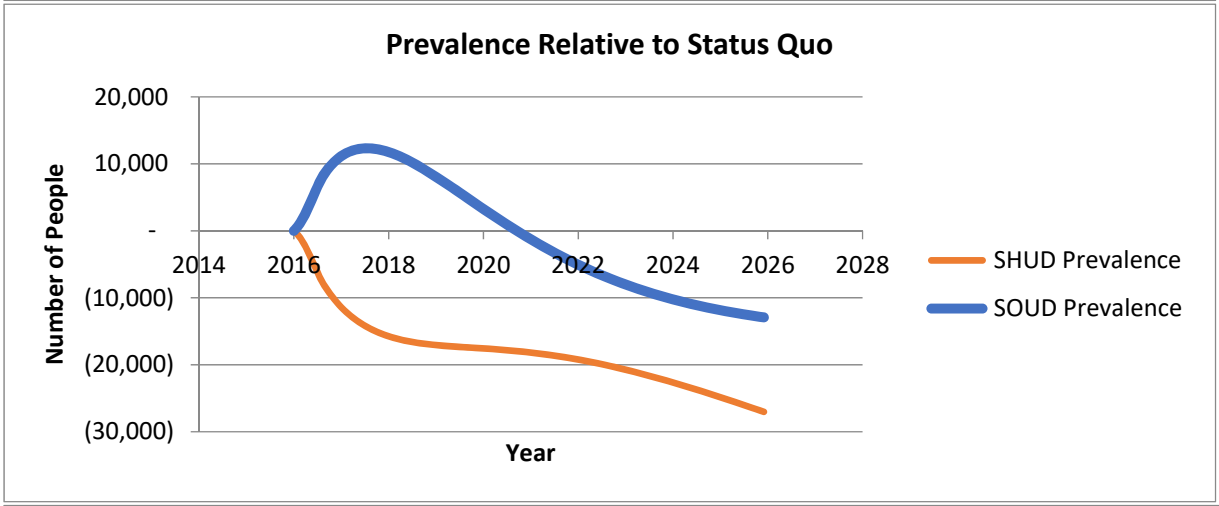


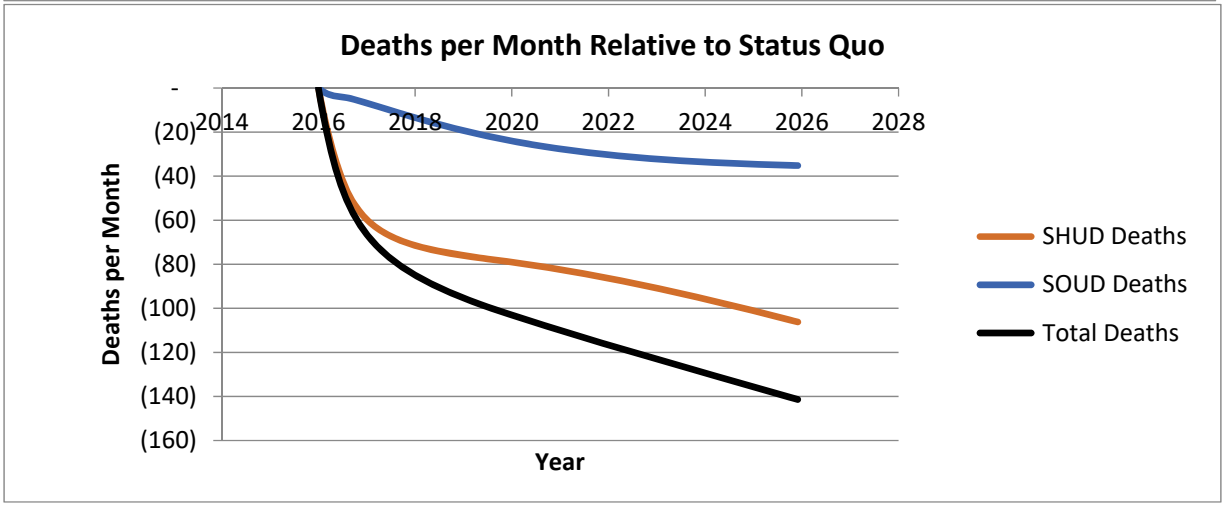




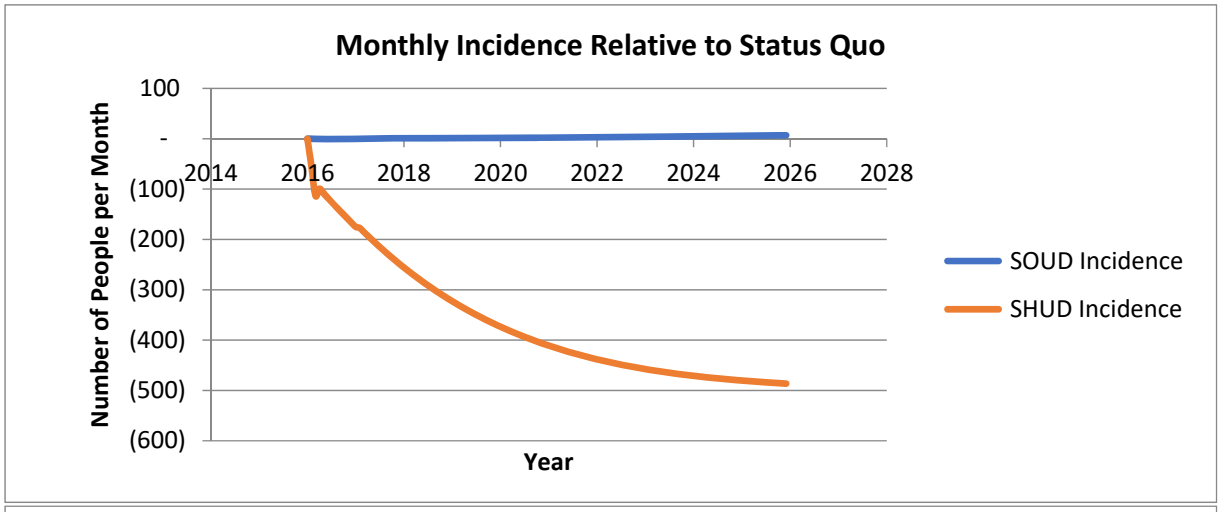
i) Increased Medication-Assisted Therapy access

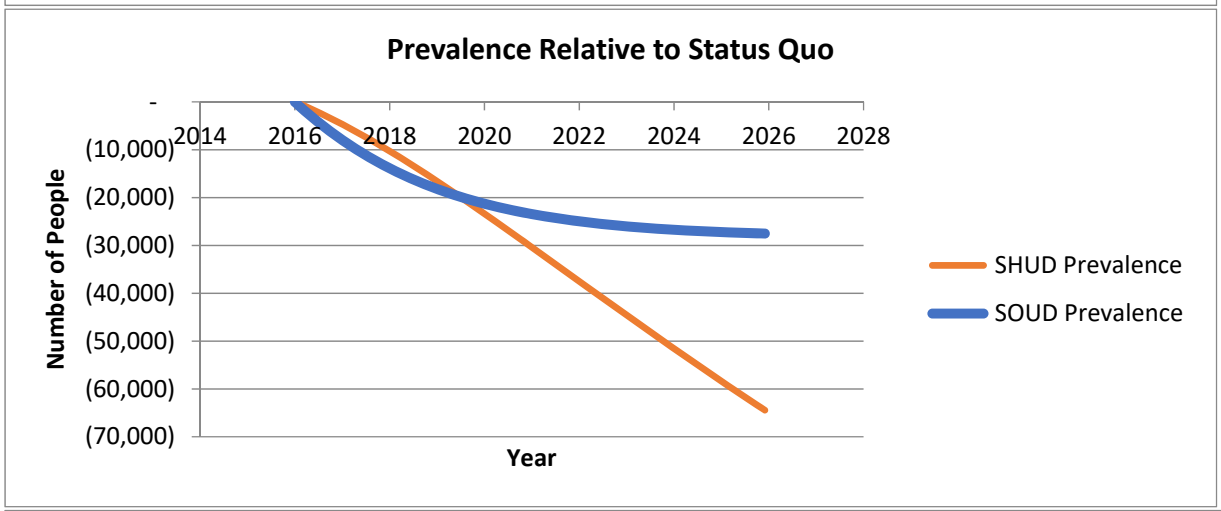


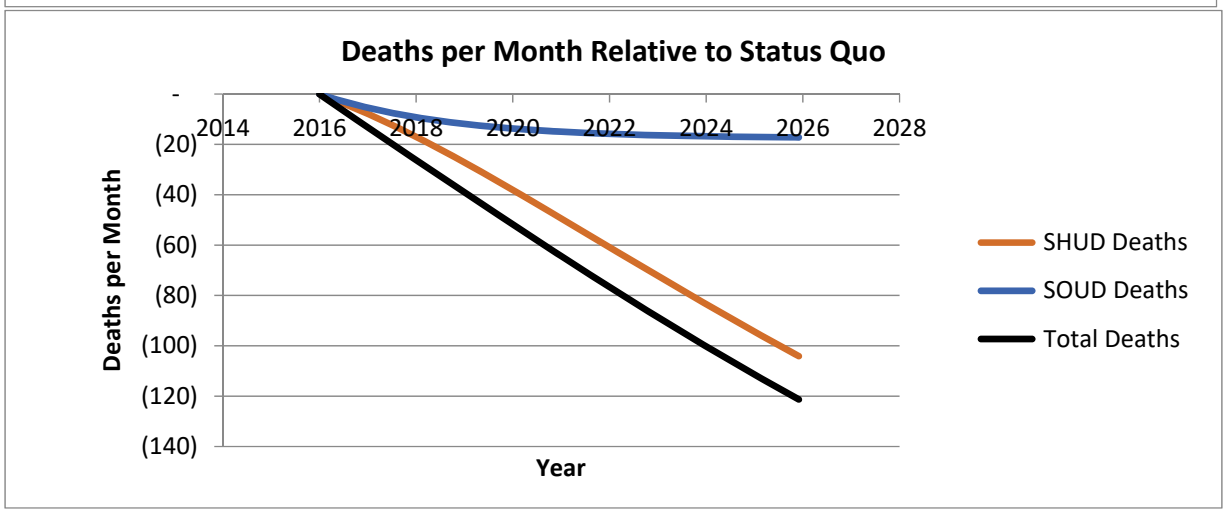




j) Increased access to psychosocial treatment



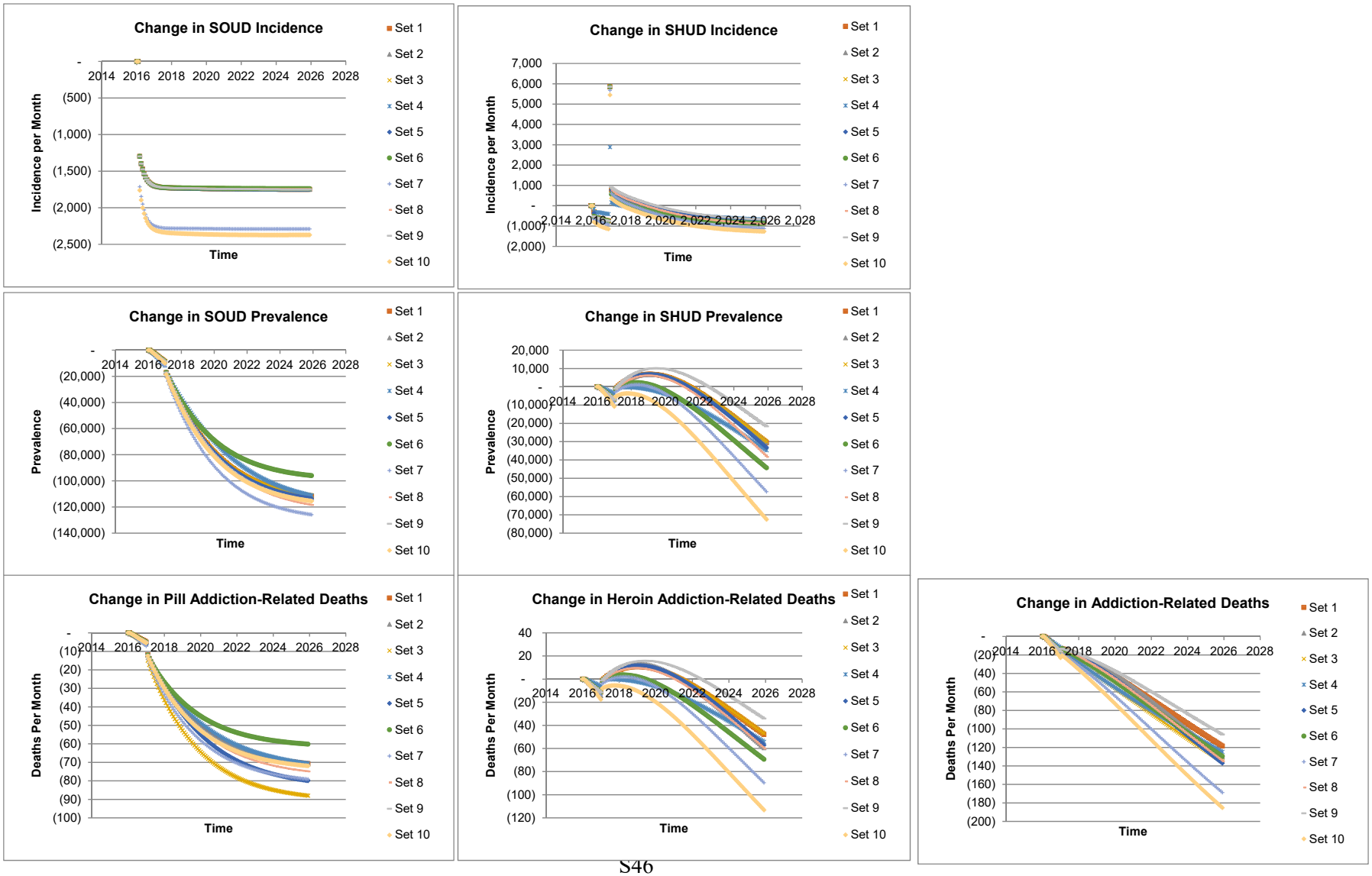




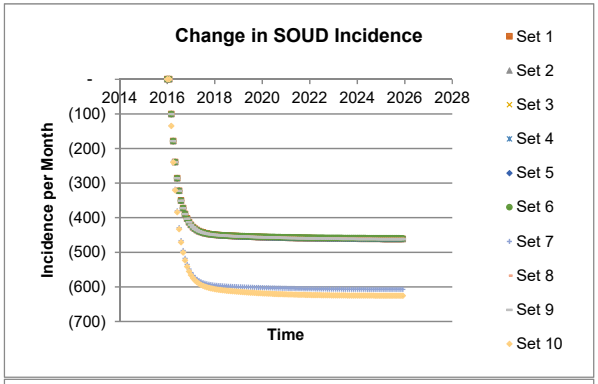
Appendix Figure 12. Distribution of effects over time for each intervention

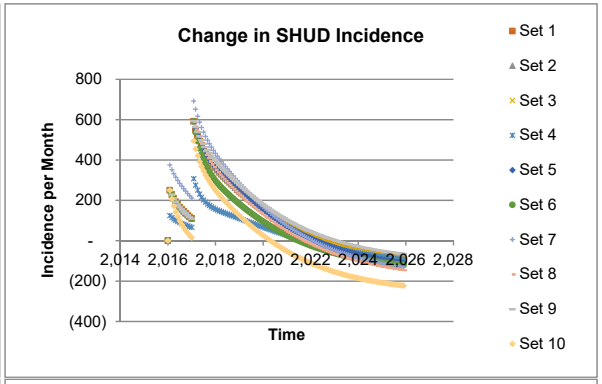
Top row: effects of the given policy on monthly incidence of SOUD (left) and SHUD (center), relative to without intervention, for each base case parameter set. Middle row: effects of the given policy on prevalence of SOUD (left) and SHUD (center), relative to without intervention, for each base case parameter set. Bottom row: effects of the given policy on monthly prescription opioid-related deaths (left), heroin-related deaths (center), and total opioid addiction-related deaths (right) relative to without intervention, for each base case parameter set. SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

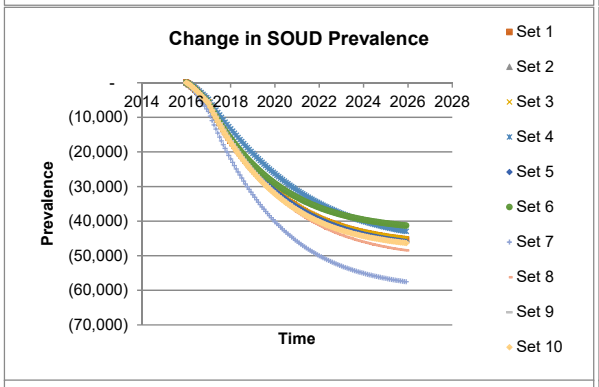
a) Reduced prescribing for acute pain

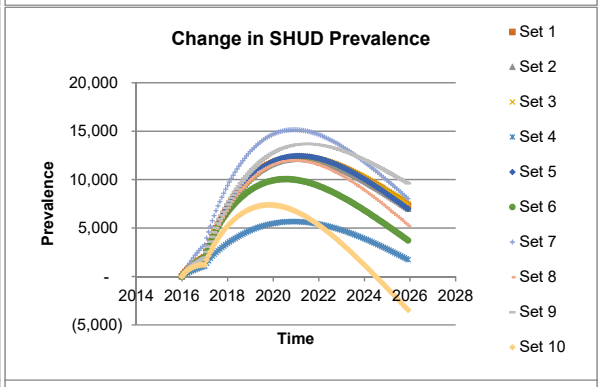


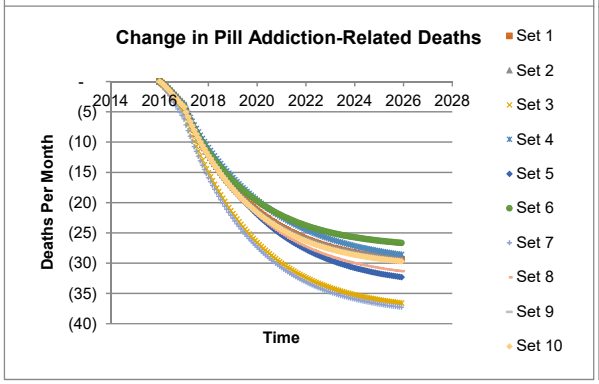
b) Reduced prescribing for transitioning pain

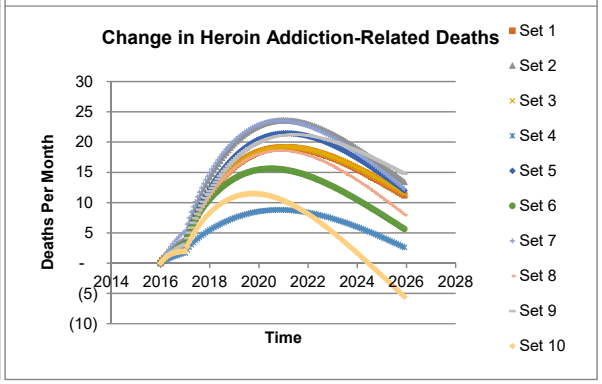


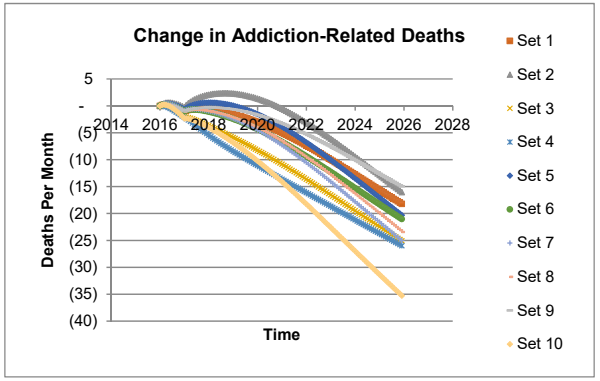




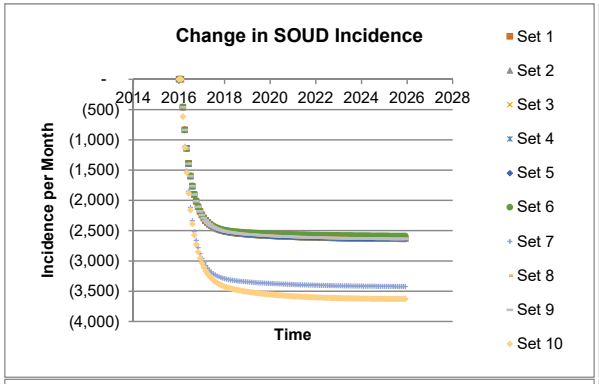


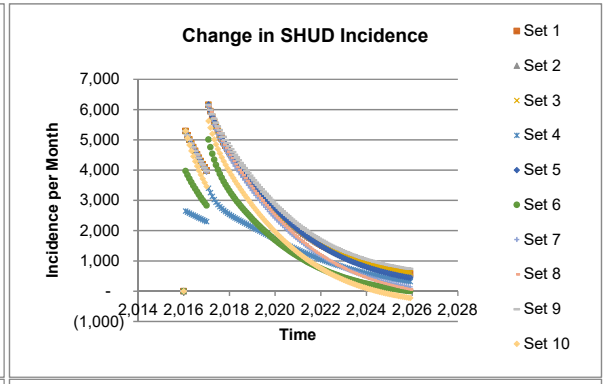


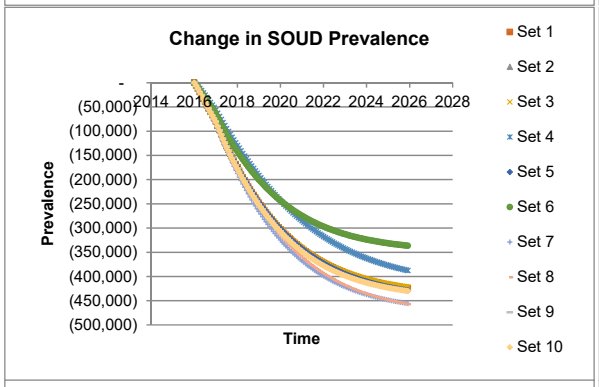


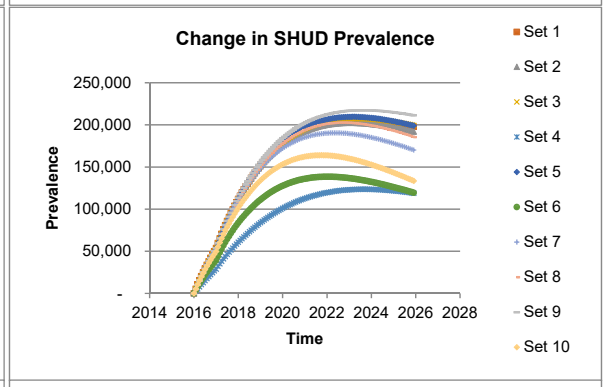


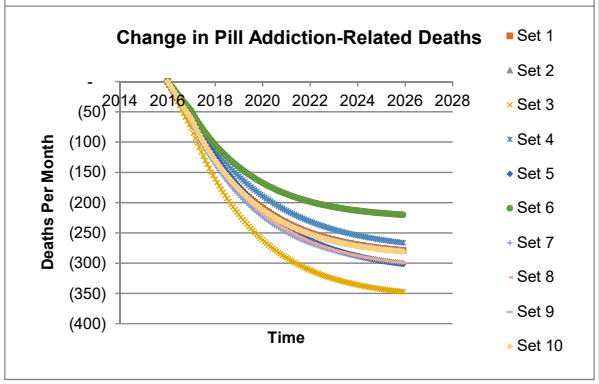
d) Reduced prescribing for chronic pain

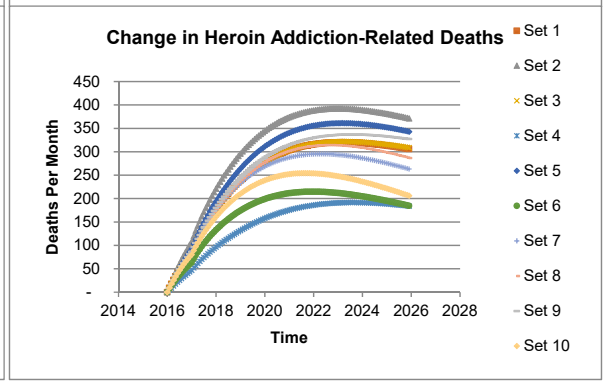


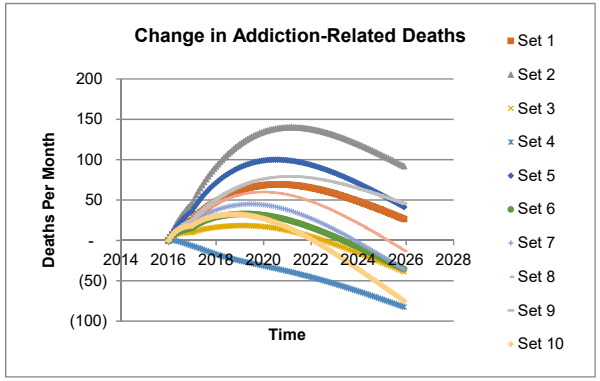




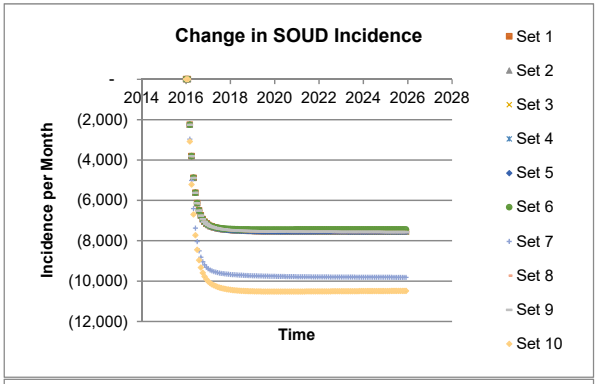


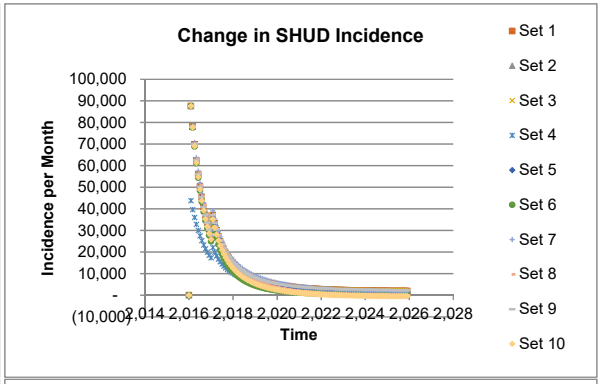


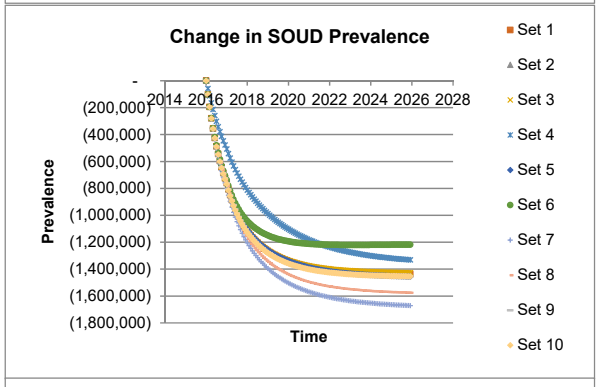


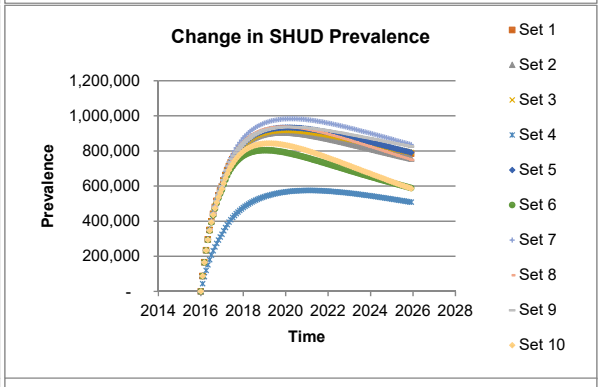


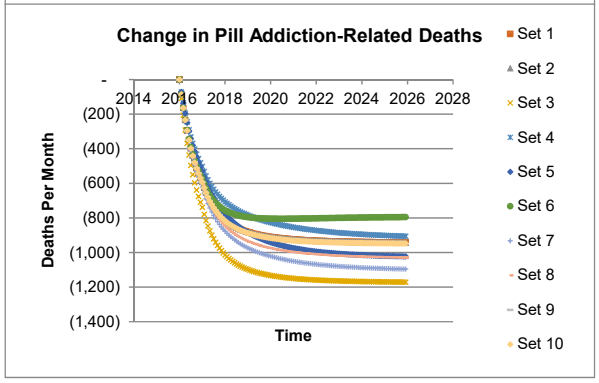
d) Drug rescheduling

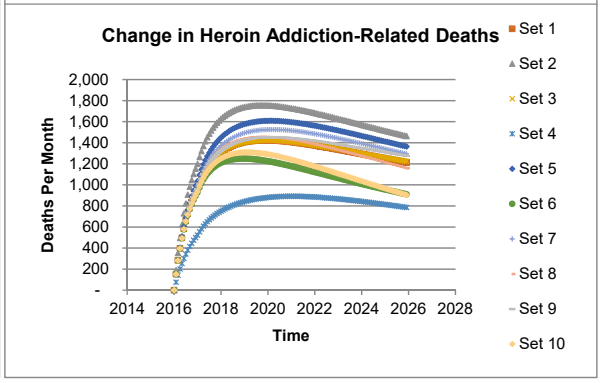


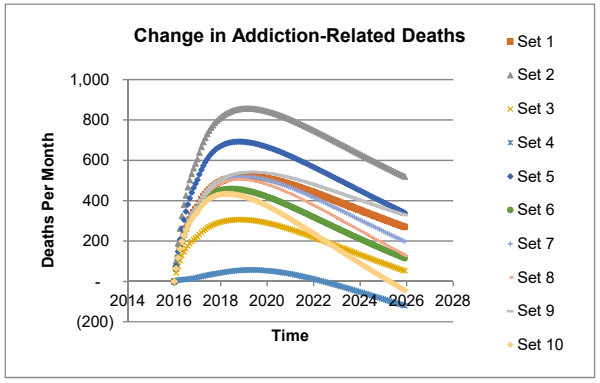




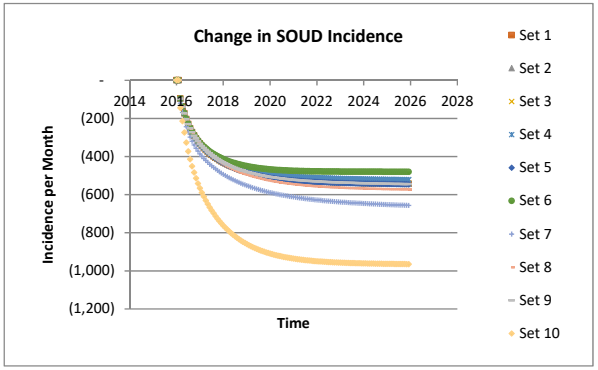


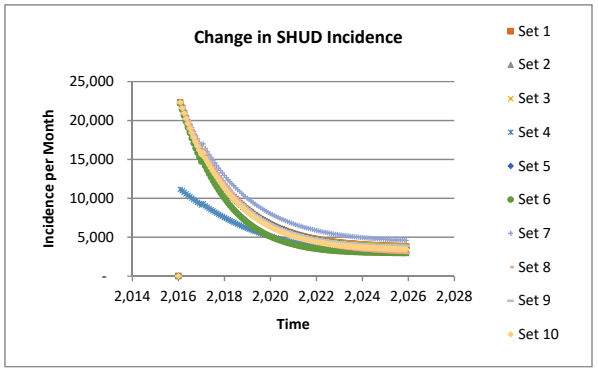


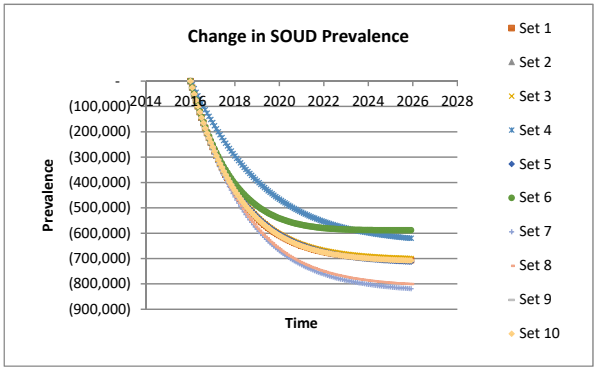


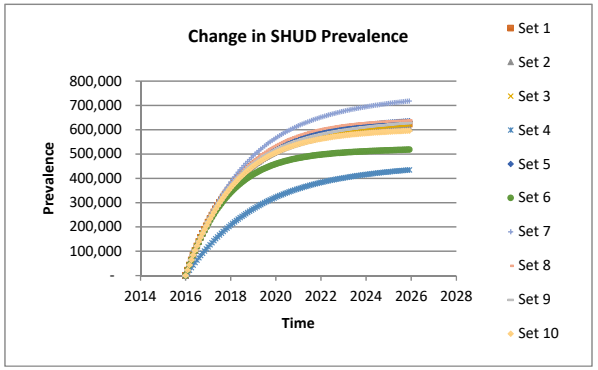


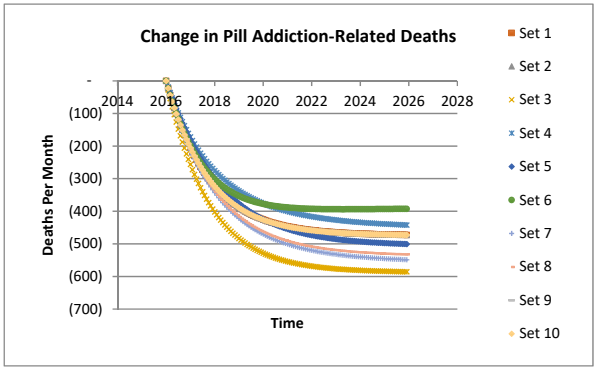
e) Prescription Monitoring Program

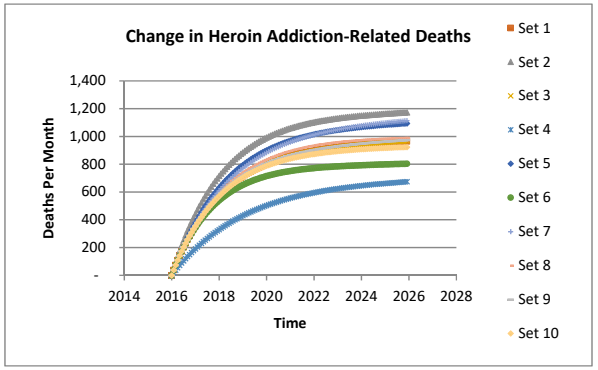


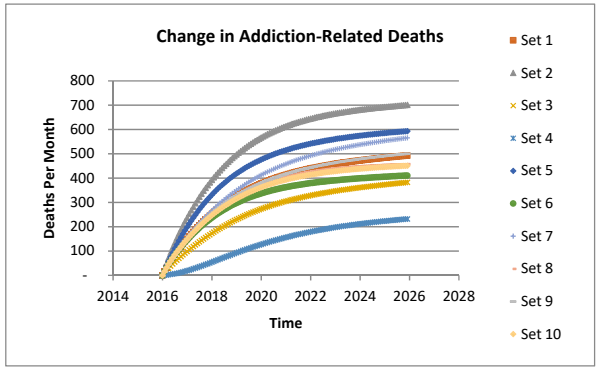




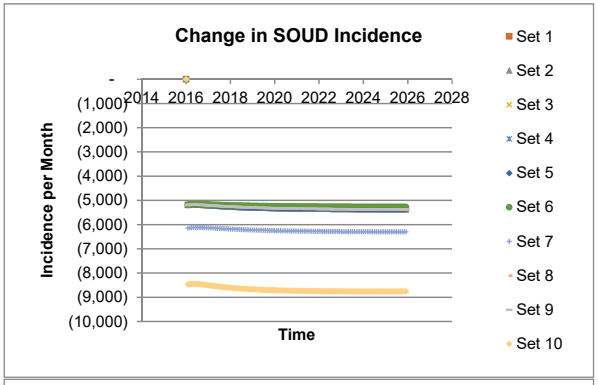


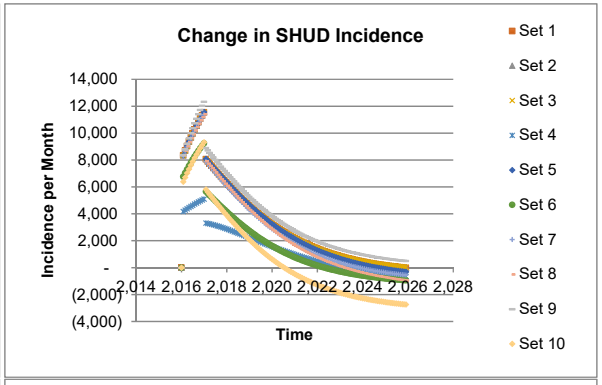


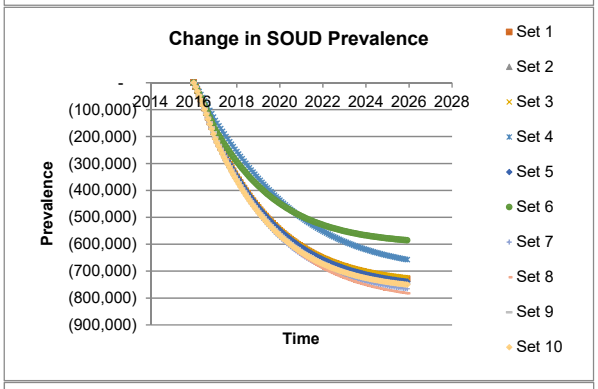


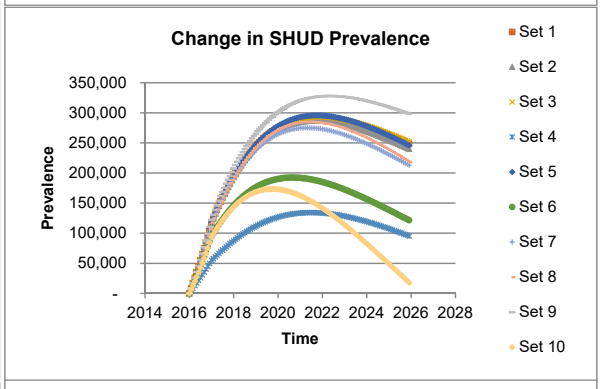


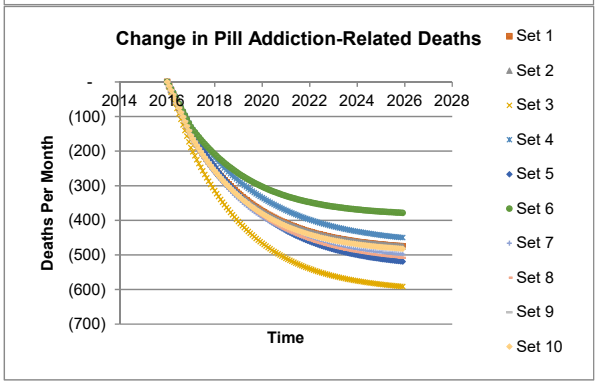
f) Drug reformulation

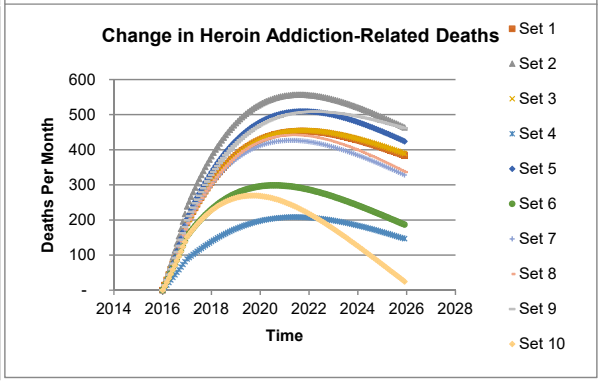


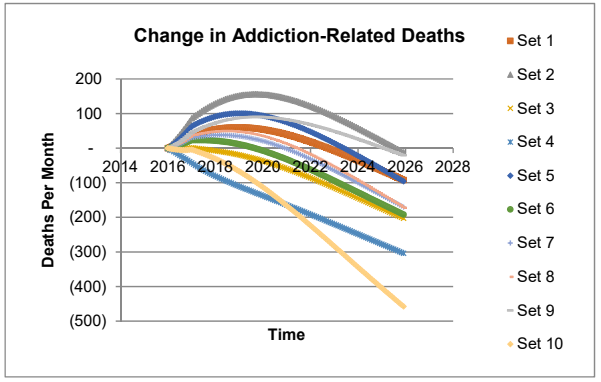




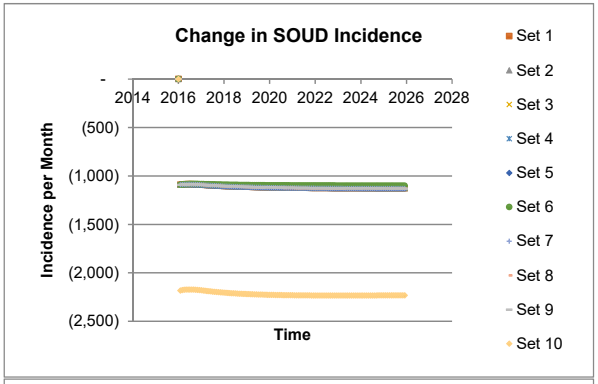


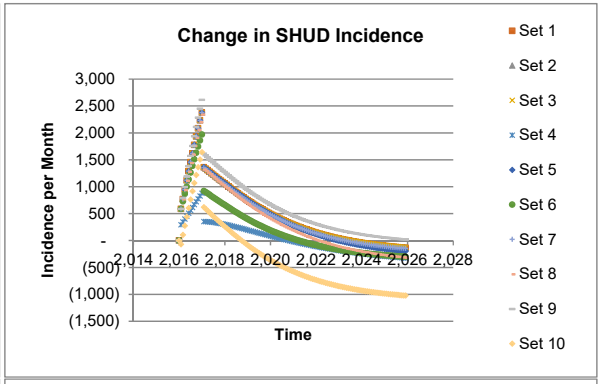


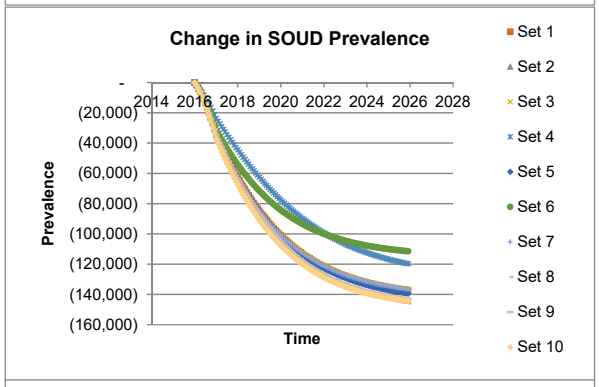


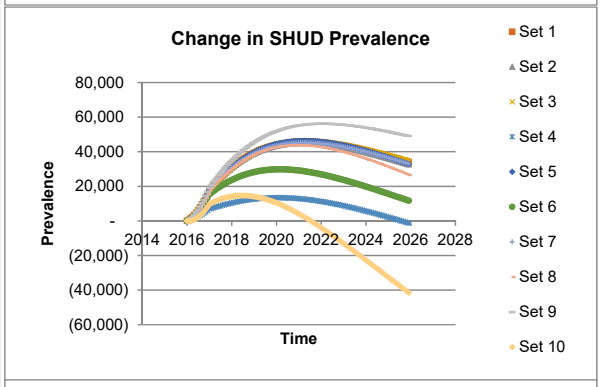


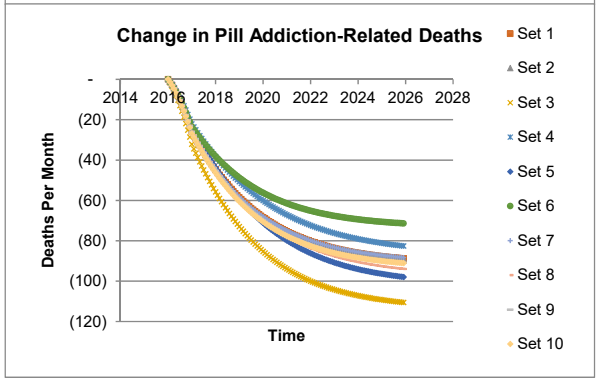
g) Excess opioid disposal

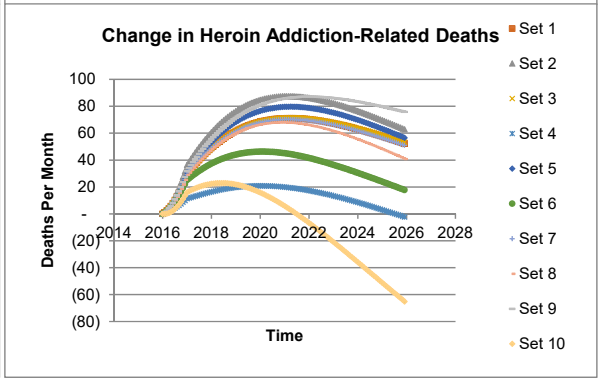


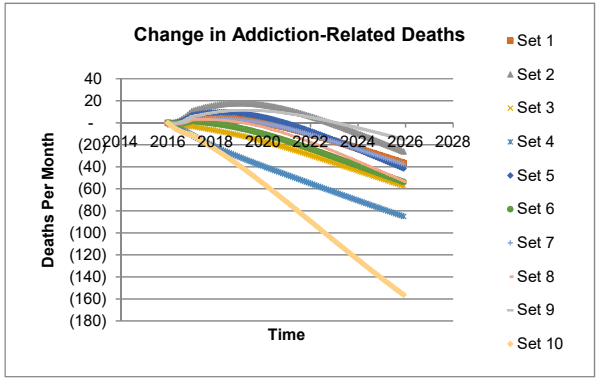




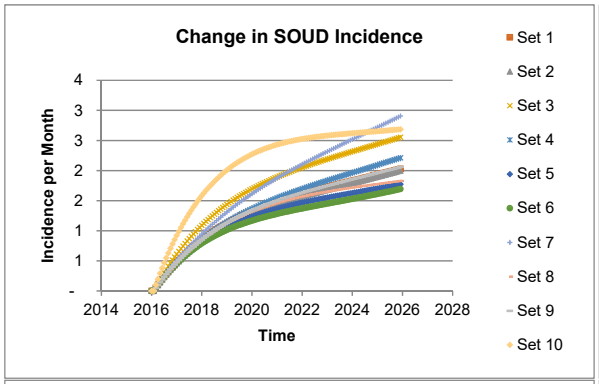


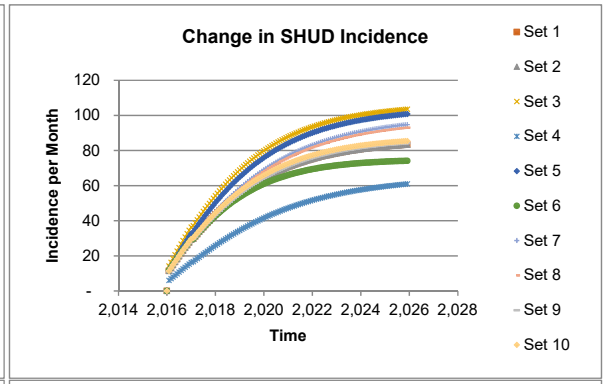


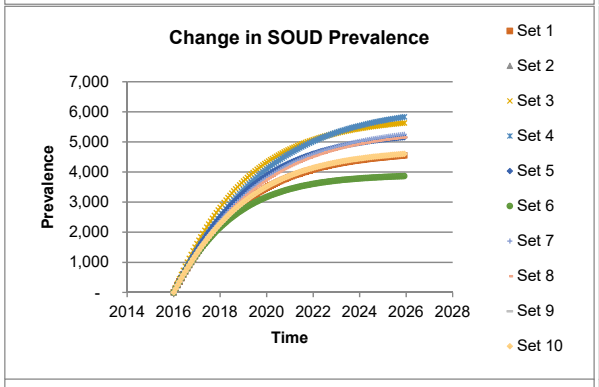


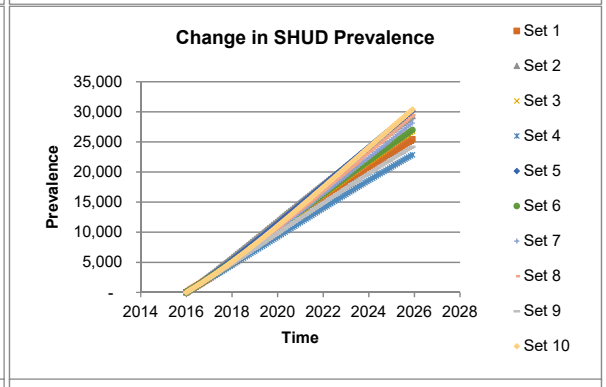


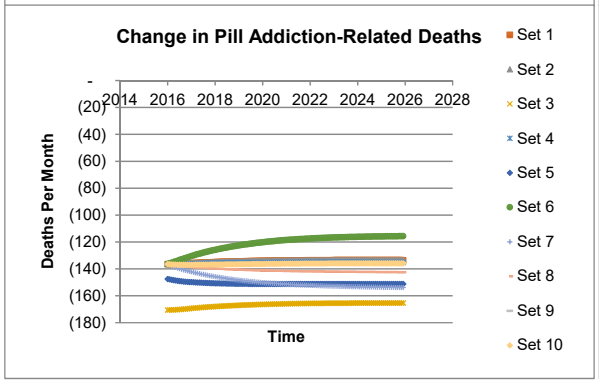
h) Increased naloxone availability

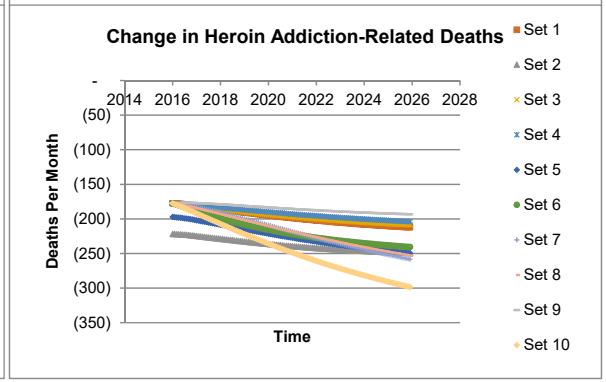


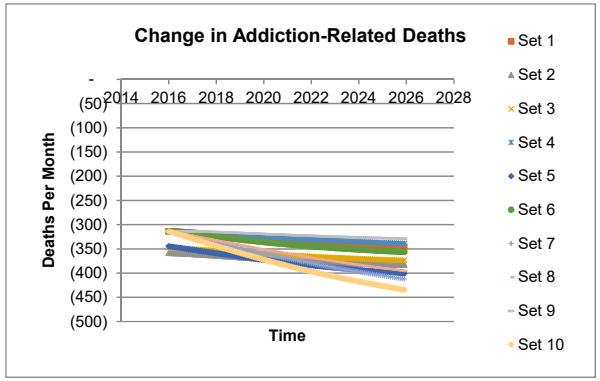




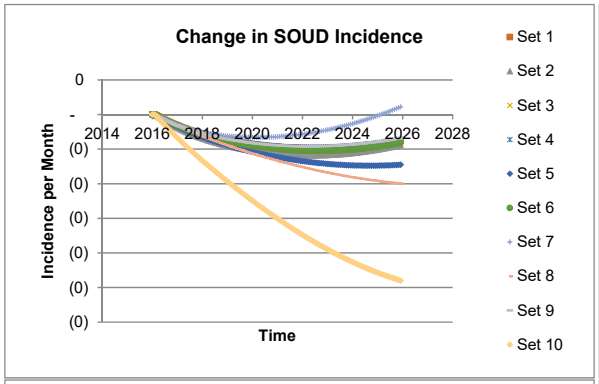


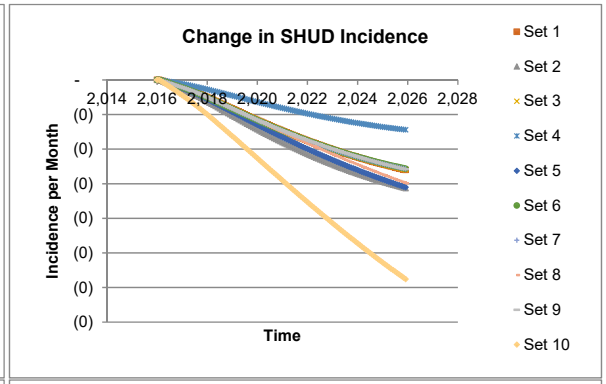


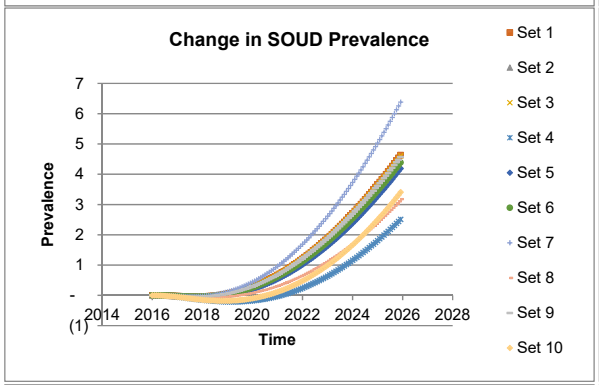


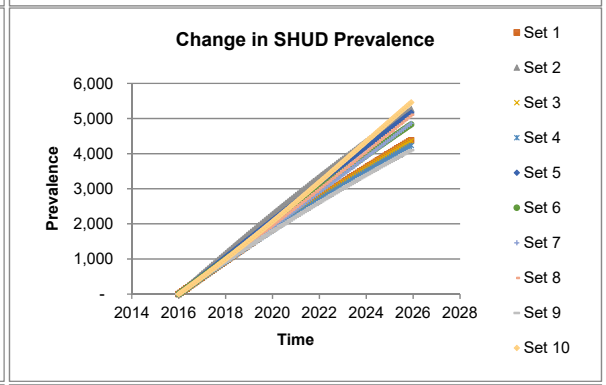


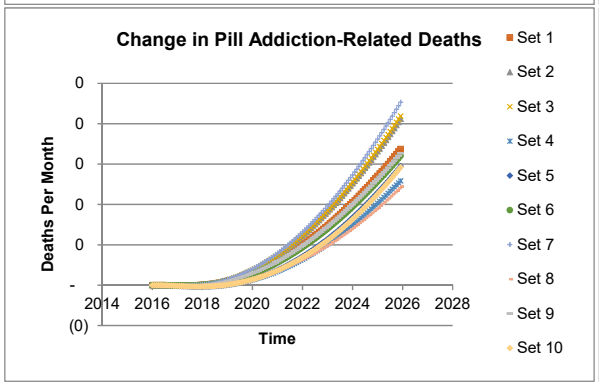
i) Needle exchange

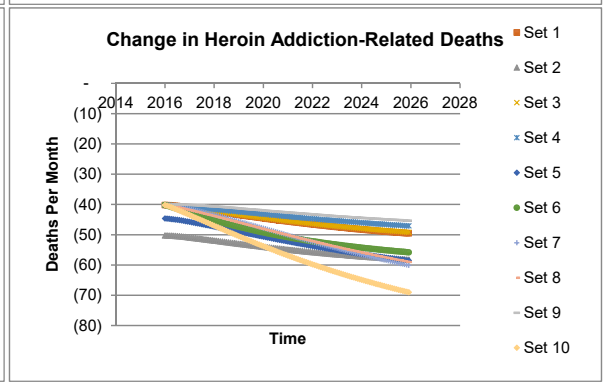


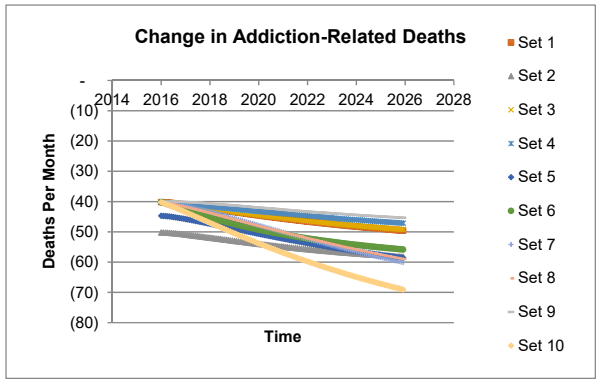




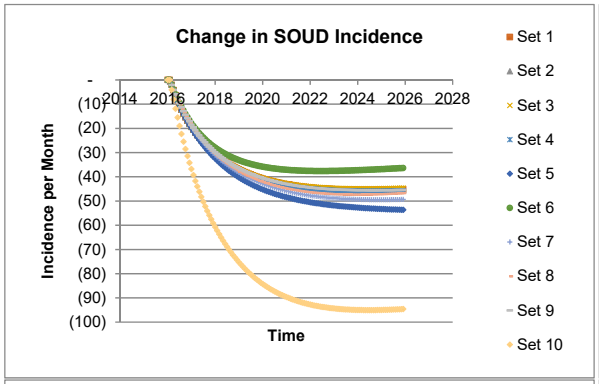


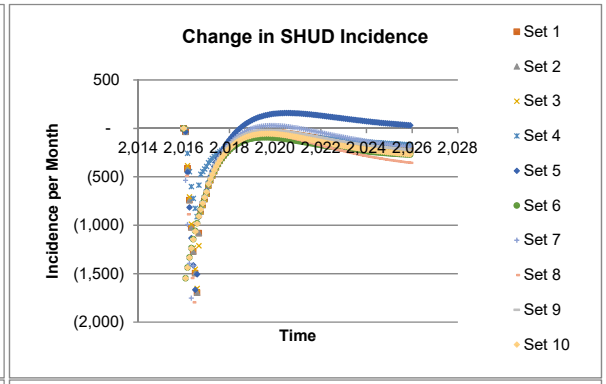


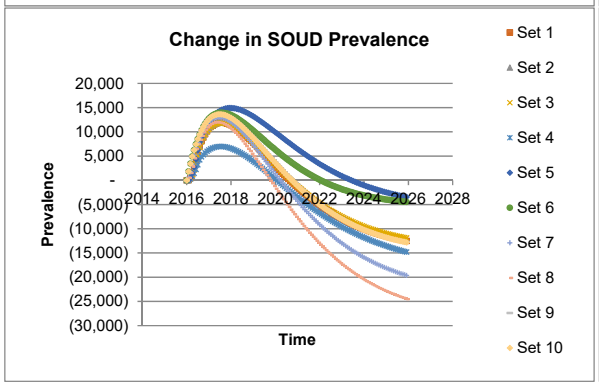


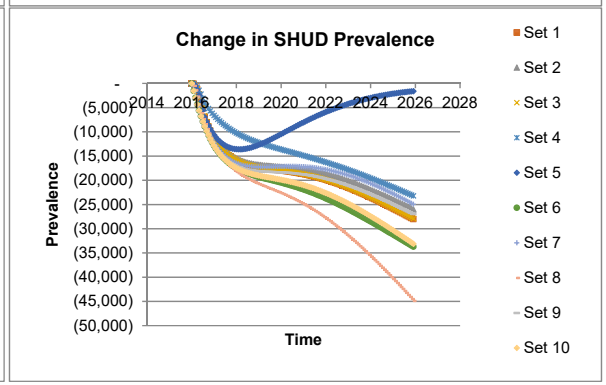


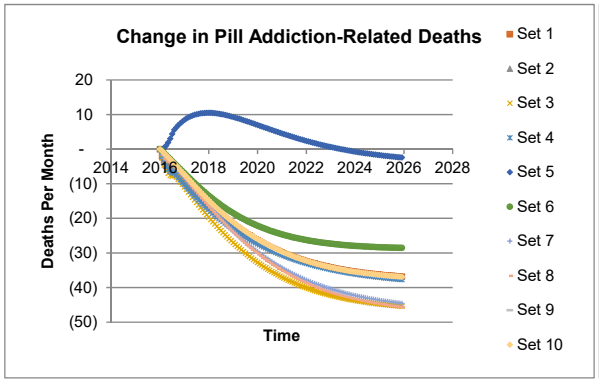
j) Increased MAT access

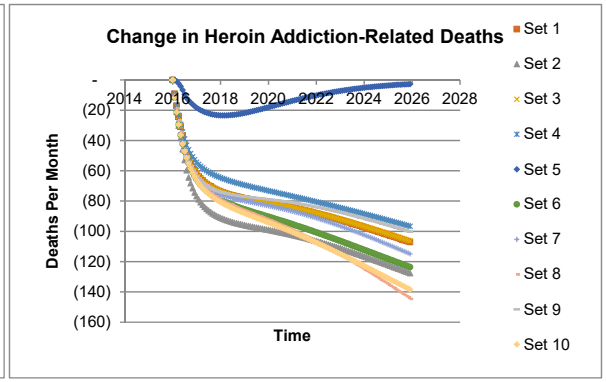


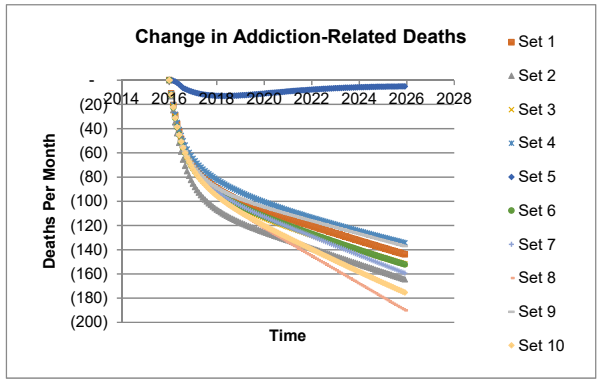




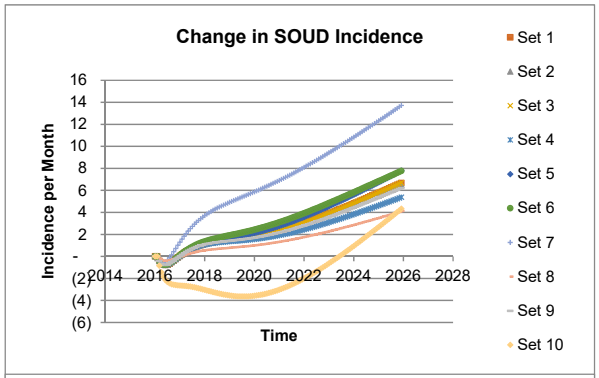


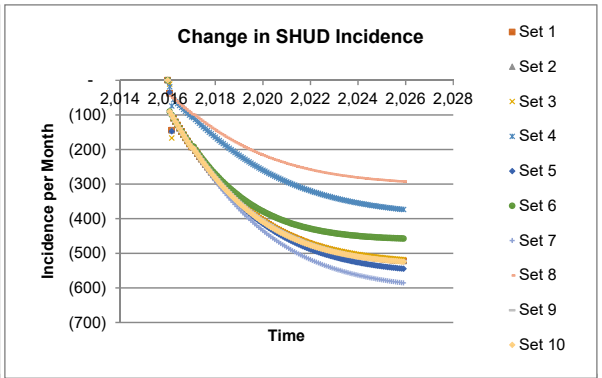


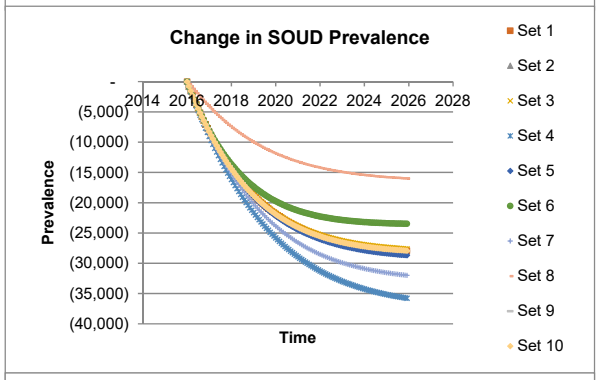


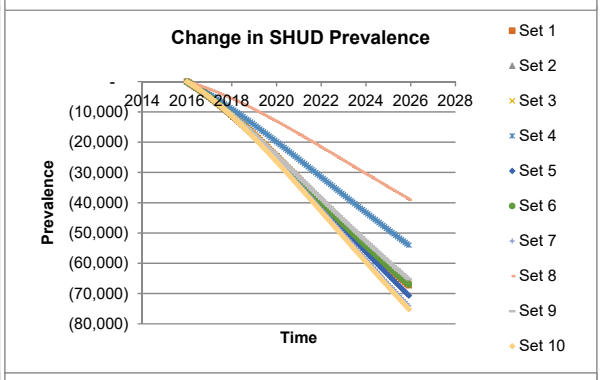


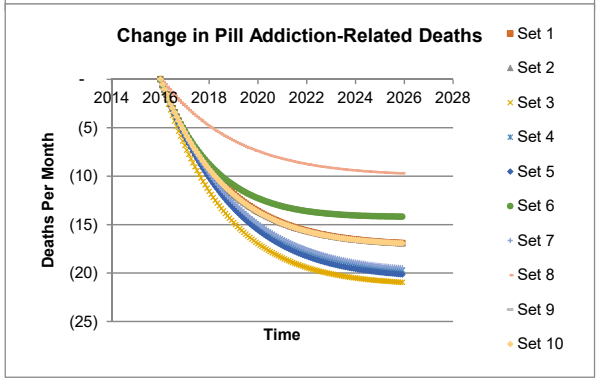
k) Psychosocial treatment

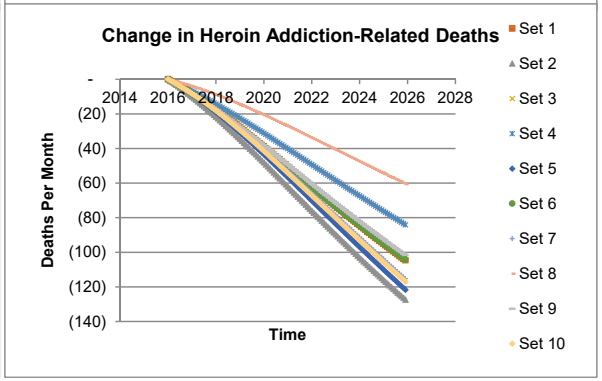


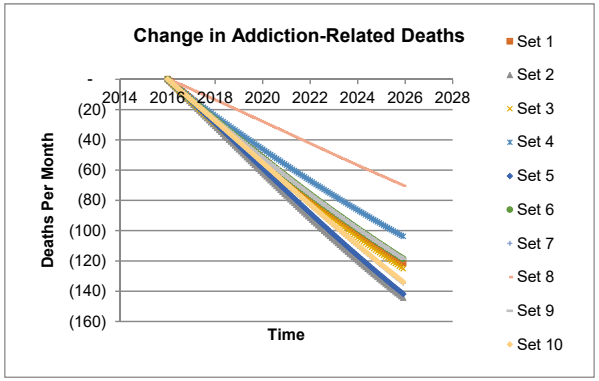






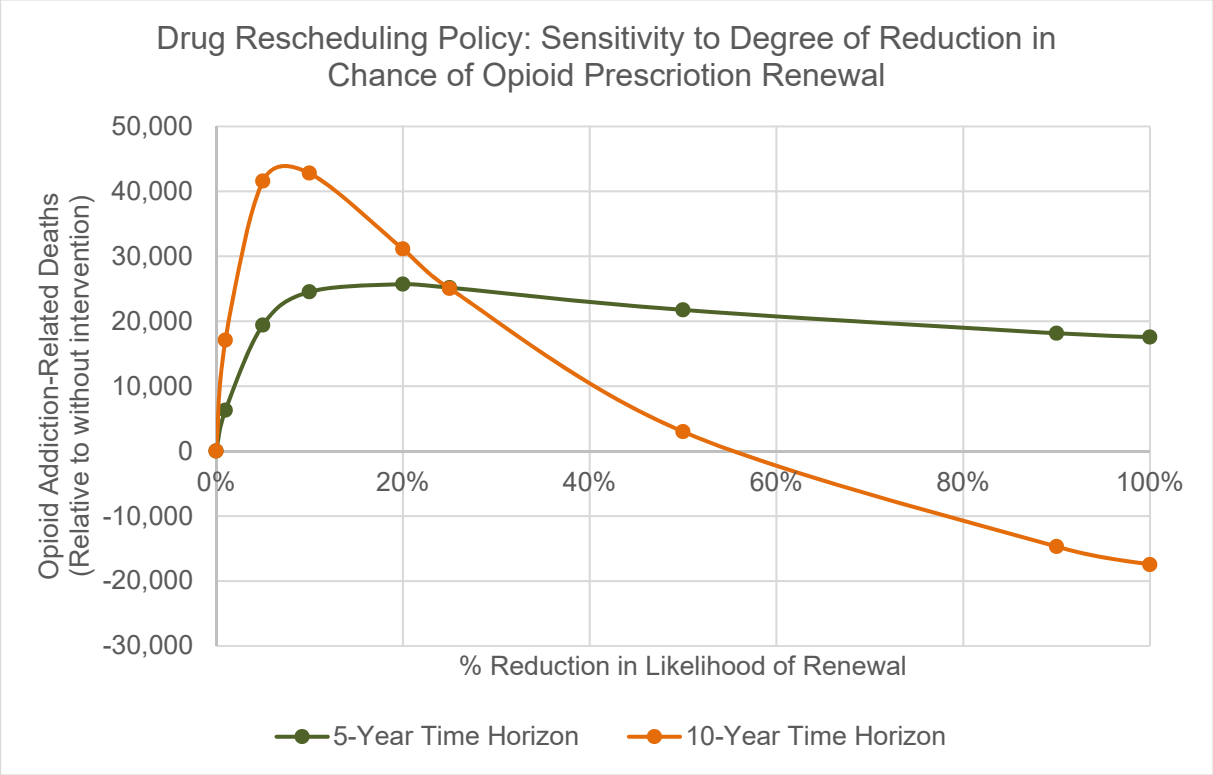






Appendix Figure 13. Deaths under drug rescheduling for various policy effect magnitudes

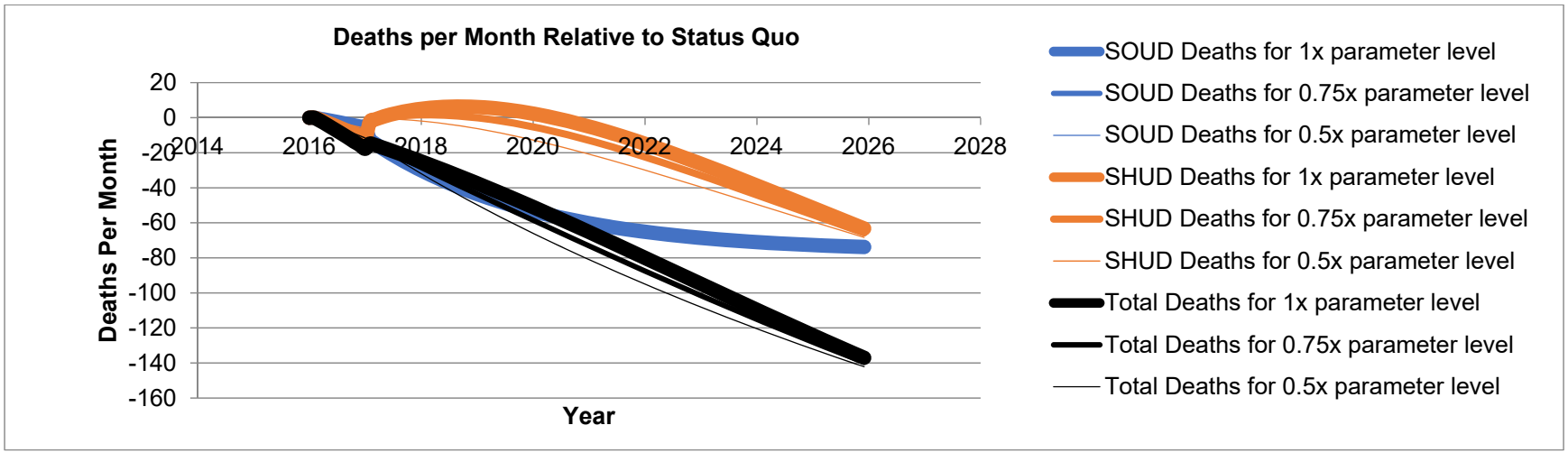
Mean total deaths, relative to without intervention, over five (green) or ten (orange) years for various assumed magnitudes of the drug rescheduling policy's effect on reducing likelihood of prescription opioid renewal.



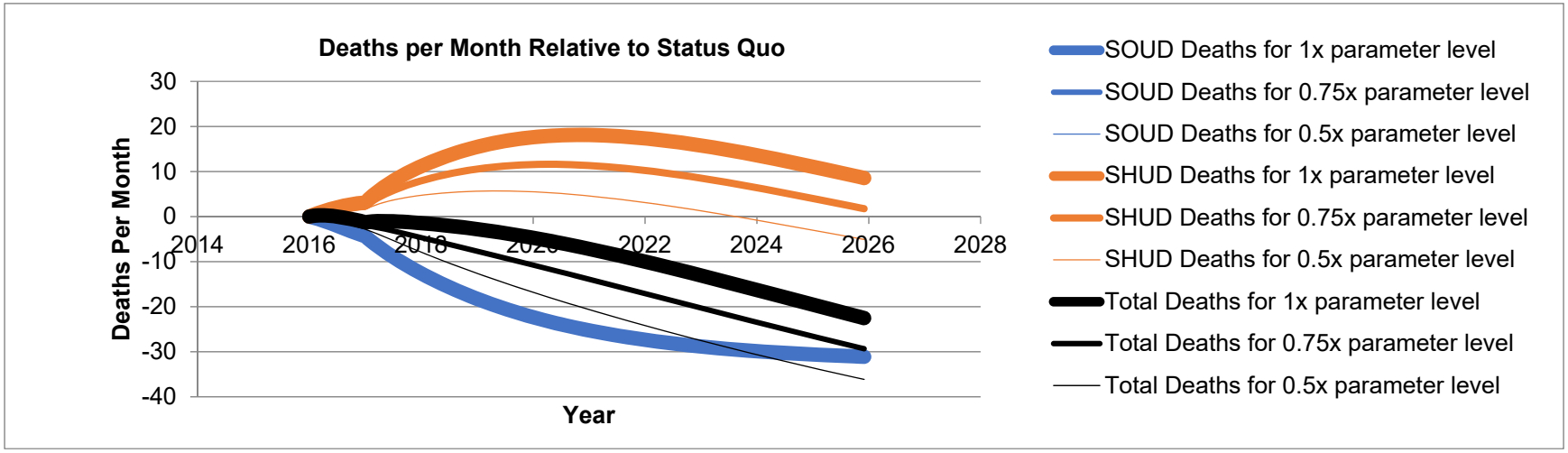
Appendix Figure 14. Sensitivity of policies' effect on addiction-related deaths to various likelihoods of escalation to SHUD

Mean monthly deaths from SOUD, SHUD, and total addiction-related deaths, relative to without intervention, under each policy, for various likelihoods of escalation to SHUD: the base case assumption level, 75% of the base case assumption level, and 50% of the base case assumption level. SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

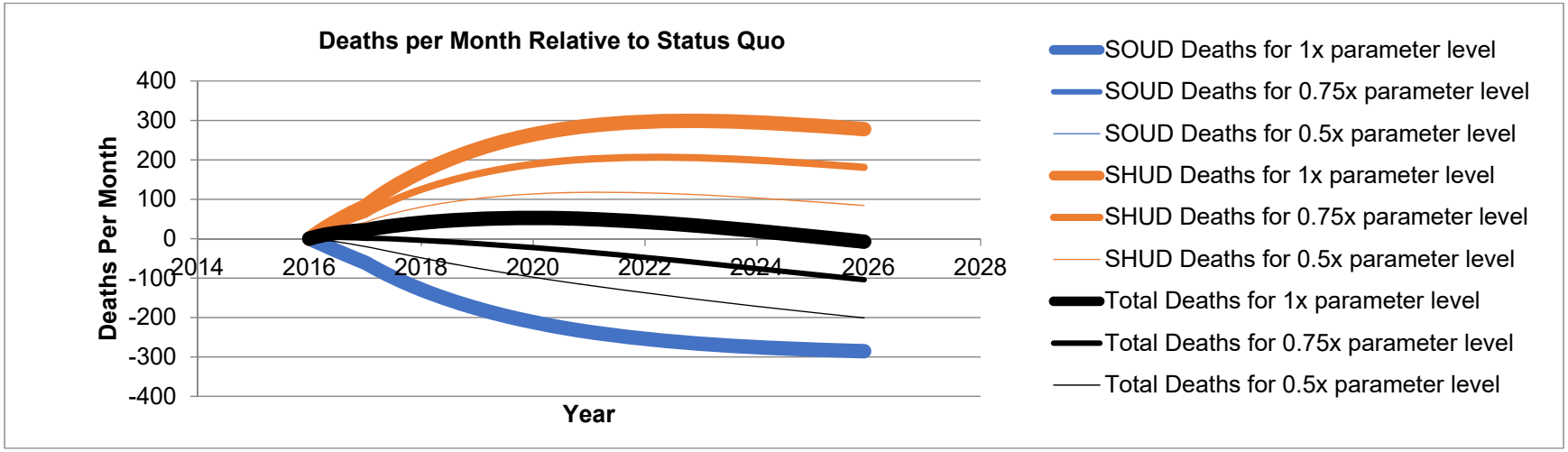
a) Reduced prescribing for acute pain



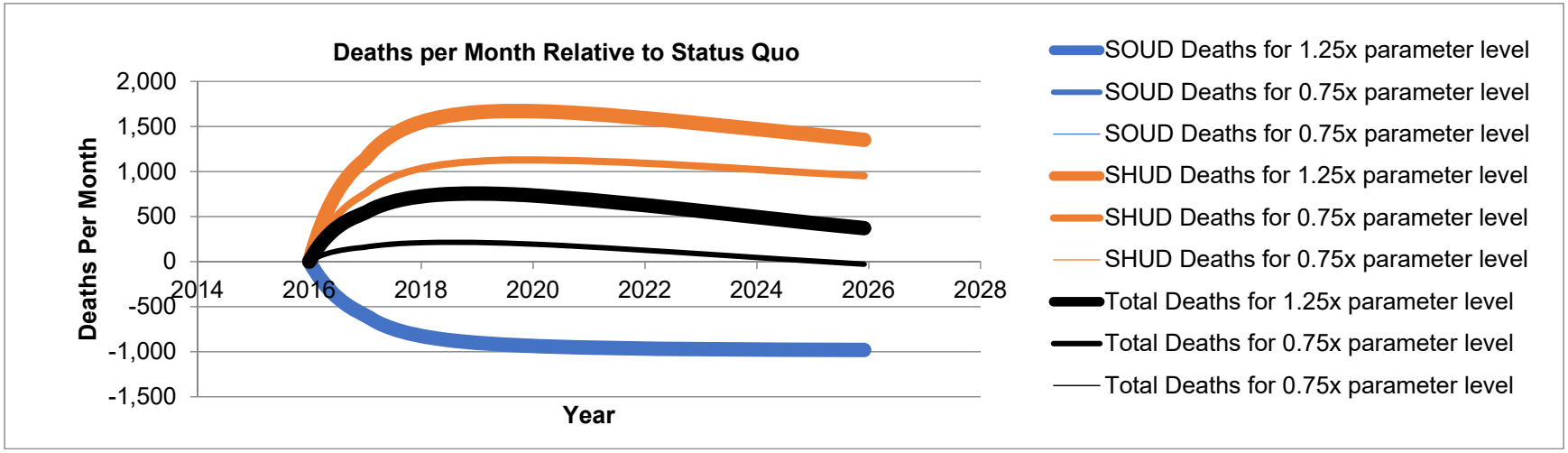
b) Reduced prescribing for transitioning pain



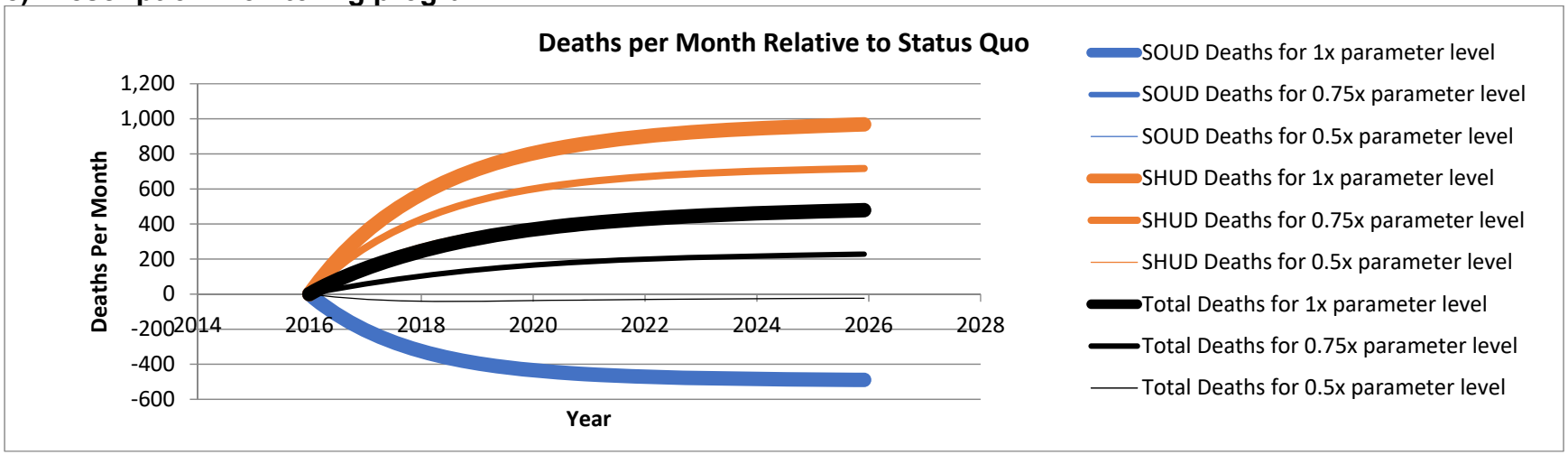
c) Reduced prescribing for chronic pain



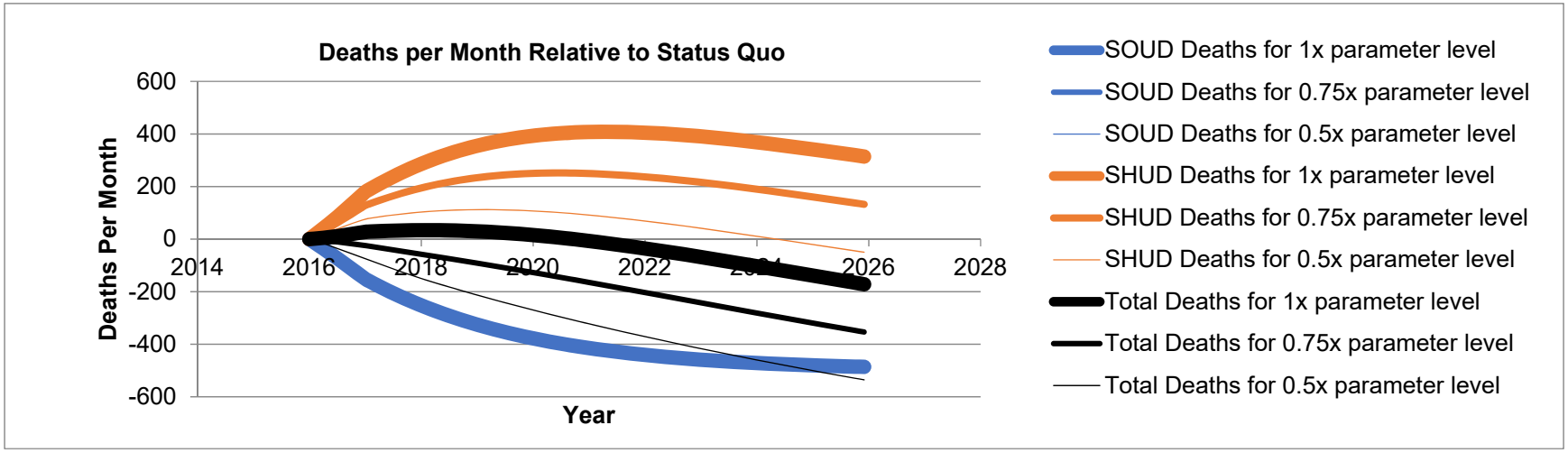
d) Drug rescheduling



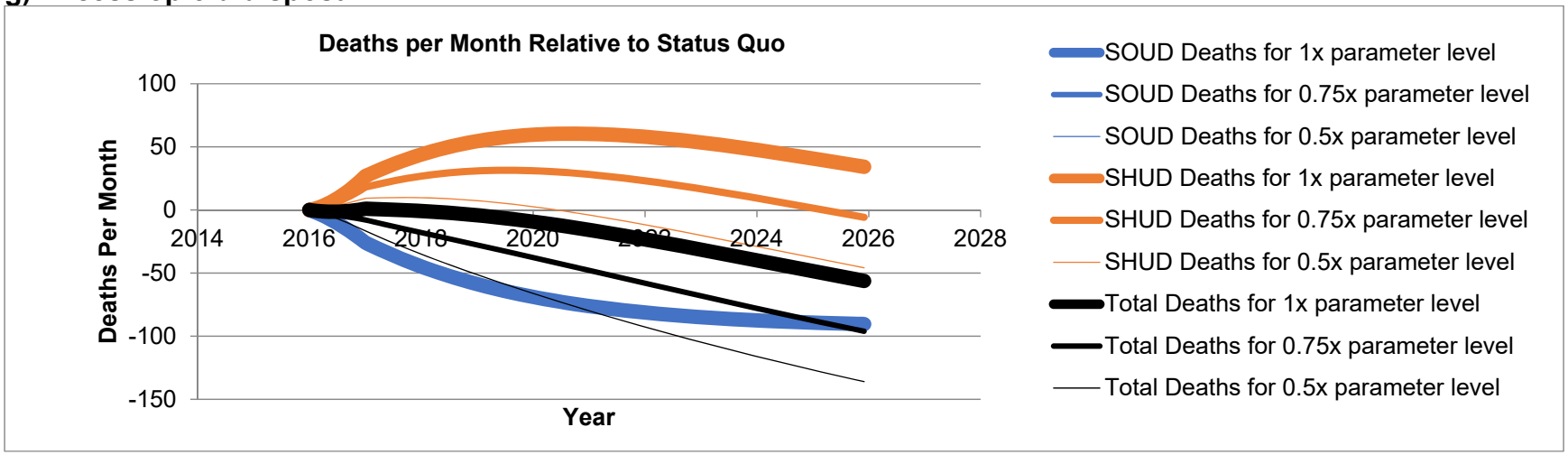
e) Prescription monitoring program



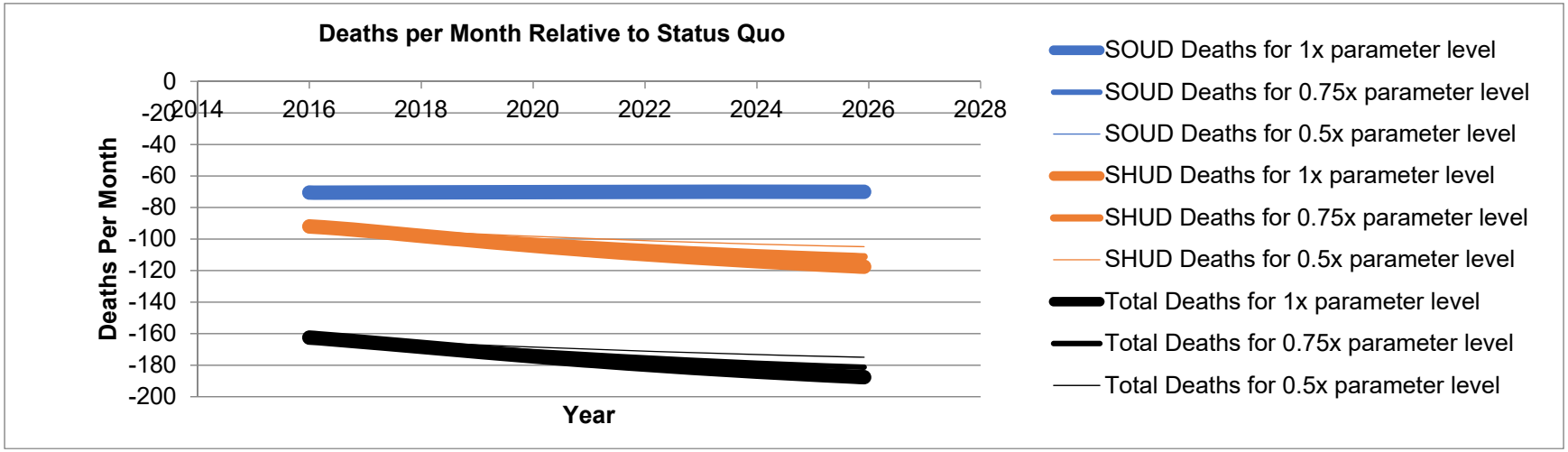
f) Drug reformulation



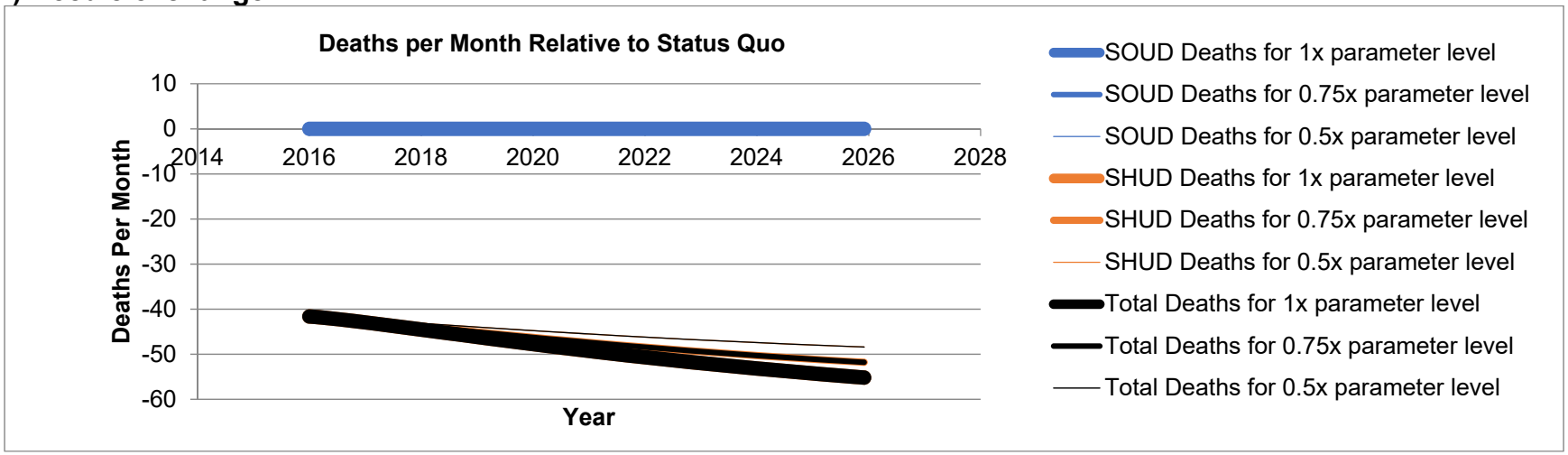
g) Excess opioid disposal



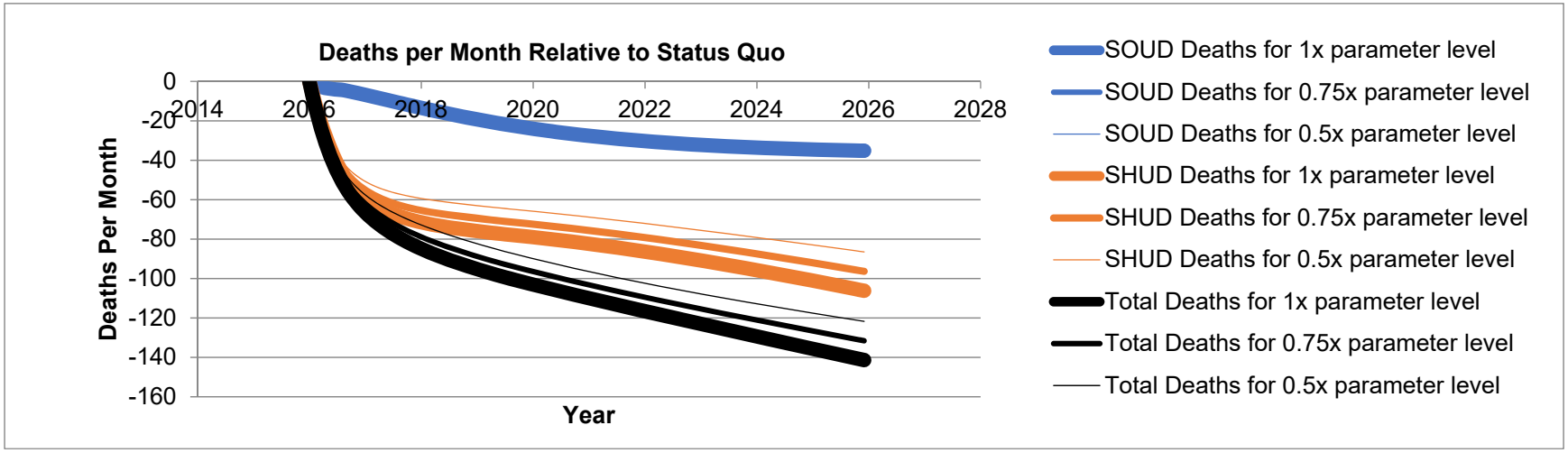
h) Naloxone availability



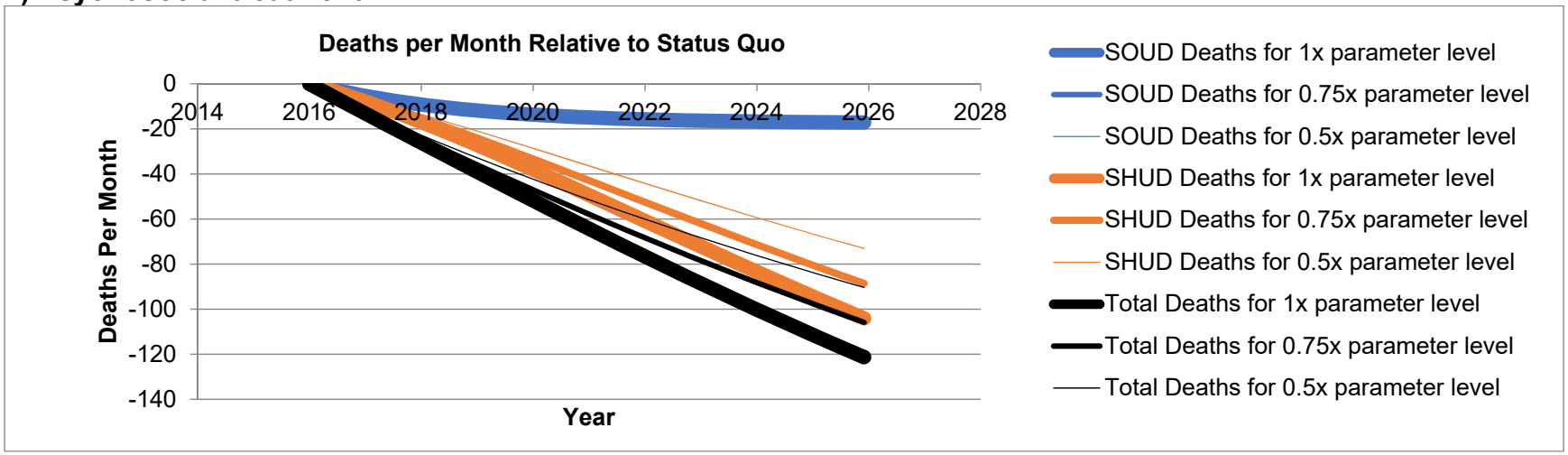
i) Needle exchange



j) Medication-assisted treatment



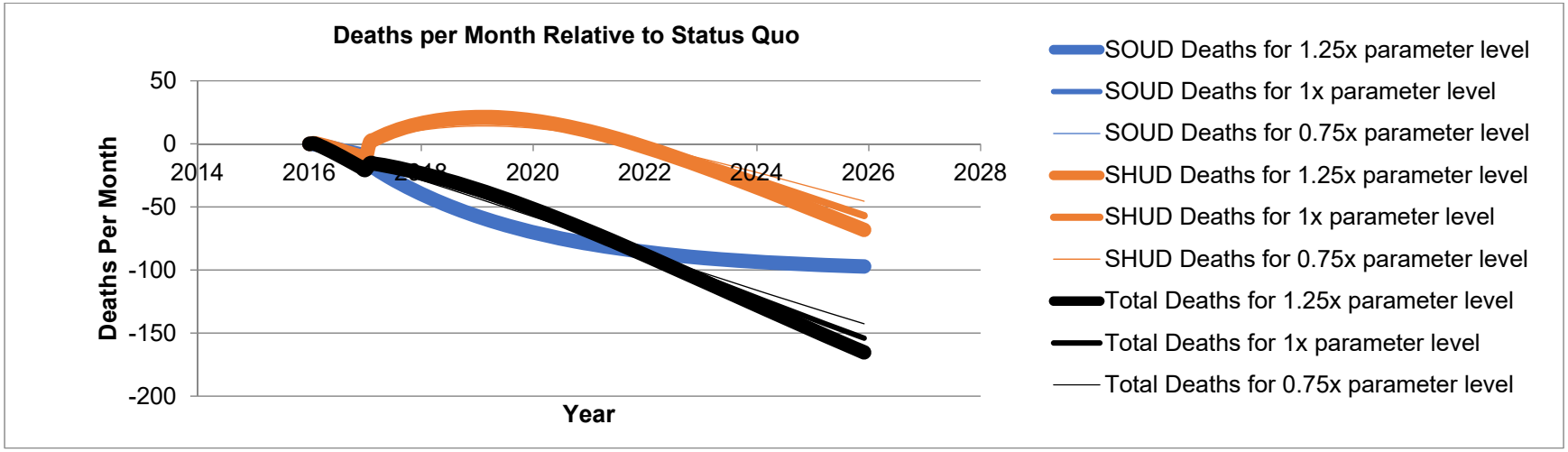
k) Psychosocial treatment



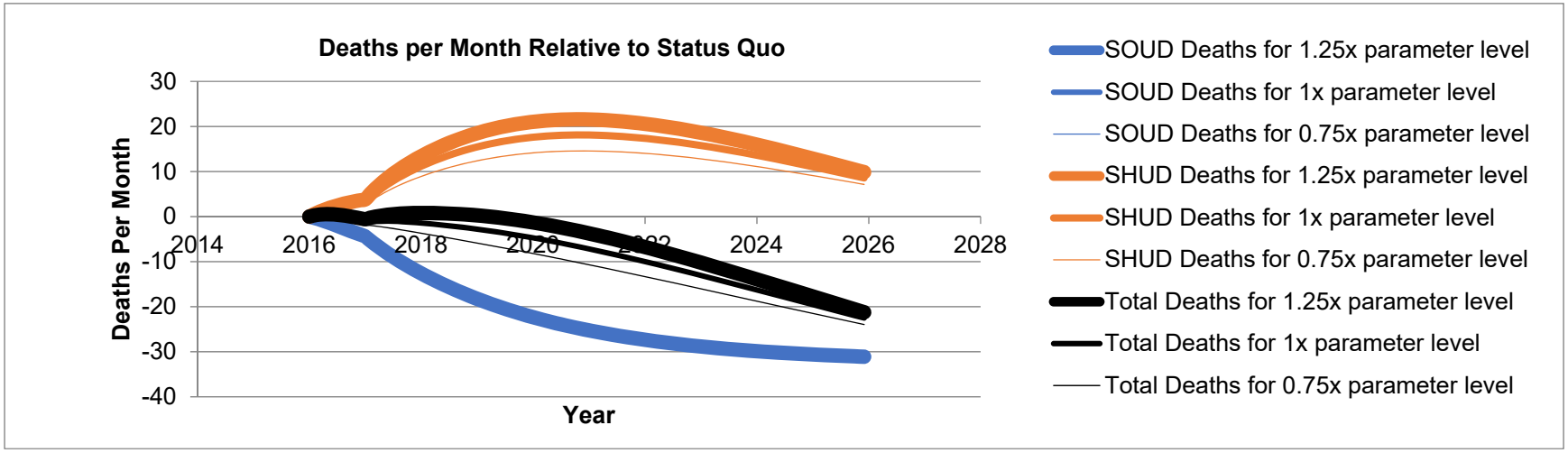
Appendix Figure 15. Sensitivity of policies' effect on addiction-related deaths to various likelihoods of SHUD overdose mortality

Mean monthly deaths from SOUD, SHUD, and total addiction-related deaths, relative to without intervention, under each policy, for various likelihoods of SHUD overdose mortality: the base case assumption level, 75% of the base case assumption level, and 50% of the base case assumption level. SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

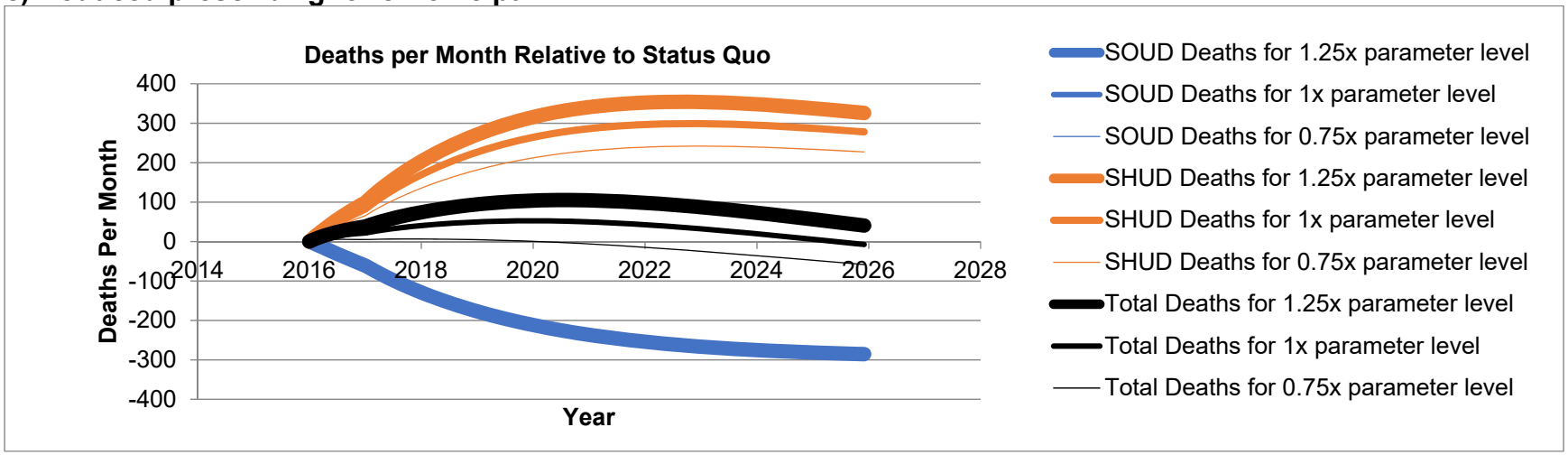
a) Reduced prescribing for acute pain



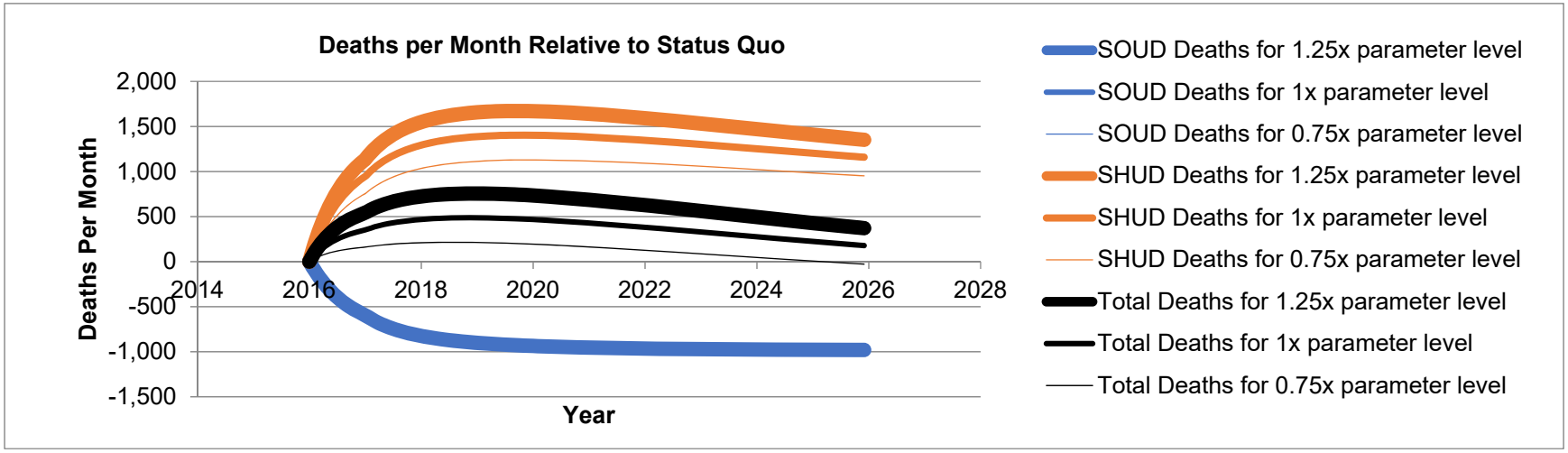
b) Reduced prescribing for transitioning pain



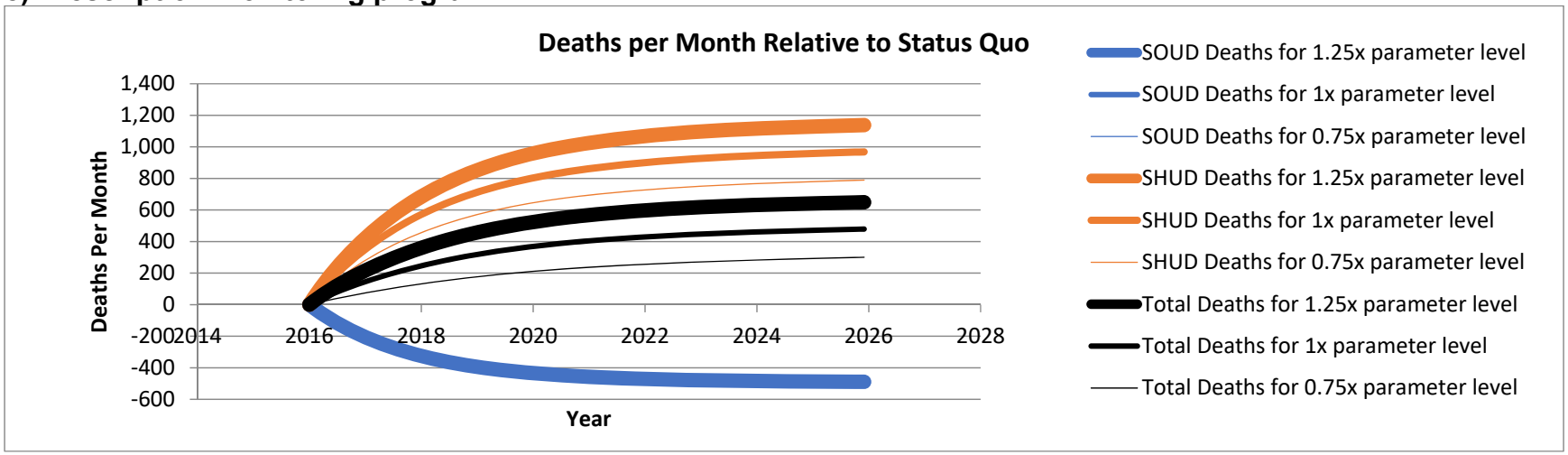
c) Reduced prescribing for chronic pain



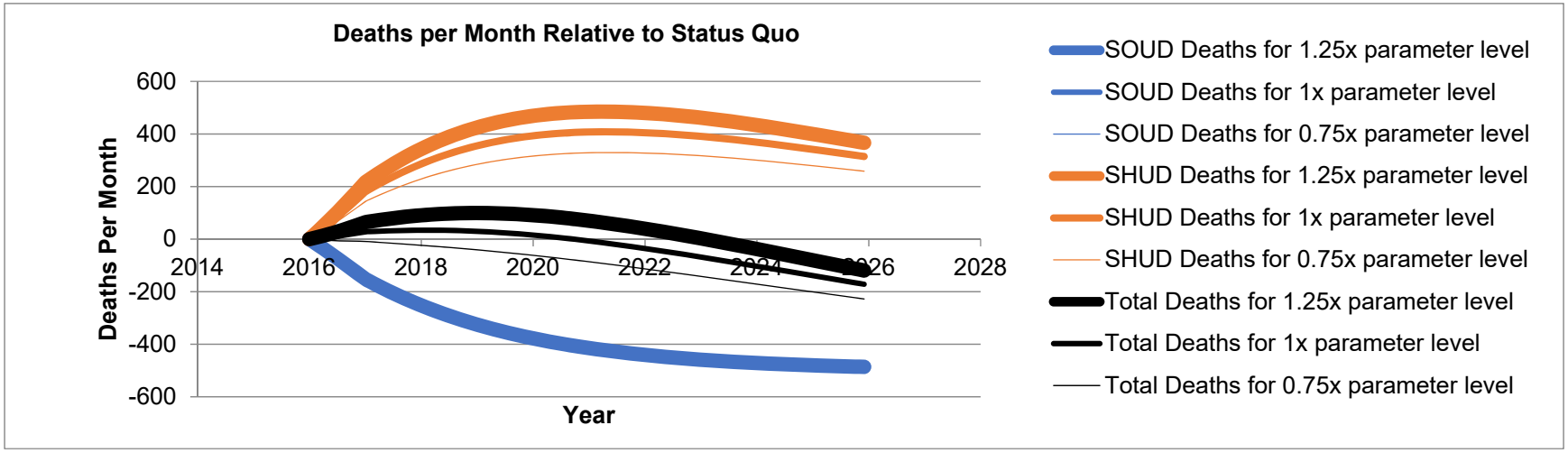
d) Drug rescheduling



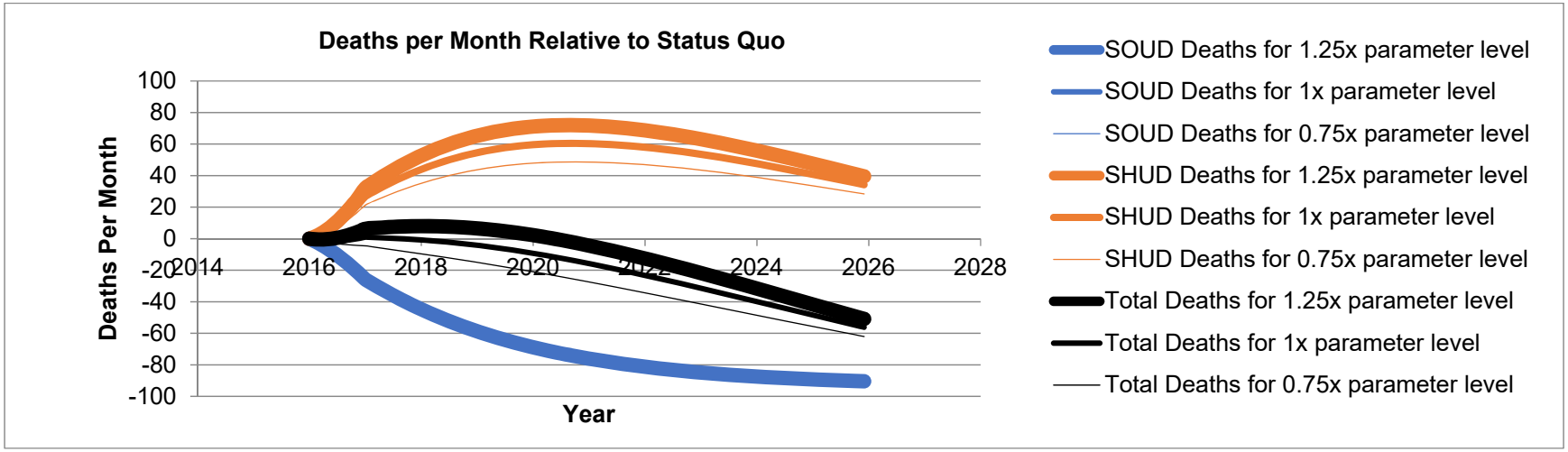
e) Prescription monitoring program



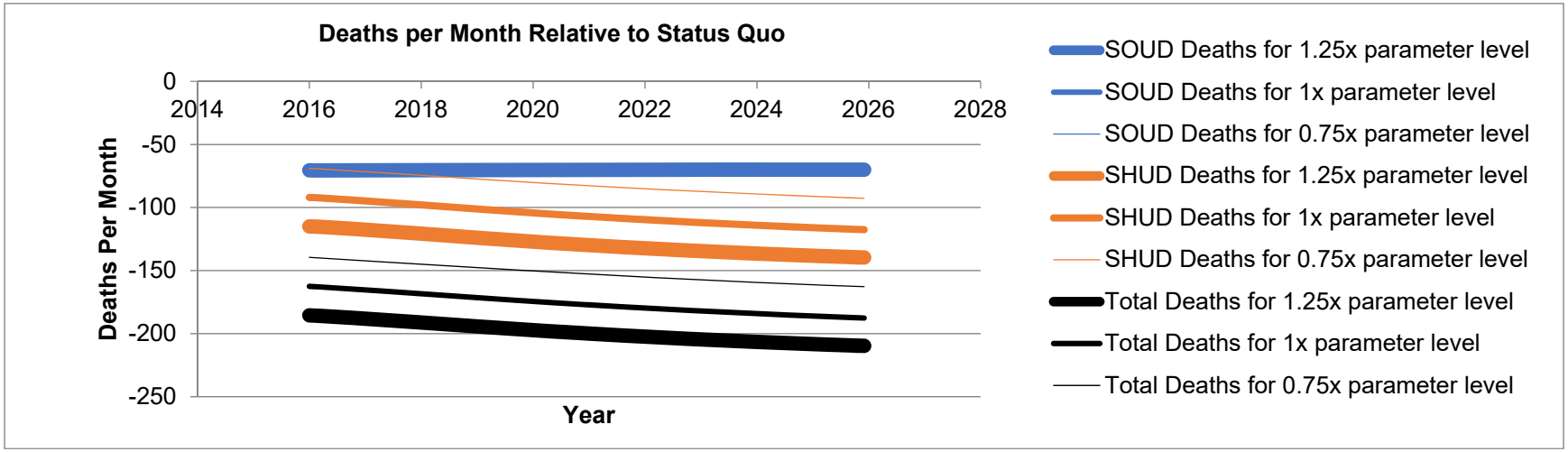
f) Drug reformulation



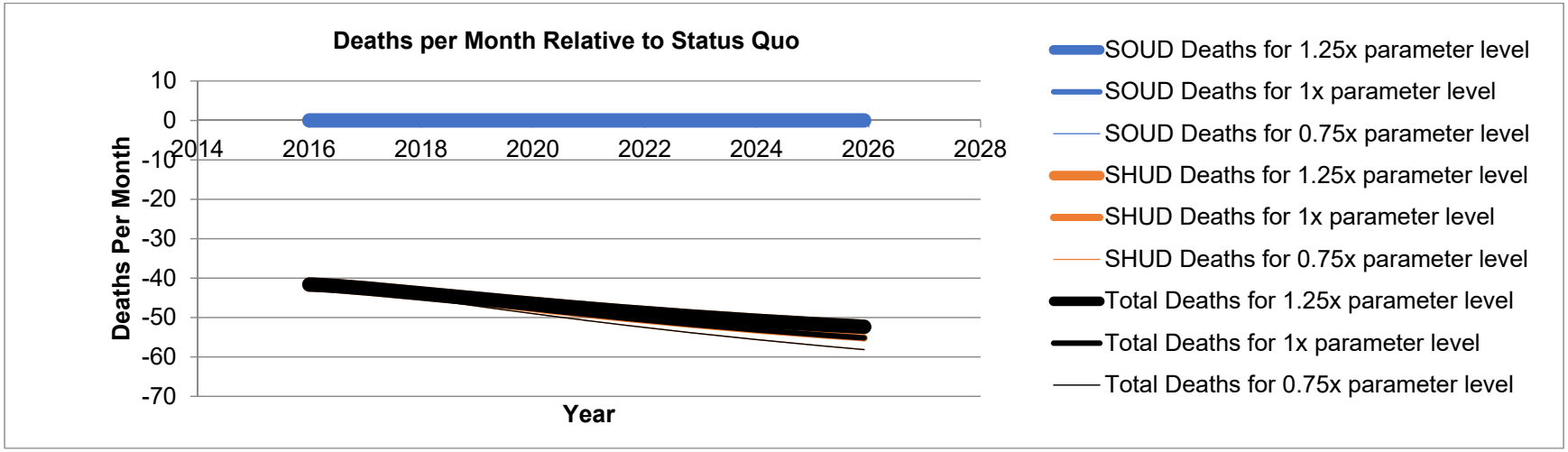
g) Excess opioid disposal



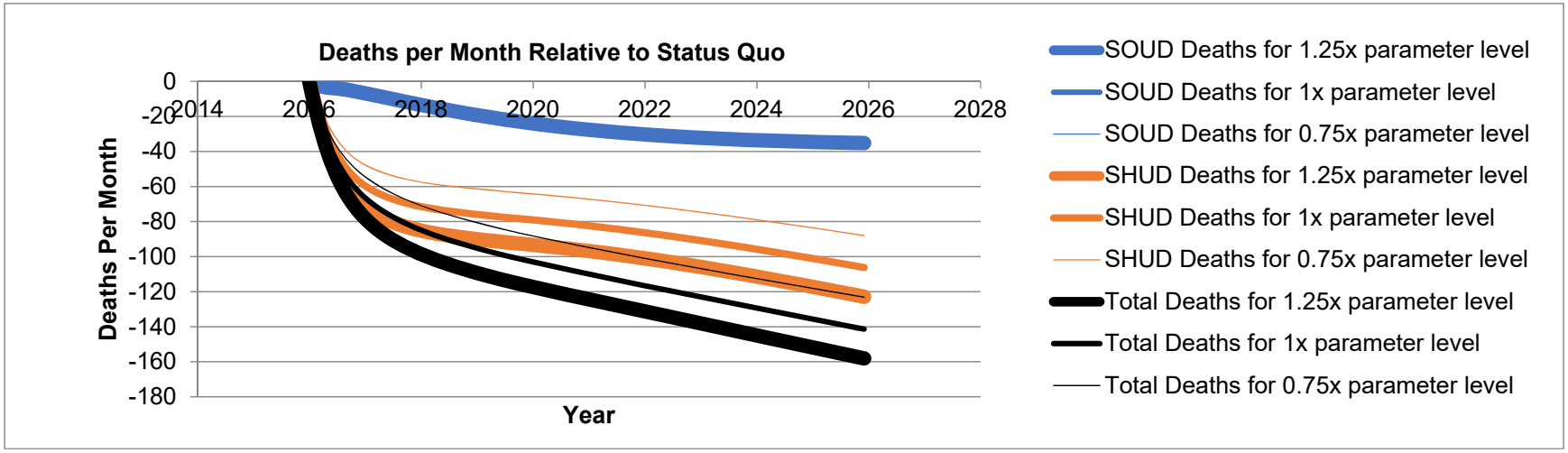
h) Naloxone availability



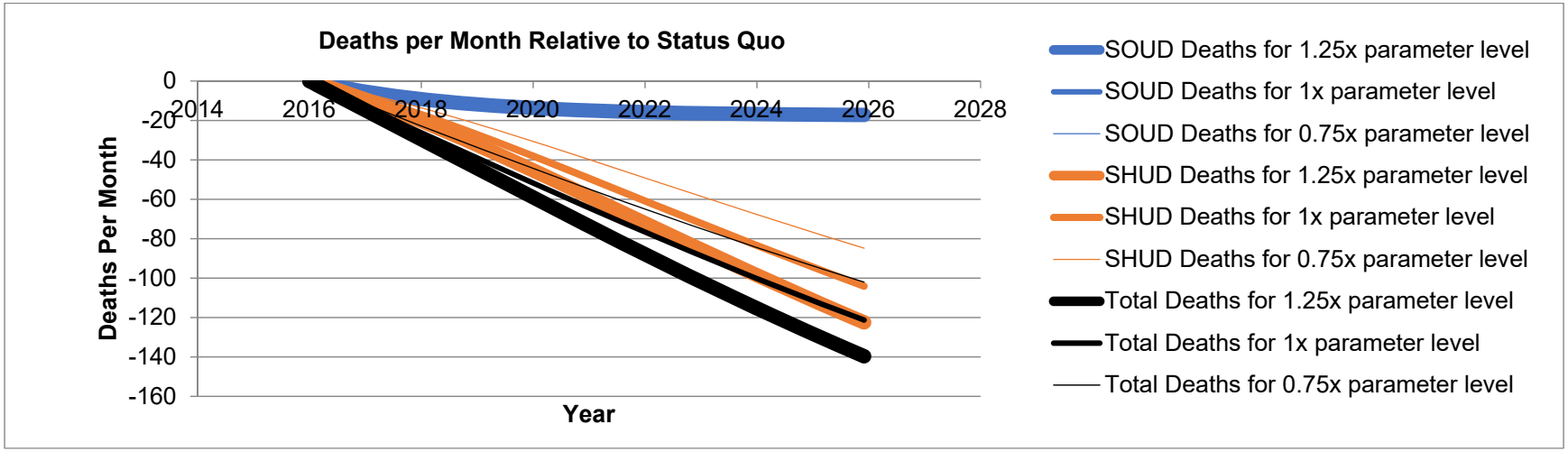
i) Needle exchange



j) Medication-assisted therapy



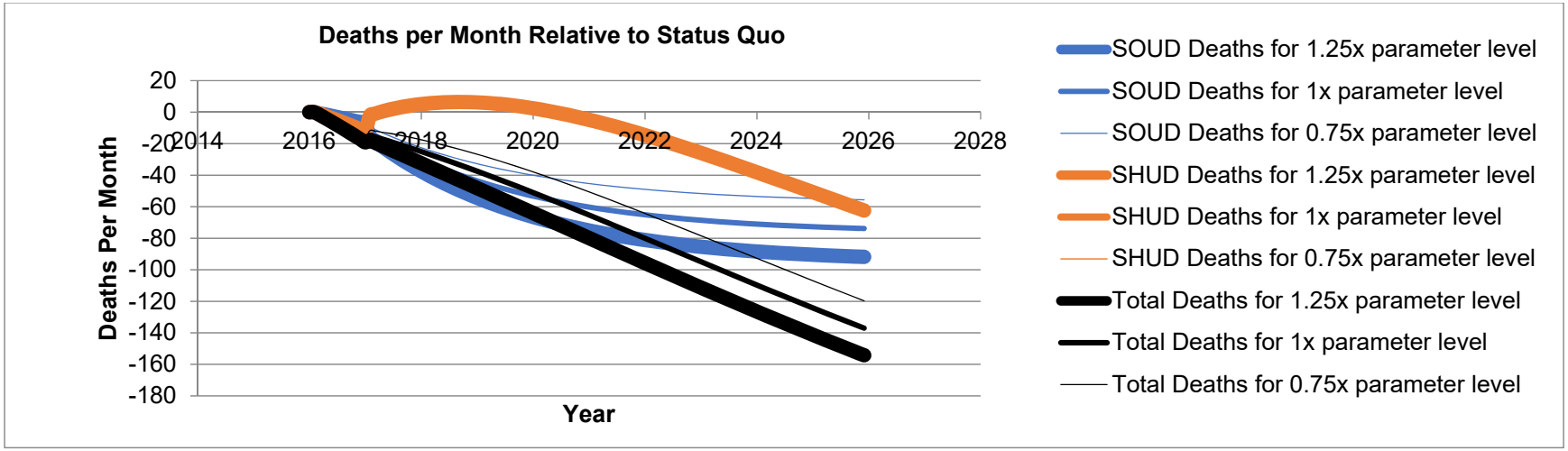
k) Psychosocial treatment



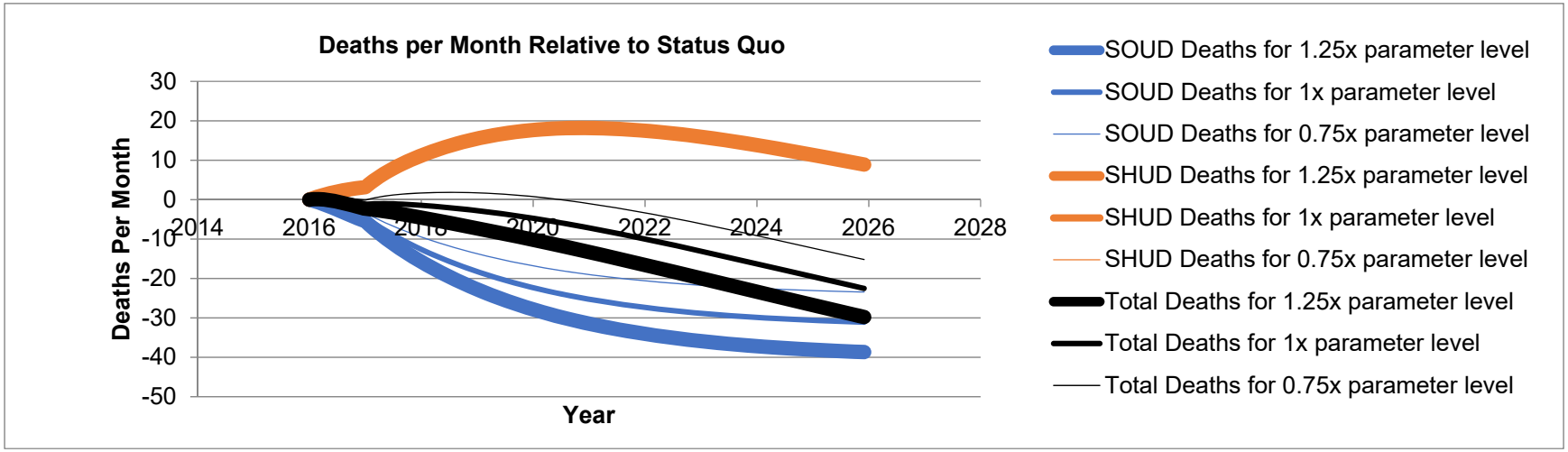
Appendix Figure 16. Sensitivity of policies' effect on addiction-related deaths to various likelihoods of SOUD overdose mortality

Mean monthly deaths from SOUD, SHUD, and total addiction-related deaths, relative to without intervention, under each policy, for various likelihoods of SOUD overdose mortality: 125% of the base case assumption level, the base case assumption level, and 75% of the base case assumption level. SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

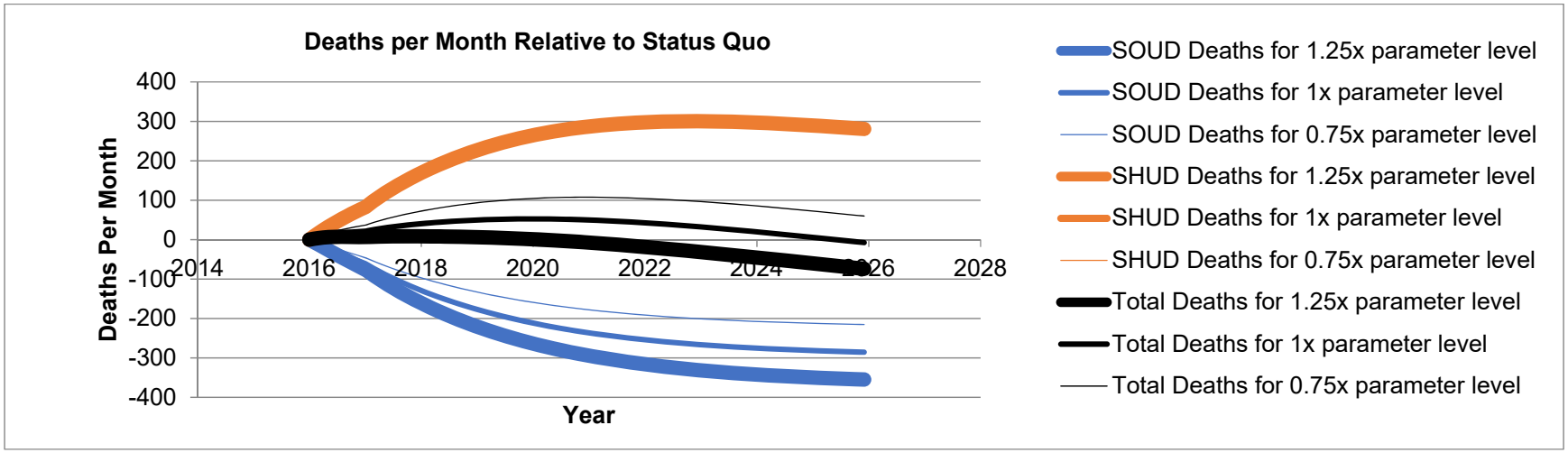
a) Reduced prescribing for acute pain



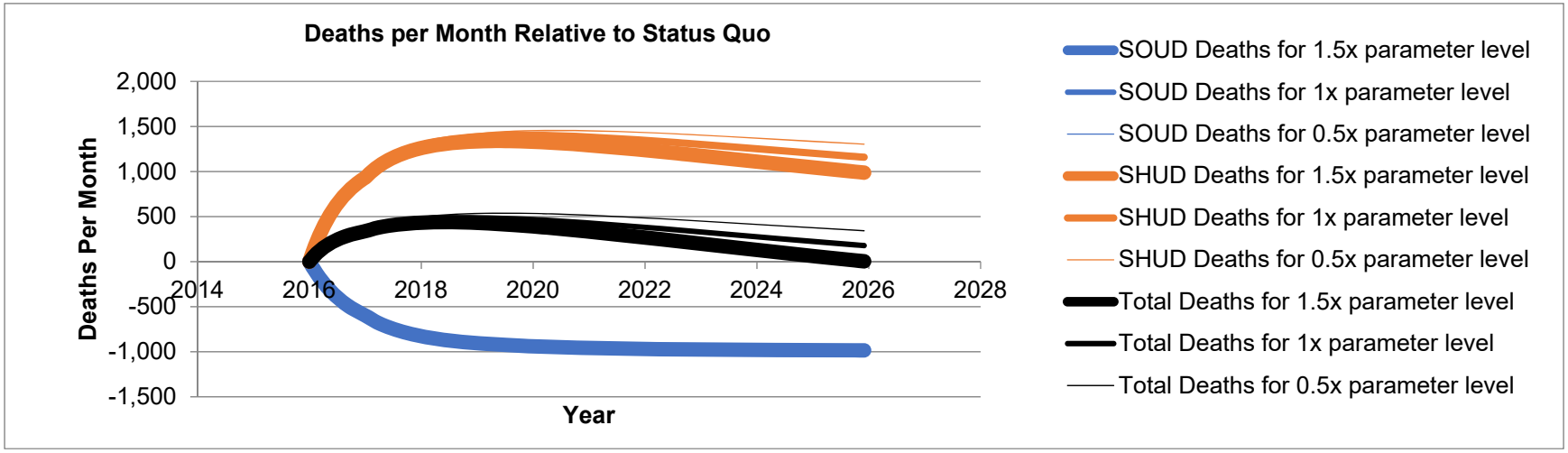
b) Reduced prescribing for transitioning pain



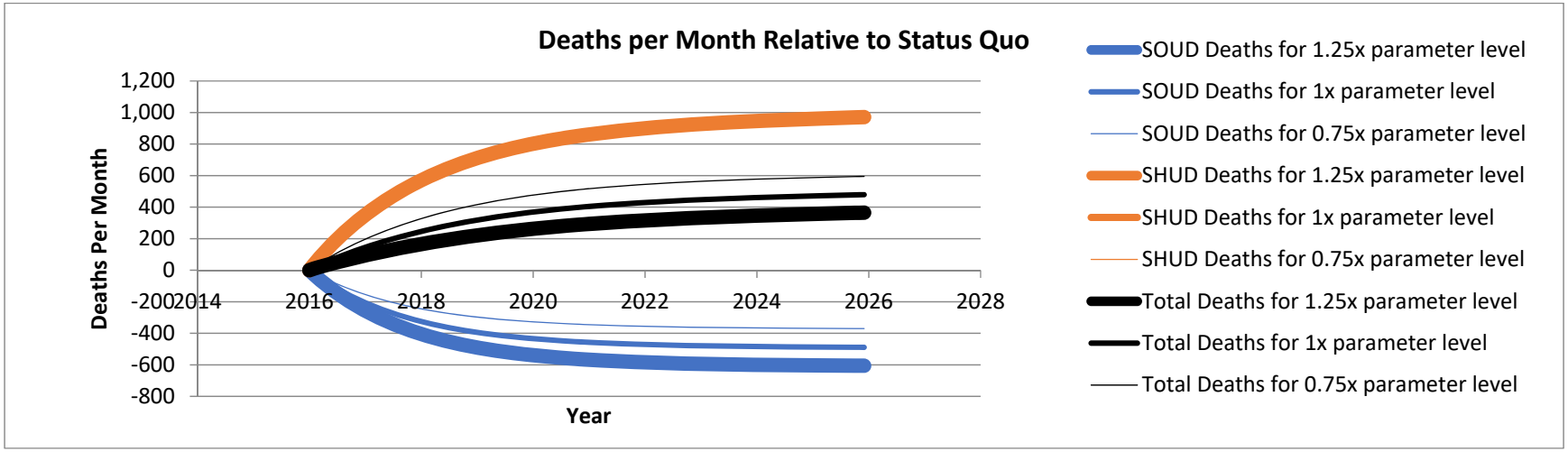
c) Reduced prescribing for chronic pain



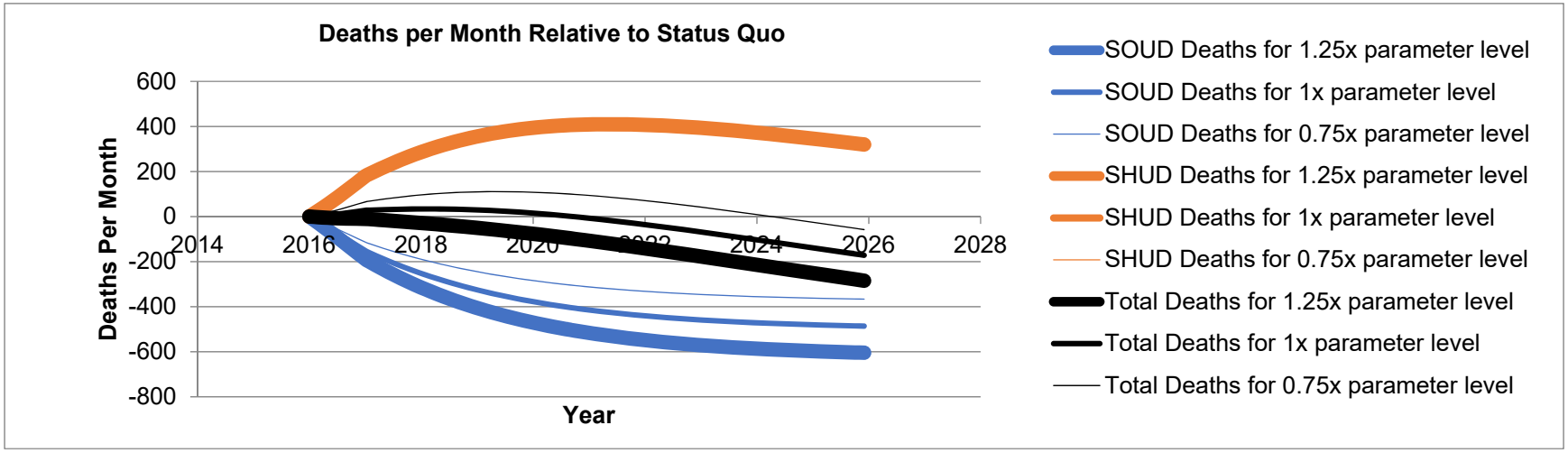
d) Drug rescheduling



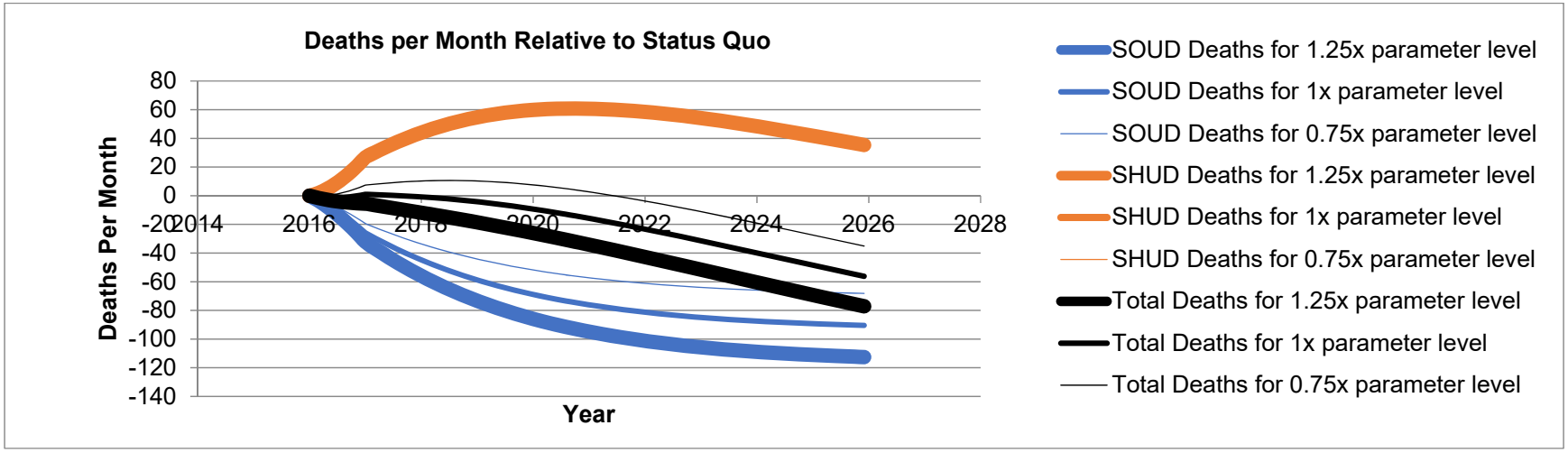
e) Prescription monitoring program



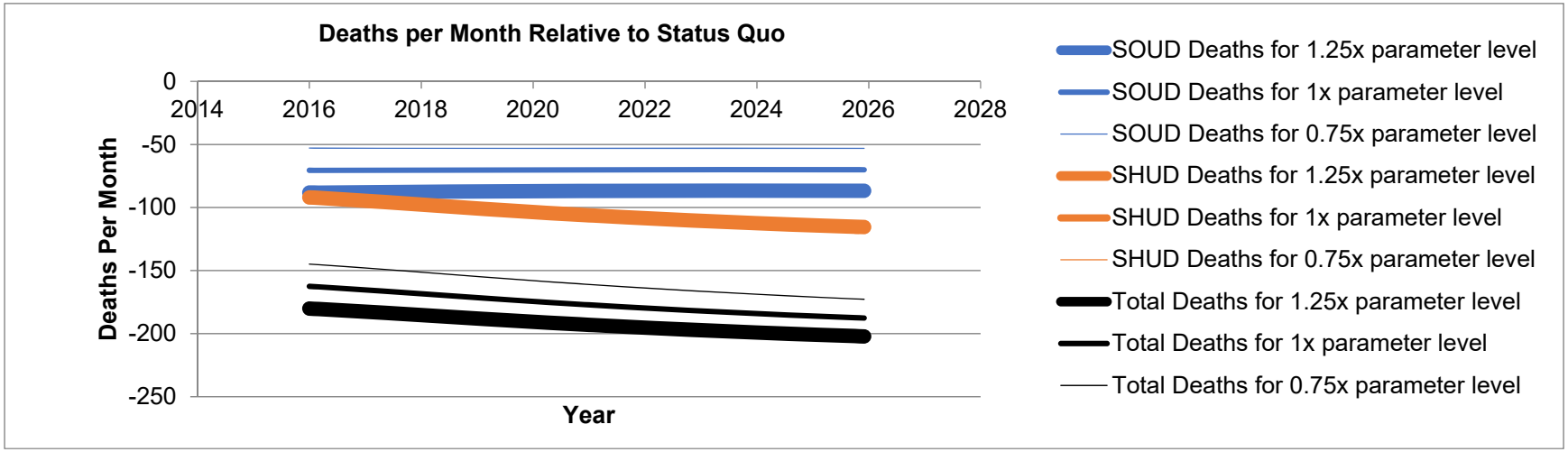
f) Drug reformulation



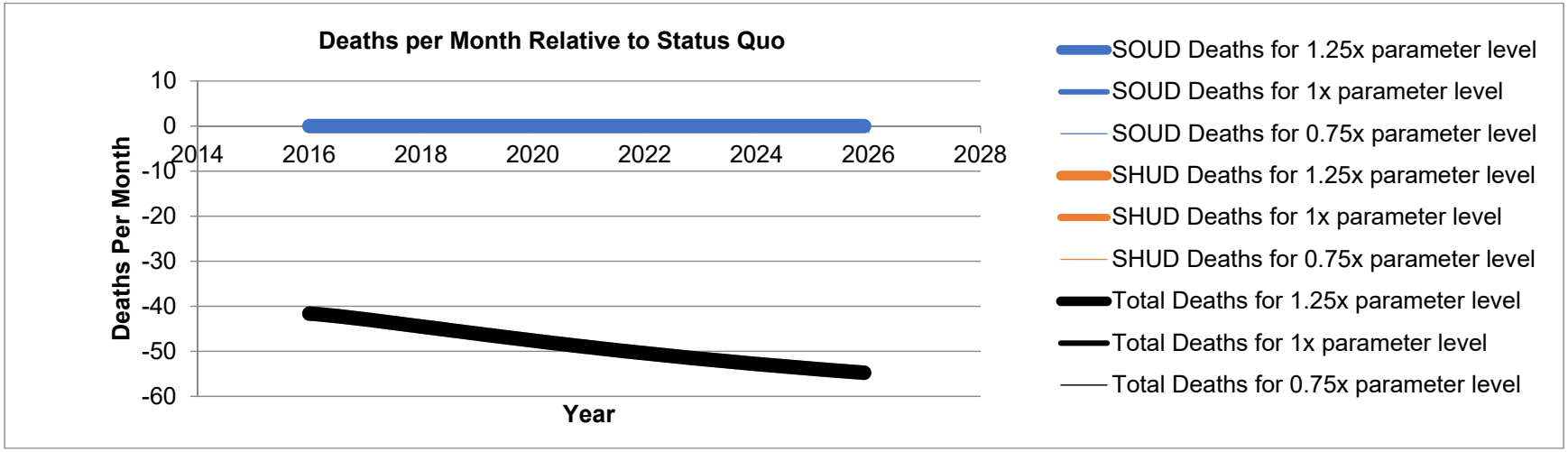
g) Excess opioid disposal



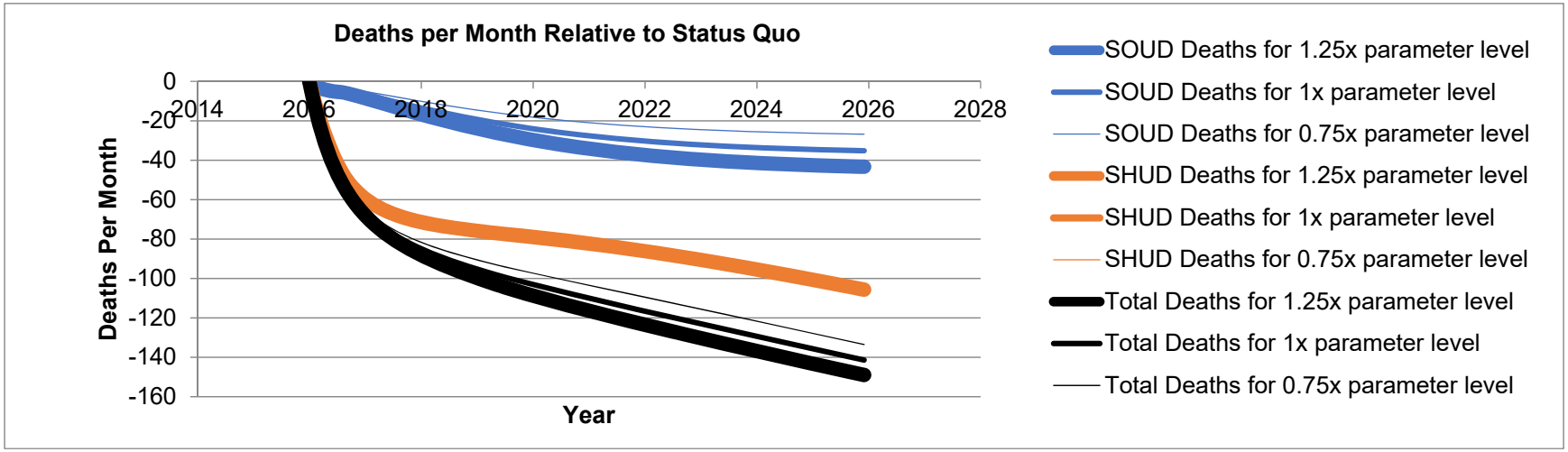
h) Naloxone availability



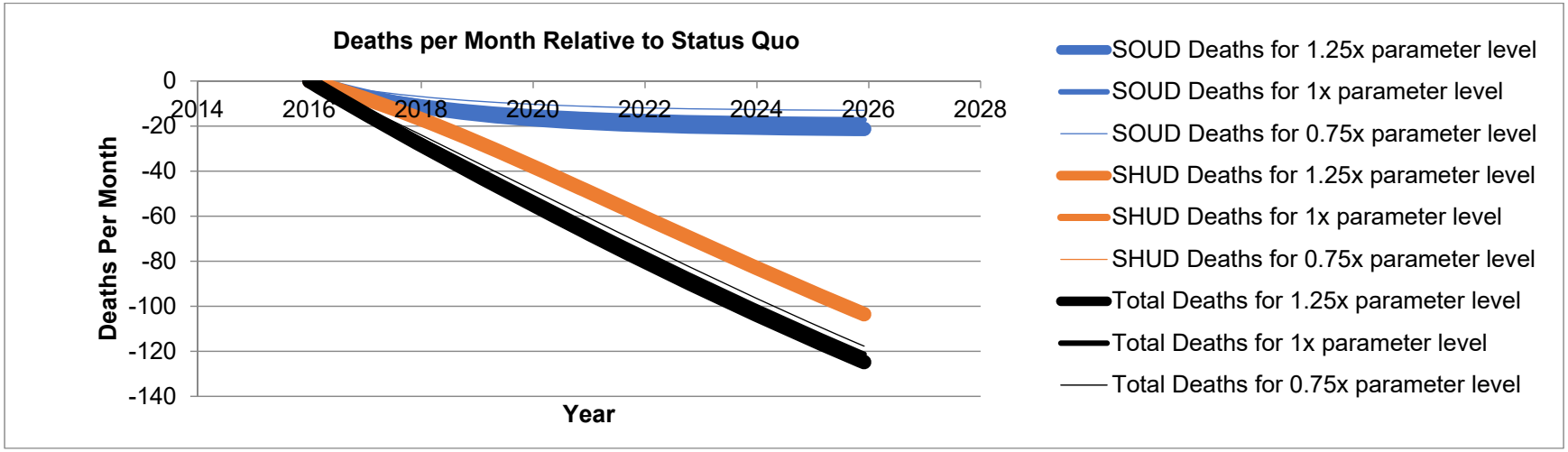
i) Needle exchange



j) Medication-assisted therapy



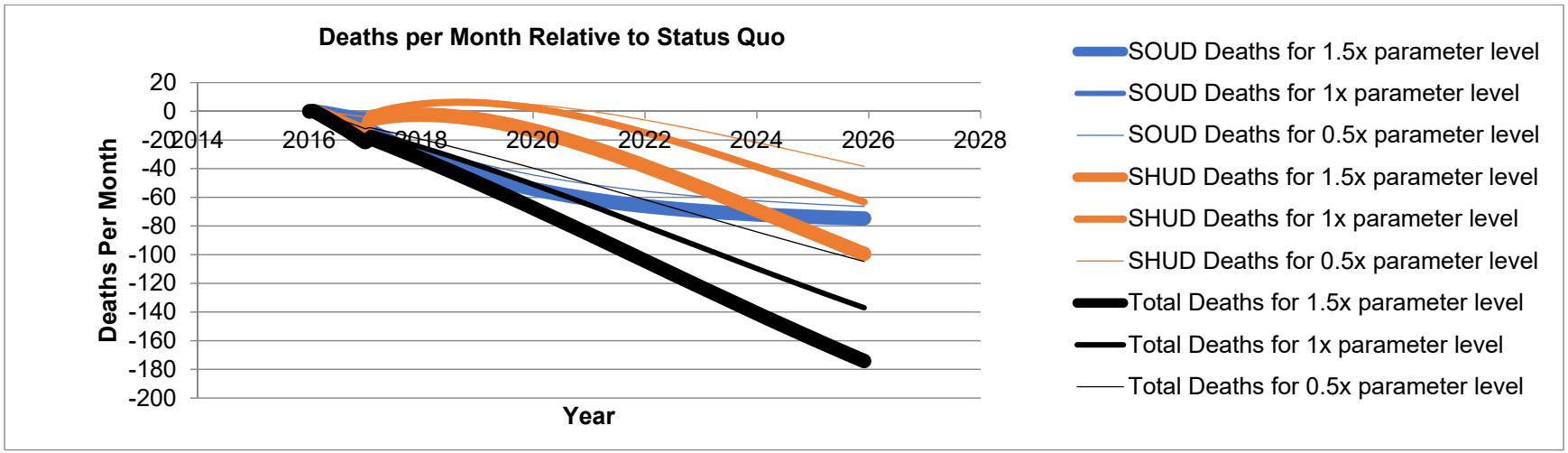
k) Psychosocial interventions



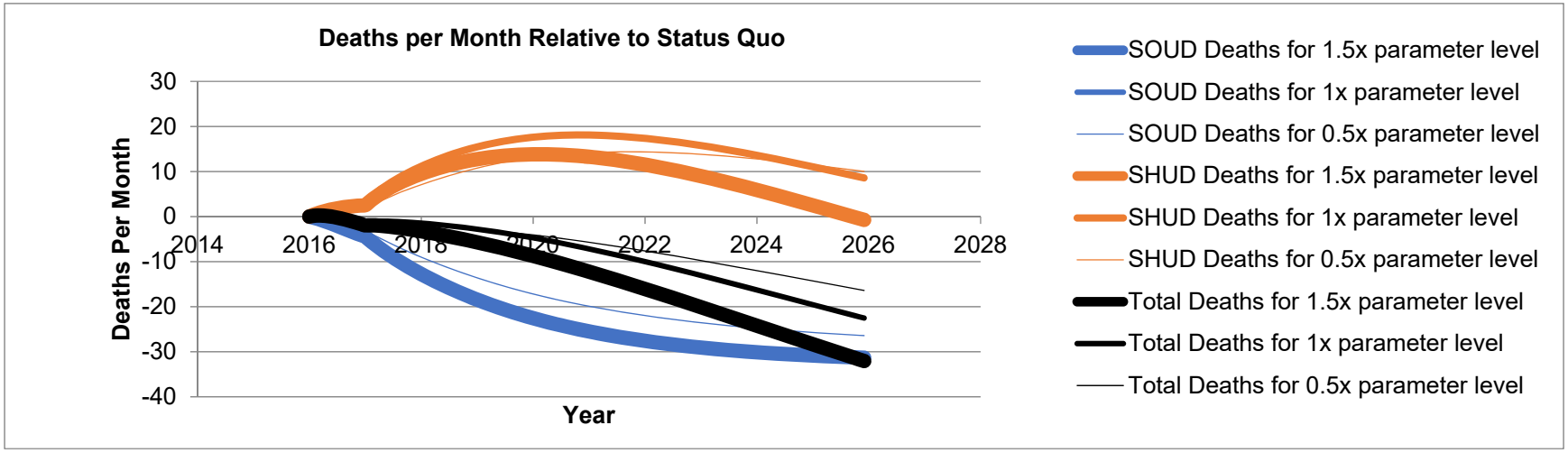
Appendix Figure 17. Sensitivity of policies' effect on addiction-related deaths to various rates of diversion to pain-free nonusers

Mean monthly deaths from SOUD, SHUD, and total addiction-related deaths, relative to without intervention, under each policy, for various rates of diversion to pain-free nonusers: 150% of the base case assumption level, the base case assumption level, and 50% of the base case assumption level. SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

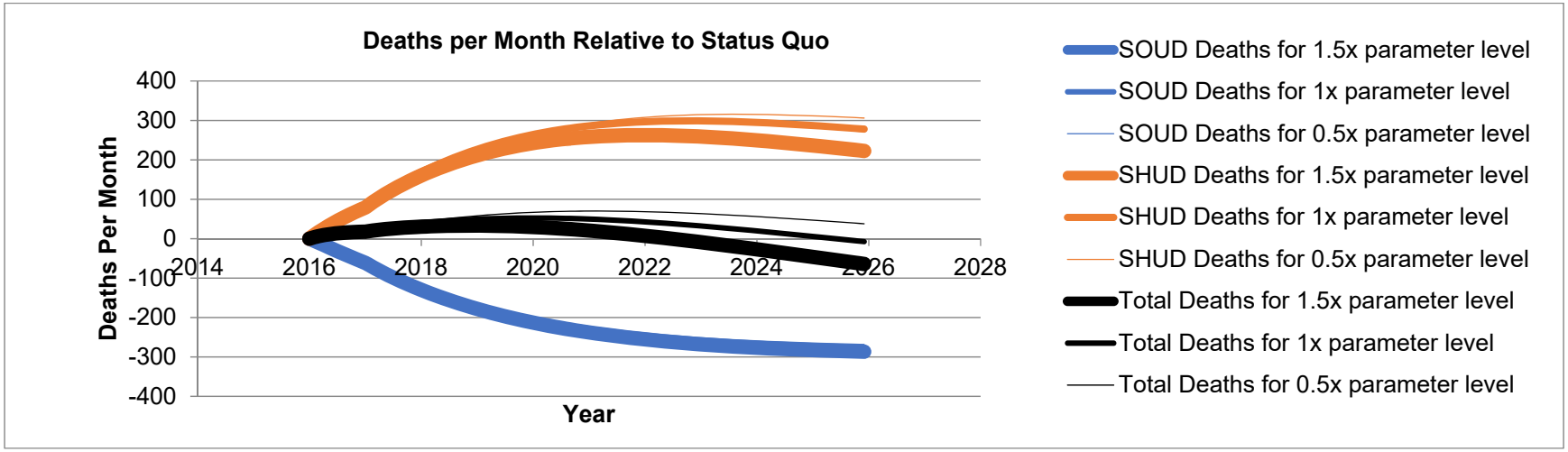
a) Reduced prescribing for acute pain



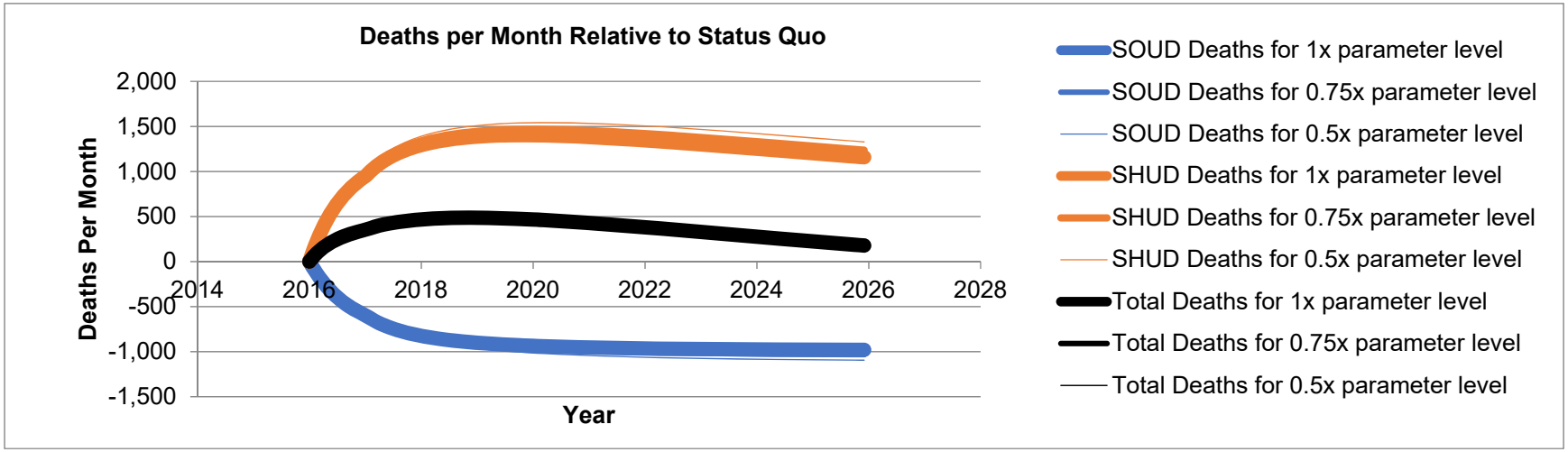
b) Reduced prescribing for transitioning pain



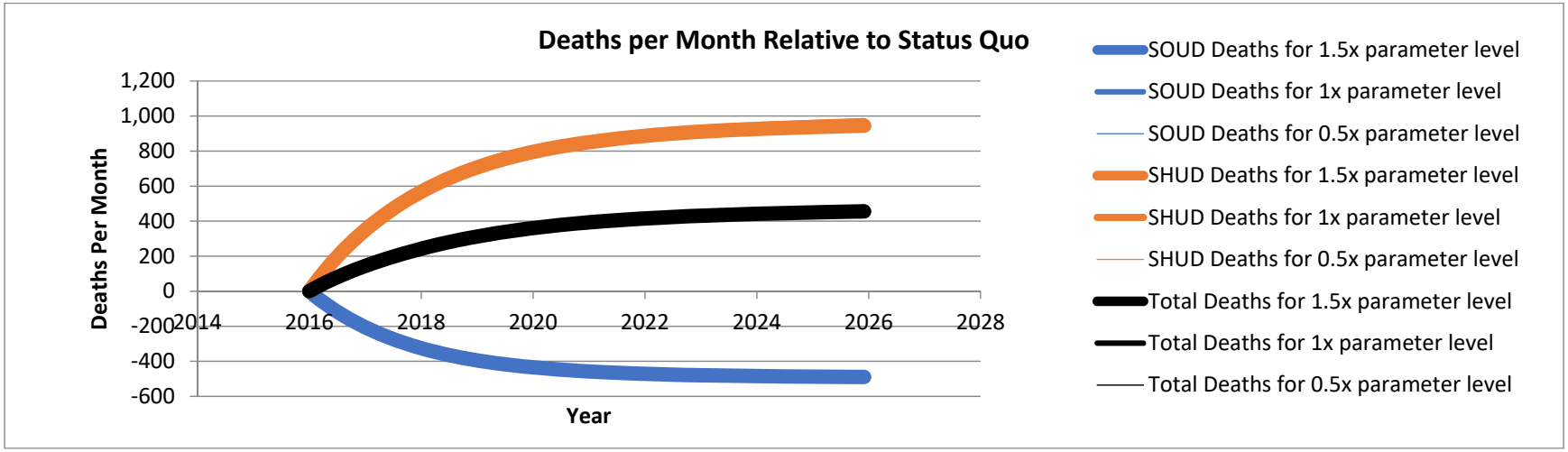
c) Reduced prescribing for chronic pain



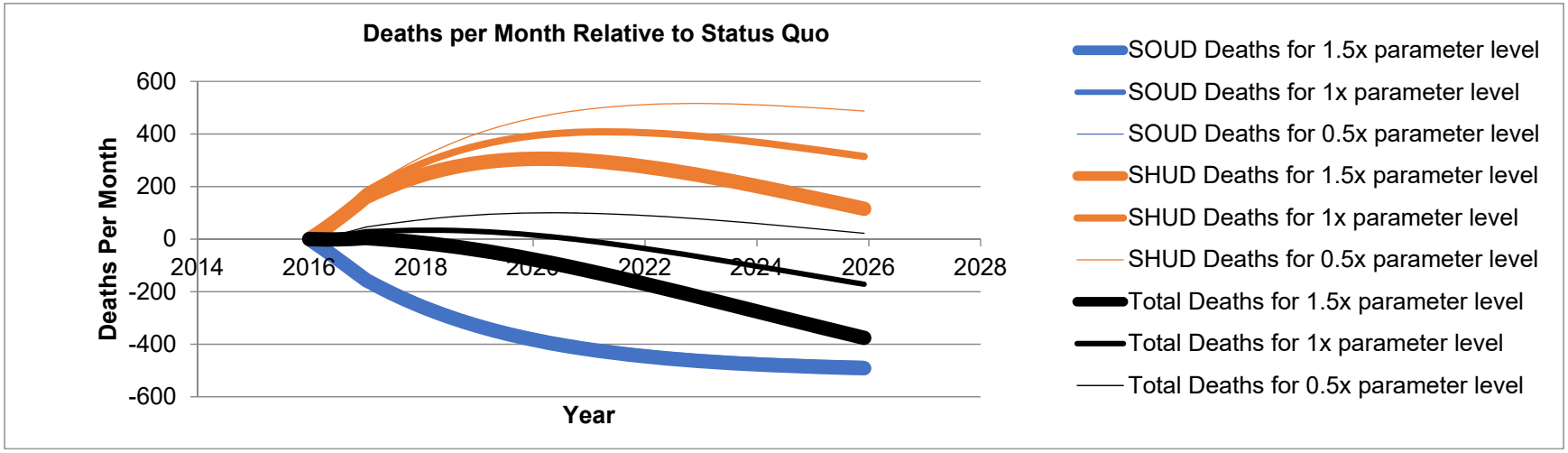
d) Drug rescheduling



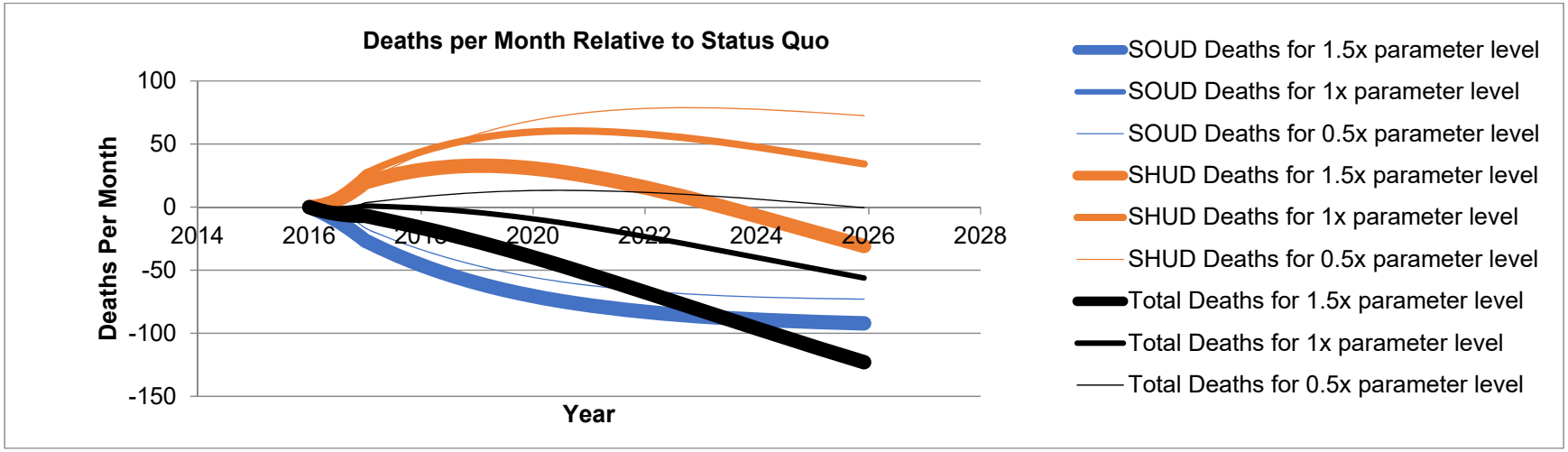
e) Prescription monitoring program



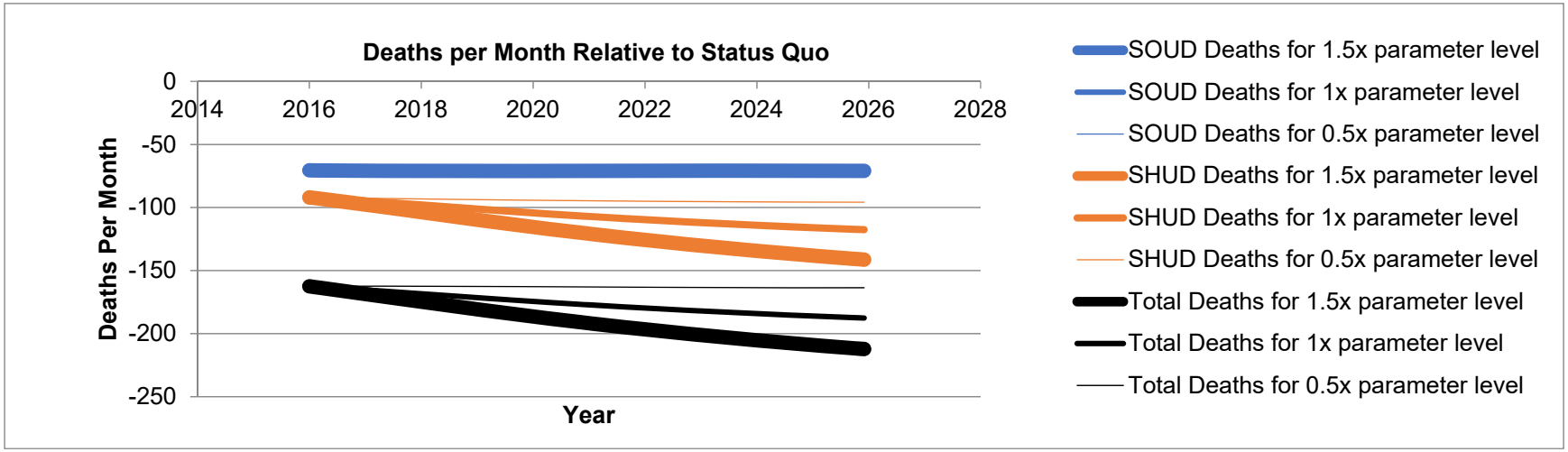
f) Drug reformulation



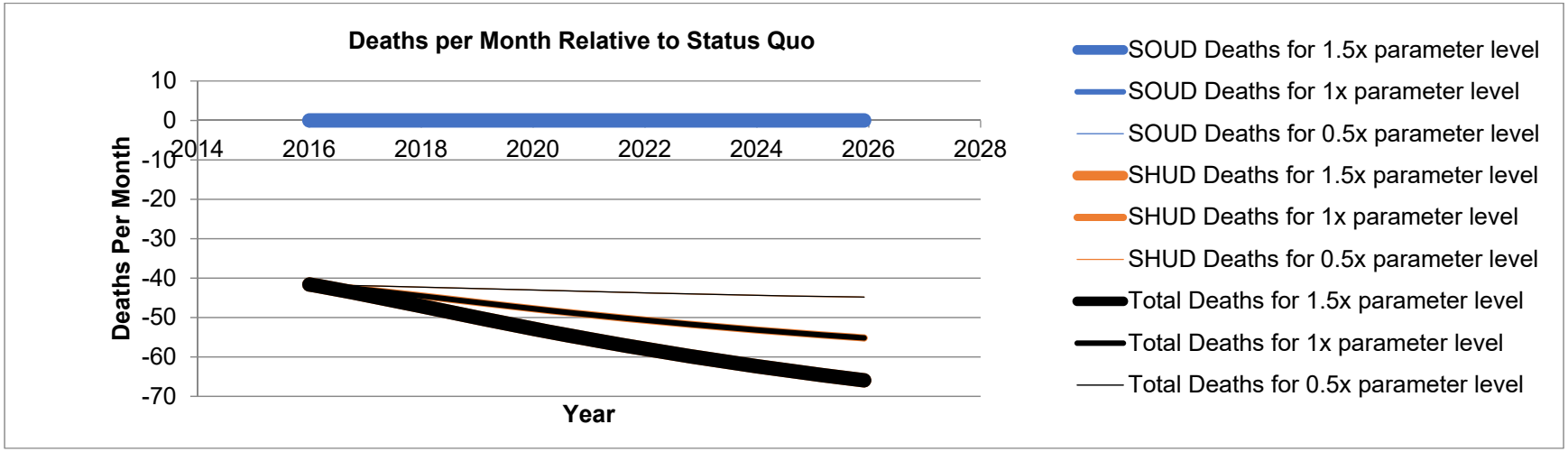
g) Excess opioid disposal



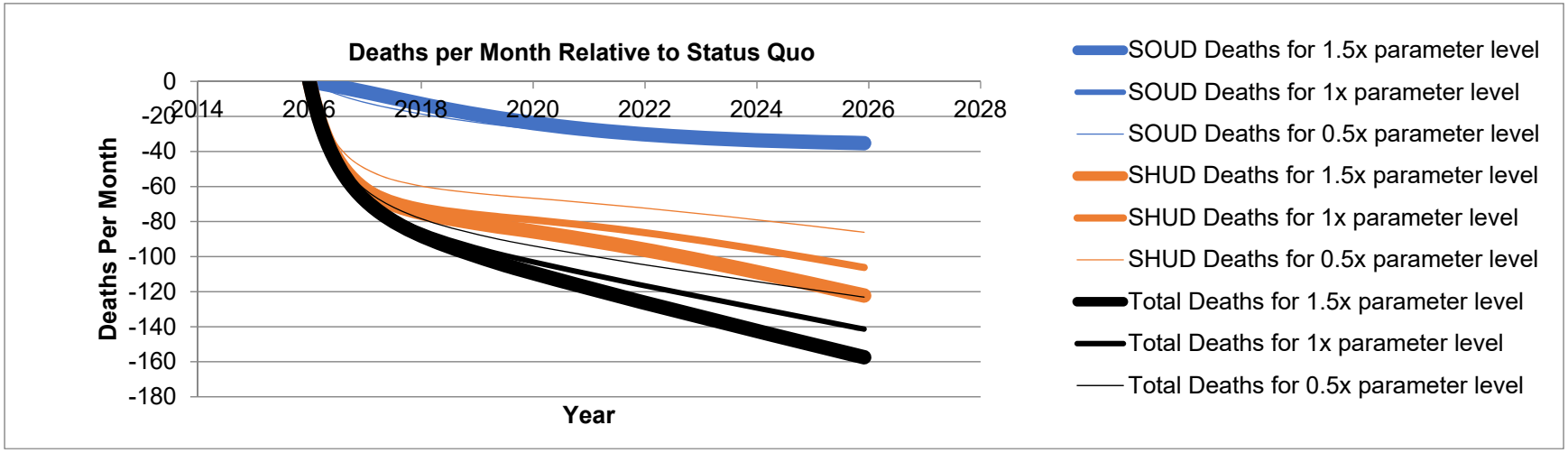
h) Naloxone availability



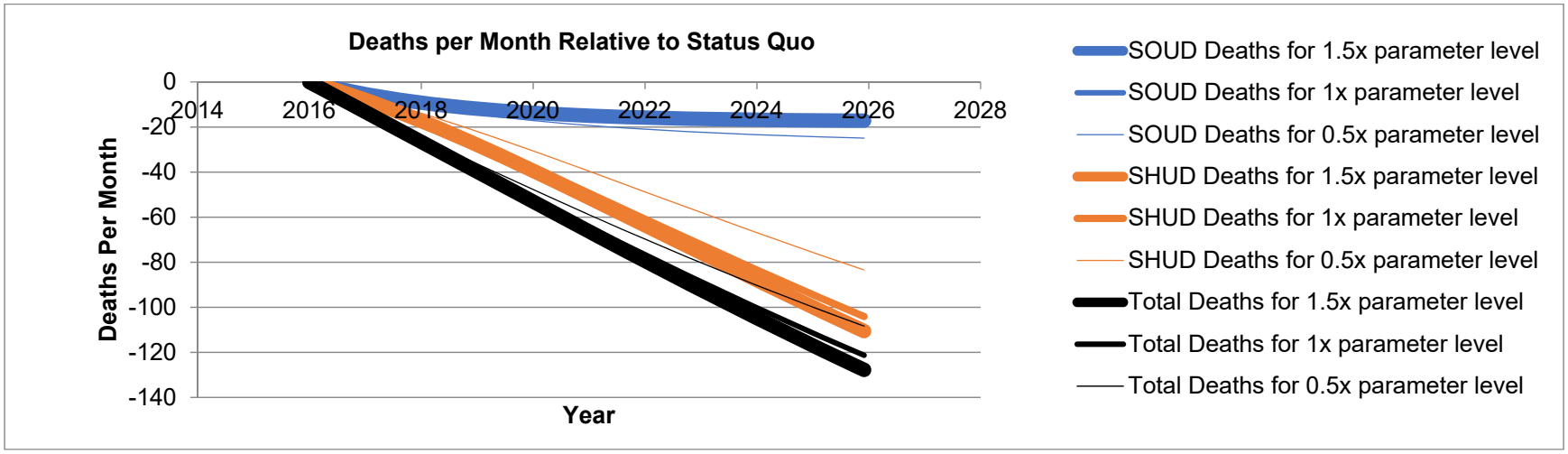
i) Needle exchange



j) Medication-assisted therapy



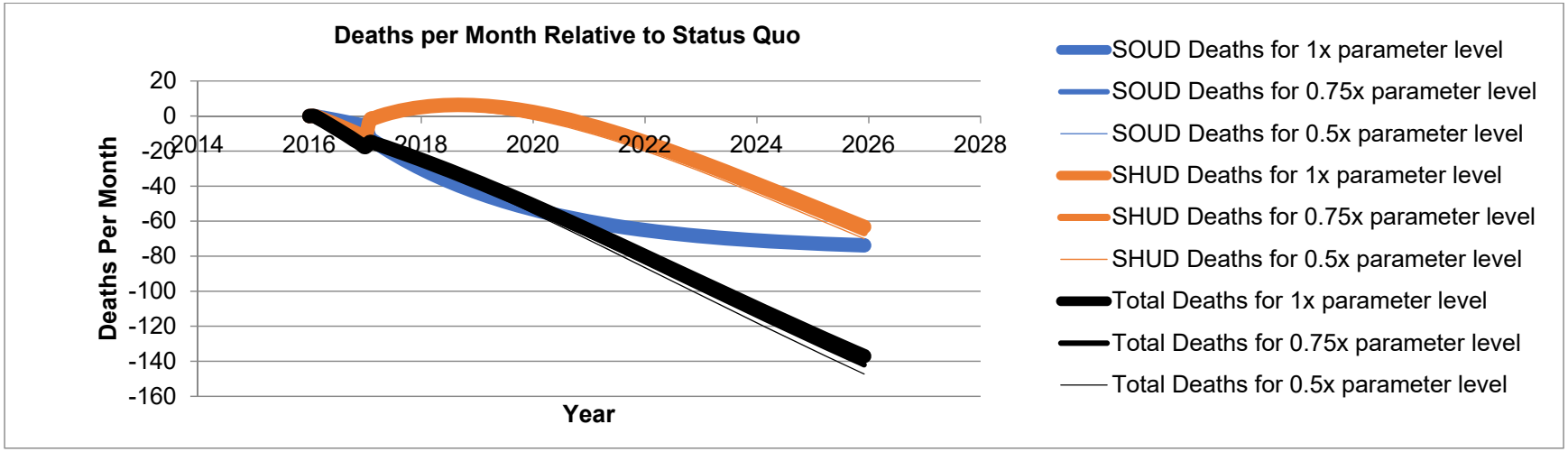
k) Psychosocial interventions



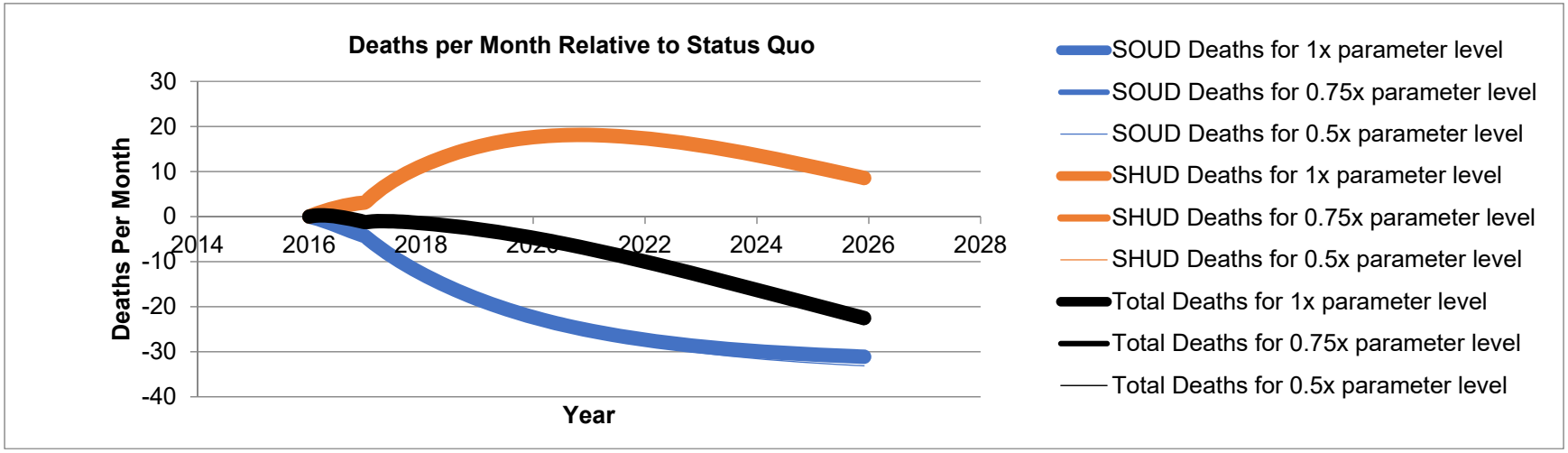
Appendix Figure 18. Sensitivity of policies' effect on addiction-related deaths to various rates of enrollment in MAT

Mean monthly deaths from SOUD, SHUD, and total addiction-related deaths, relative to without intervention, under each policy, for various rates of enrollment in MAT: the base case assumption level, 75% of the base case assumption level, and 50% of the base case assumption level. MAT, medication-assisted treatment; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

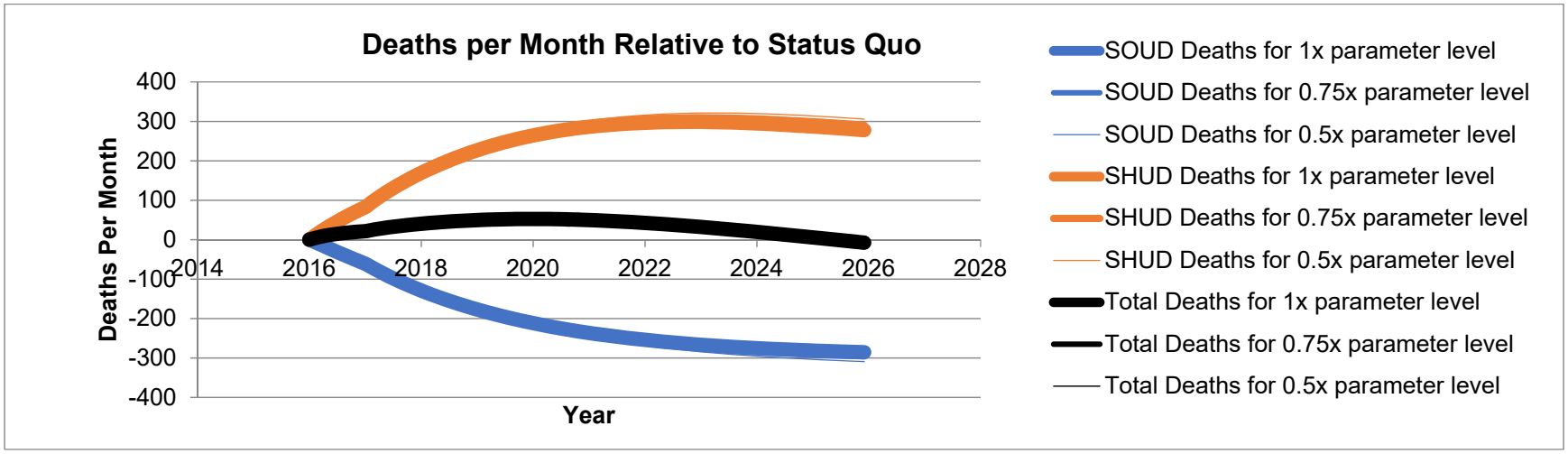
a) Reduced prescribing for acute pain



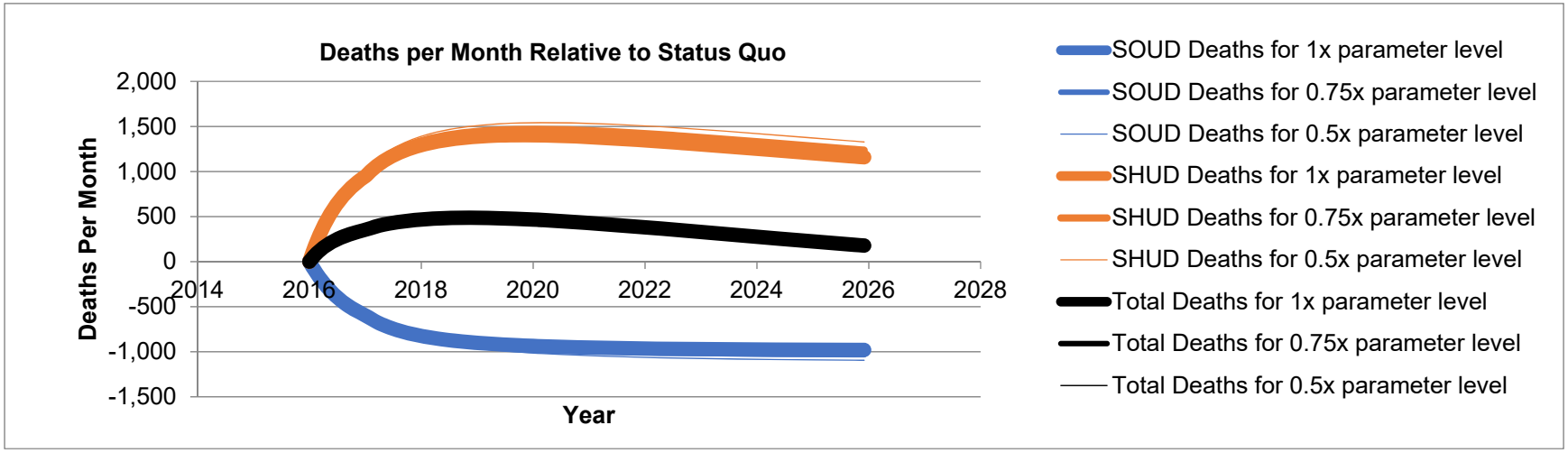
b) Reduced prescribing for transitioning pain



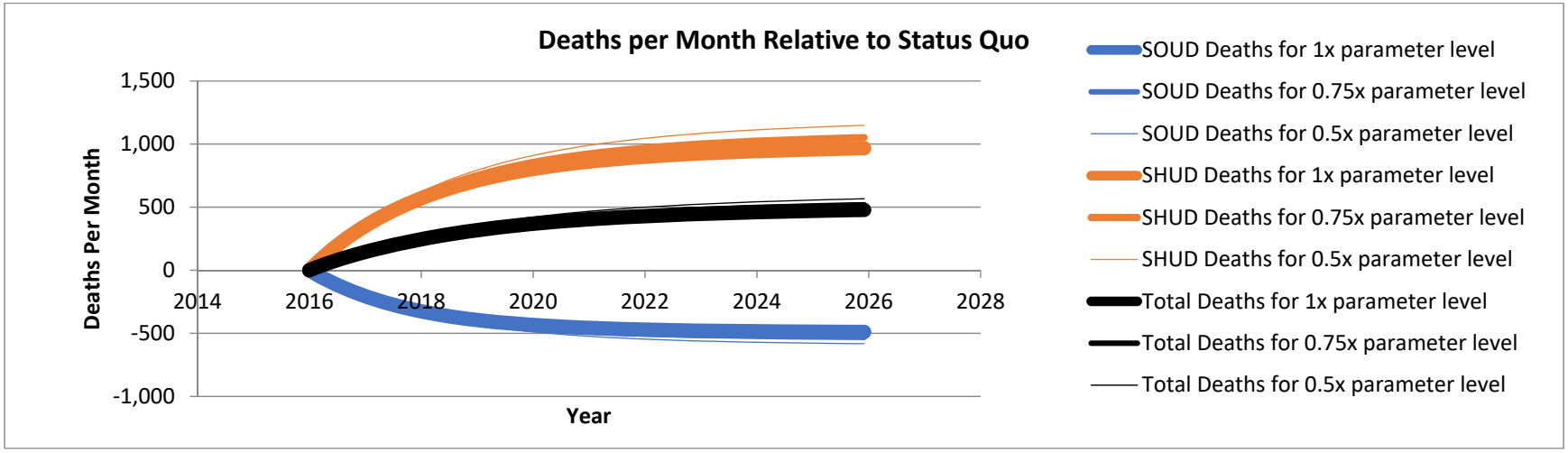
c) Reduced prescribing for chronic pain



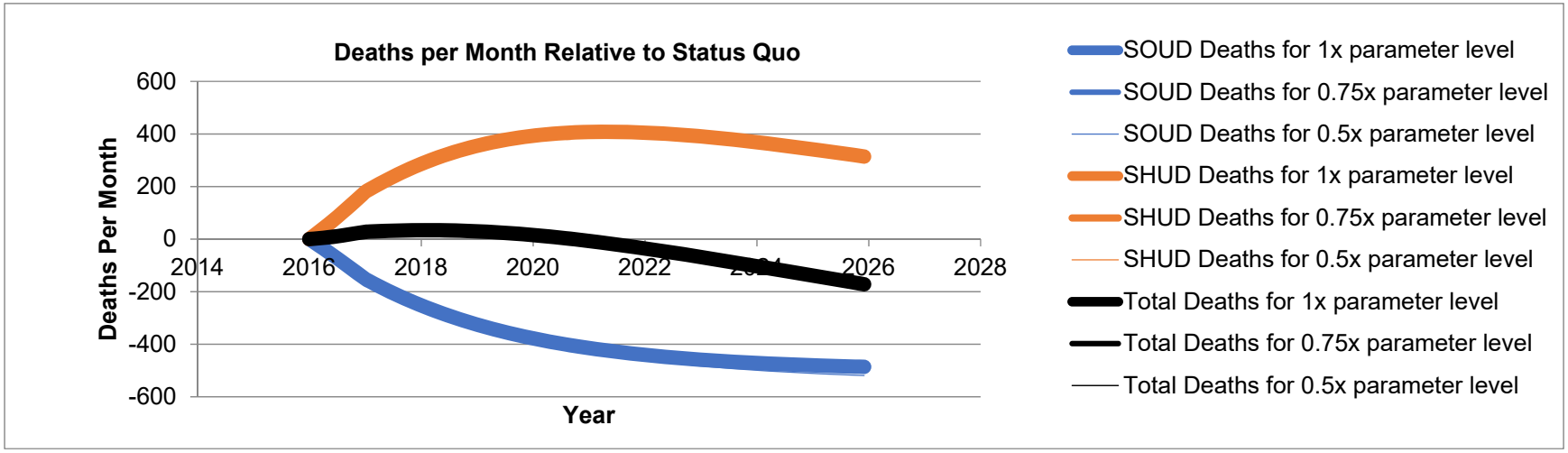
d) Drug rescheduling



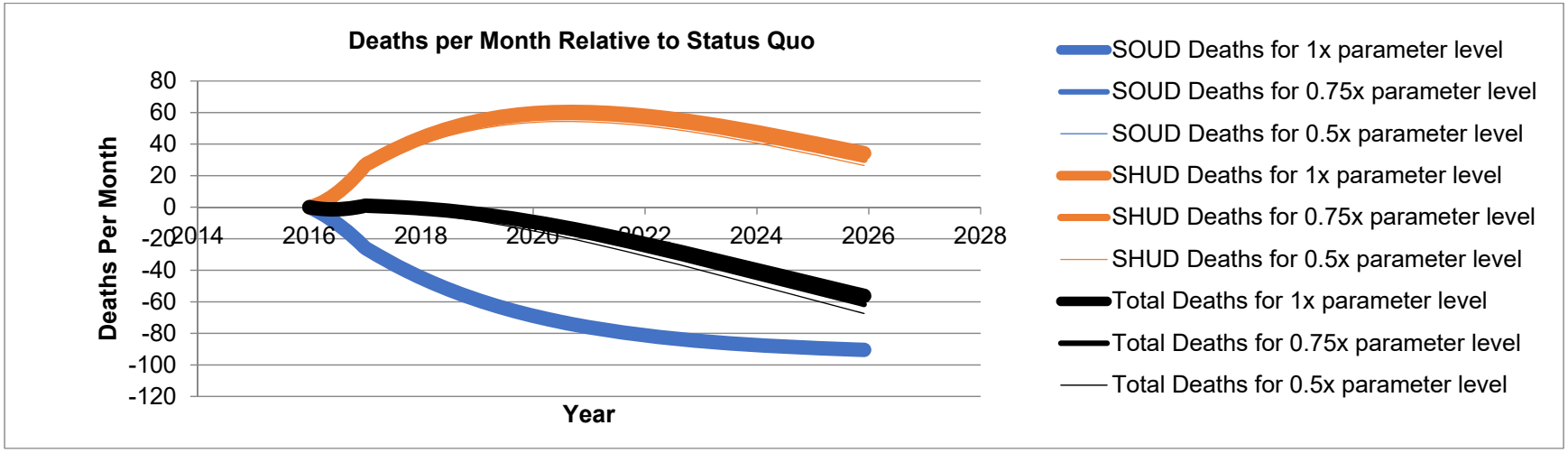
e) Prescription monitoring program



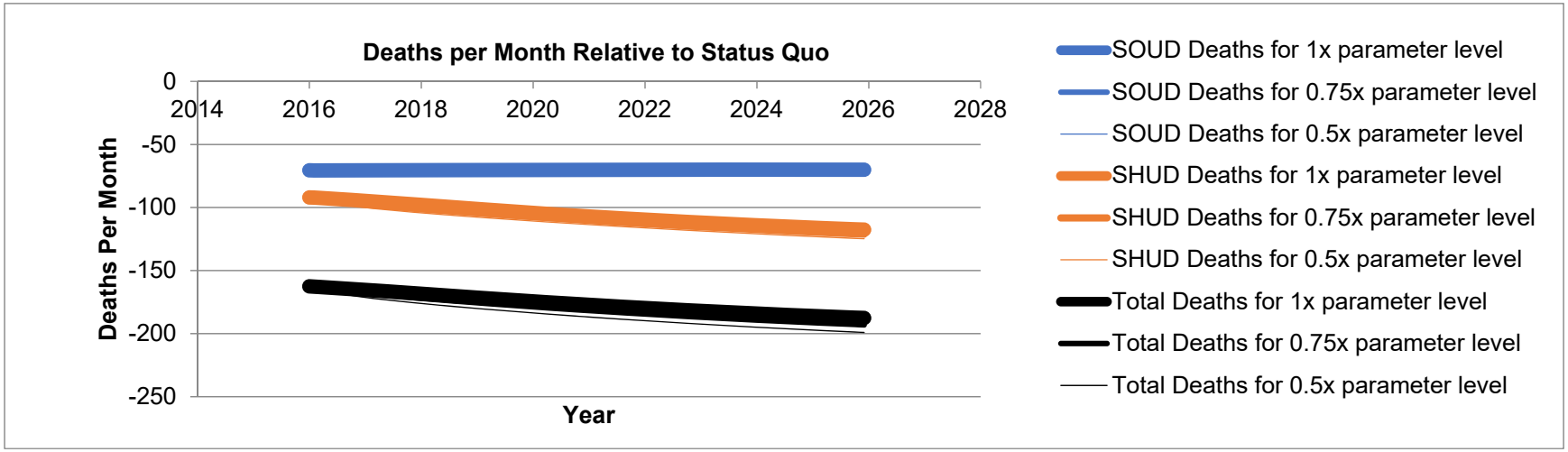
f) Drug reformulation



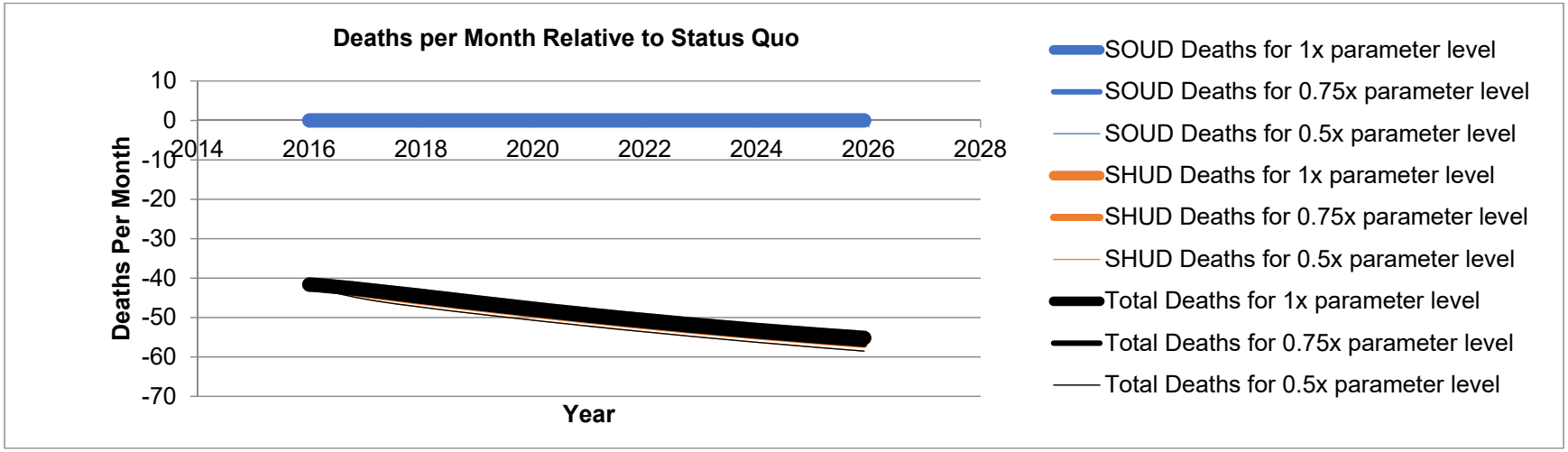
g) Excess opioid disposal



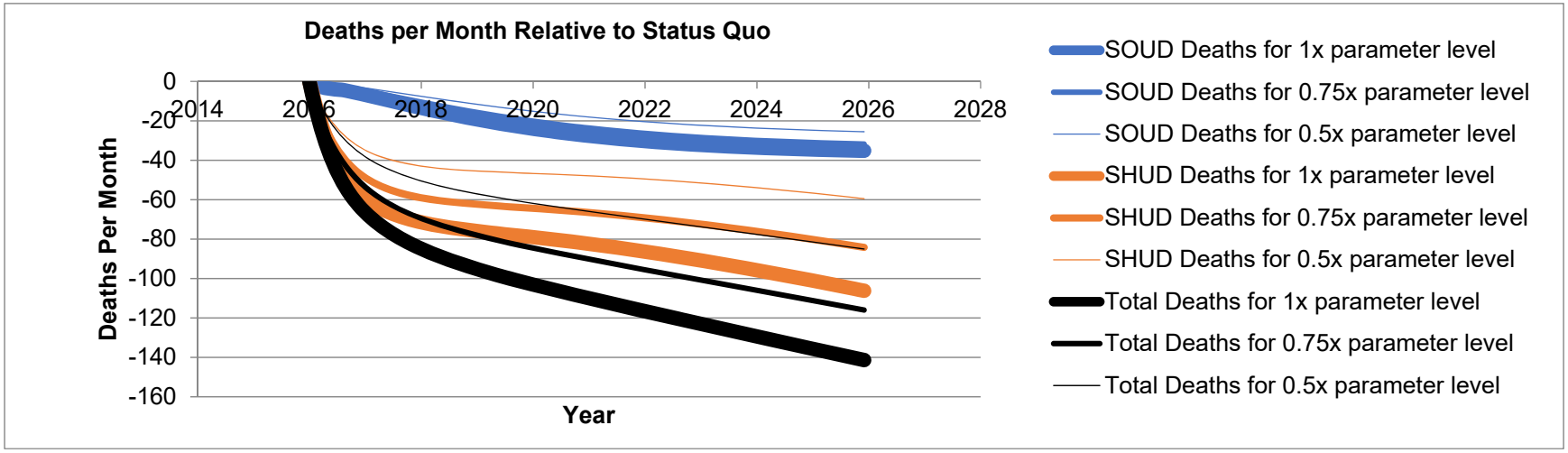
h) Naloxone availability



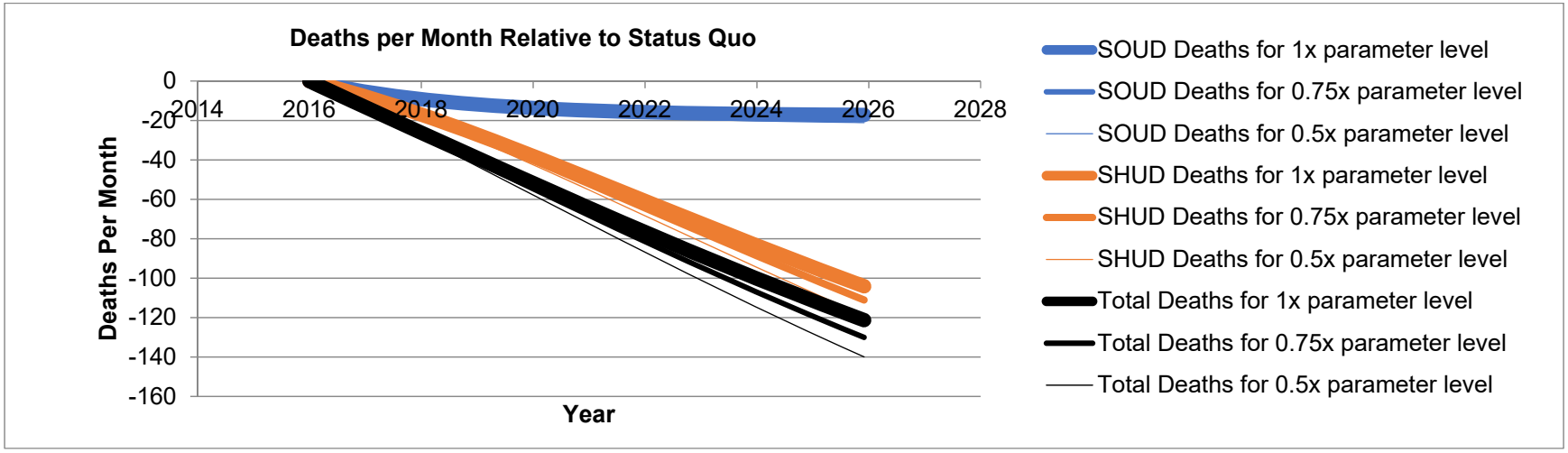
i) Needle exchange



j) Medication-assisted therapy



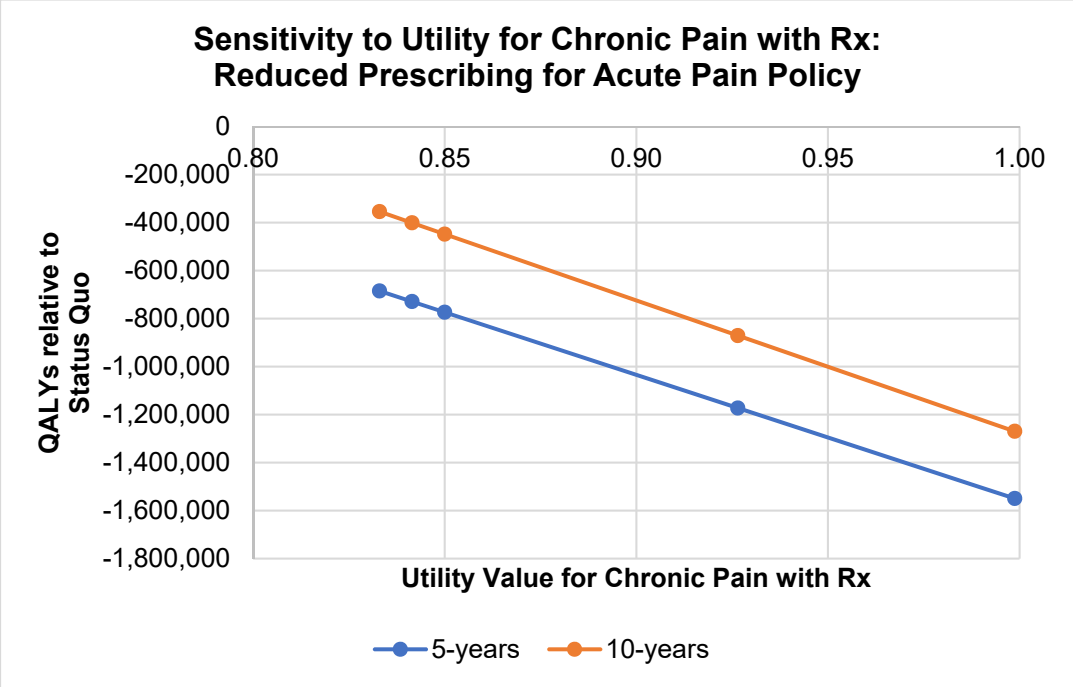
k) Psychosocial interventions



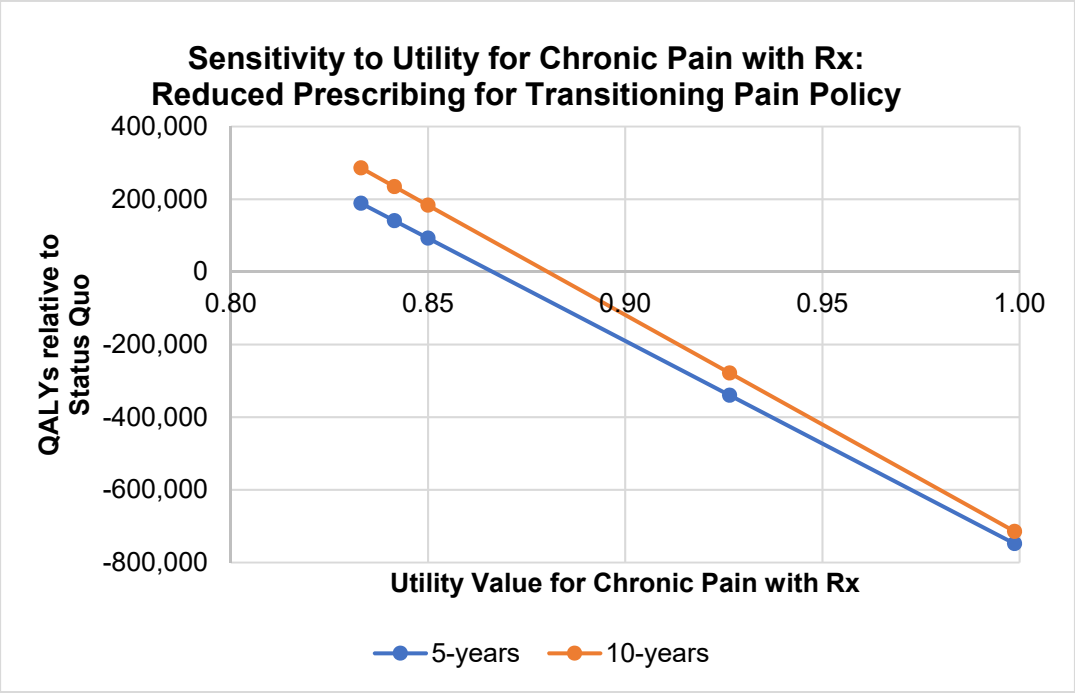
Appendix Figure 19. Sensitivity of policies' effect on QALYs to various utility values for opioid treatment for chronic pain

Mean total QALYs, relative to without intervention, under the given policy, for various utility values for the "chronic pain SOUD with Rx" state: 0.83, 0.84, 0.85, 0.93, 1.00. QALYs, quality-adjusted life years; Rx, prescription; SOUD, severe [prescription] opioid use disorder.

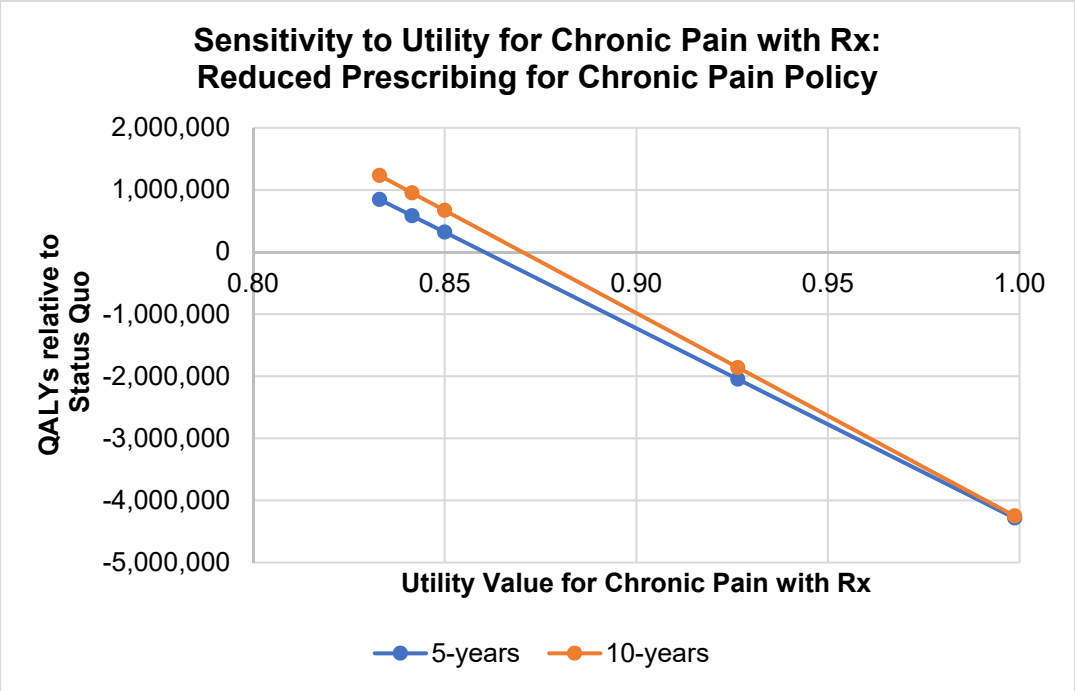
a) Reduced prescribing for acute pain



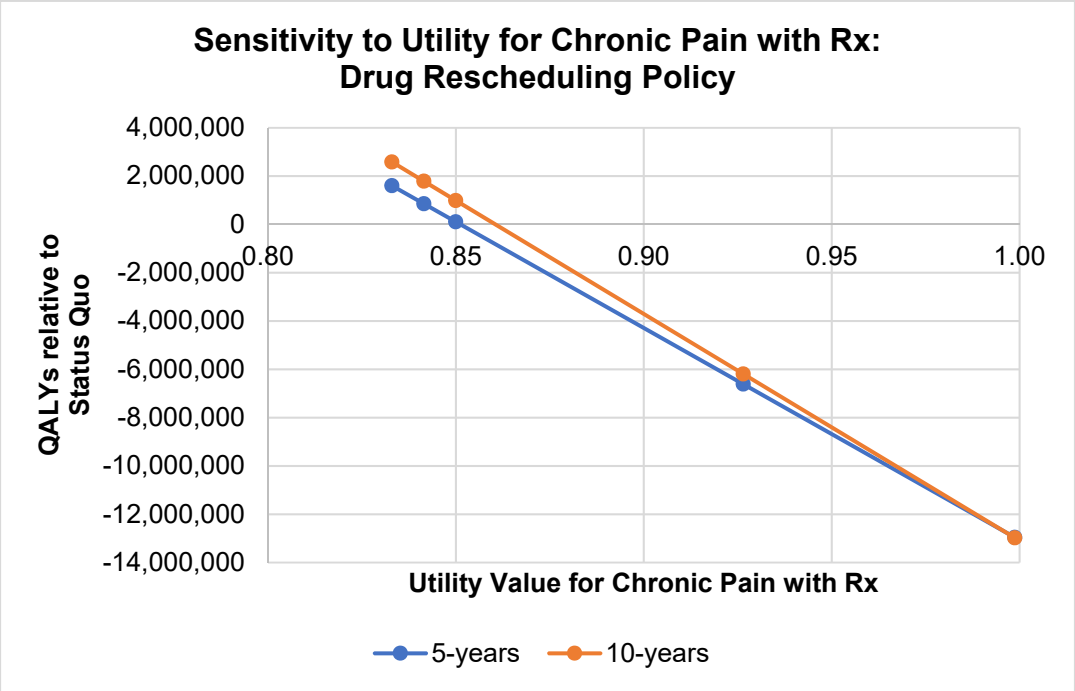
b) Reduced prescribing for transitioning pain



c) Reduced prescribing for chronic pain



d) Drug rescheduling policy



Appendix Table 1. Values and Sources for Model Parameters

Parameter	Value	Source
Demographic data		
Total population size, age 12+	272,772,746	[1]
Chronic pain prevalence (moderate to severe)	8.6%	Calculated[25-28]
Acute pain prevalence (moderate to severe)	2.5%	Calculated[2-7]
Severe opioid use disorder prevalence	0.77%	Assumed [22,23]
Severe heroin use disorder prevalence	0.51%	Calculated[14-17]
Rate of maturation into the population, people/month	216,322	[31]
Pain natural history		
Acute pain incidence for pain-free nonusers, %/month	2.5%	Calculated[2-7]
Chronic pain incidence for pain-free nonusers, %/month	0.3%	Assumed
Chronic pain subsidence, %/month	8%	Assumed[35]
Probability that acute pain persists without opioid prescription	15.0%	Assumed[32]
Probability that acute pain persists with opioid prescription	14.7%	Assumed
Percent of 12+ population with chronic pain of any severity	43%	Calculated[25-27]
Percent of chronic pain population with moderate to severe severity	20%	Assumed[28]
Percent of 12+ population getting surgery	4%	Calculated[2-5]
Percent of surgeries resulting in moderate to severe pain	61%	[7]
Percent of prescription-holding SOUD population who suffer from chronic pain	65%	[13]
Percent of SOUD without Rx and SHUD populations who have with chronic pain	45%	Assumed[29]
Risk ratio for chronic pain developing during acute pain treatment with vs. without opioids	0.98	Assumed
Prescribing behavior		
Percent of acute pain patients prescribed opioids	50%	Assumed[8-10]
Probability of continued use of opioids for pain that persists from acute	50%	Assumed[8]
Percent of total population prescribed opioids for chronic pain	6%	Calculated[11]
Probability of chronic pain sufferer being prescribed opioids, %/month	13%	Assumed
Probability of SOUD individual being prescribed opioids, %/month	13%	Assumed
Probability of opioid renewal for non-addicted chronic pain patients, %/month	98%	Assumed
Probability of opioid renewal for individuals SOUD, %/month	98%	Assumed
Estimated annual decline in opioid prescriptions from 2013-2015	4.6%	[36]
Probability of iatrogenically addicted continuing use of opioids after acute pain treatment	50%	Assumed
Probability that chronic pain opioid user w/o SOUD wants to get prescription renewed, %/month	99%	Assumed
Probability that an opioid user is able to get renewal for chronic pain prescription if they choose, %/month	99%	Assumed

Parameter	Value	Source
Addiction		
Probability of iatrogenic addiction during opioid treatment, %/month	0.13%	[40]
Probability of a non-medical user becoming addicted to diverted pills, %/month	7%	Calculated[21,41]
Baseline[a] rate of escalation to SHUD from SOUD without Rx, %/month	4%	Assumed
Probability of escalation to SHUD if there are not diverted pills for SOUD without Rx	60%	Expert opinion
SOUD prevalence among population with opioid prescription for chronic pain	10%	[12]
Percent of SHUD population who escalated from SOUD	80%	[16,17]
Number of pain-free nonusers a prescription holder diverts opioids to, #/month	0.01	Assumed
Proportionality factory relating SOUD without Rx population able to be sustained by diverted pills to lagged number of prescription holders	0.01	Calculated
Treatment and desistance		
Percent of SOUD population enrolled in MAT	15%	Expert opinion
Percent of SHUD population enrolled in MAT	20%	Expert opinion
Rate of SOUD with Rx enrollment in MAT, %/month	1%	Assumed
Rate of SOUD without Rx enrollment in MAT, %/month	4%	Assumed
Rate of SHUD enrollment in MAT, %/month	4%	Assumed[50]
Rate of drop out from MAT for SOUD, %/month	5%	Assumed
Rate of drop out from MAT for SHUD, %/month	14%	Calculated[51]
Rate of desistance from SOUD in MAT, %/month	1%	Assumed[29]
Baseline* rate of desistance from SOUD without MAT, %/month	0.5%	Assumed[24,29]
Rate of desistance from SHUD in MAT, %/month	0.5%	Assumed
Rate of desistance from SHUD not in MAT, %/month	0.25%	Assumed
Probability of enrollment in MAT if there are not diverted pills for SOUD without Rx	30%	Expert opinion
Probability of desistance if there are not diverted pills for SOUD without Rx	10%	Expert opinion
Mortality		
Mortality rate for the general population, %/month	0.07%	[53]
Mortality rate for SOUD not in MAT %/month	0.14%	Assumed
Mortality rate for SHUD not in MAT %/month	0.24%	Calculated[15,23,54]
Mortality rate for SOUD in MAT %/month	0.10%	Assumed[24]
Mortality rate for SHUD in MAT %/month	0.15%	[24]
Overdose mortality for person with SHUD, not in MAT, %/month	0.14%	Calculated[15,23]
Overdose mortality for person with SOUD, not in MAT, %/month	0.07%	Assumed
Infection-related mortality for person with SHUD, not in MAT, %/month	0.03%	Calculated[54]
1-month relative risk of addiction-related mortality in vs. out of MAT for person with severe use disorder	0.50	[24]

Parameter	Value	Source
Utility values		
Pain-free nonuser	1	Assumed
Chronic pain nonuser	0.85	Assumed
Acute pain nonuser	0.88	Calculated[7,56]
Acute pain with Rx	0.94	Calculated[7,56]
Chronic pain with Rx	0.85	Assumed
SOUD not in MAT	0.83	Assumed
SOUD in MAT	0.92	Assumed
SHUD not in MAT	0.80	[63-65]
SHUD in MAT	0.90	[63,65]
Dead	0	Assumed

Abbreviations: MAT = medication-assisted treatment; SHUD = severe heroin use disorder; SOUD = severe opioid use disorder

[a] Baseline indicates the rate of transition if the prescription opioid supply is unconstrained.

Appendix Table 2. Interventions and Assumed Magnitude

Intervention	Assumed Magnitude
Reduced Prescribing for Acute Pain	25% reduction in incidence of prescribing opioids for acute pain
Reduced Prescribing for Transitioning Pain	25% reduction in incidence of prescribing opioids for acute pain that transitions to chronic
Reduced Prescribing for Chronic Pain	25% reduction in incidence of prescribing opioids for chronic pain
Drug Rescheduling	10% reduction in chance of getting prescription renewed
Prescription Monitoring Program (PMP)	2.5% reduction in SOUD individual's ability to get prescription renewed 1% reduction in the relative likelihood of an SOUD individual's ability to get a new opioid prescription, compared to that of a non-SOUD chronic pain sufferer 1% reduction in incidence of prescribing opioids for acute pain, transitioning pain, and chronic pain
Drug Reformulation	10% reduction in iatrogenic addiction 30% reduction in chance of addiction via diversion for pain-free non-users 30% reduction in pill-seeking for SOUD w/o Rx
Excess Opioid Disposal	10% reduction in diversion to pain-free non-users 10% reduction in number of SOUD without Rx able to be sustained by non-SOUD Rx holders
Naloxone Availability	5% reduction in overdose mortality
Needle Exchange	10% reduction in infection mortality
Medication-Assisted Treatment (MAT)	25% increased likelihood of entering MAT
Psychosocial Treatment	10% increased likelihood of desistance

Abbreviations: SHUD = severe heroin use disorder; SOUD = severe [prescription] opioid use disorder

Appendix Table 3. Base Case Descriptions

Set	Parameter Set Brief Description	Detail
1	Reference case	Values as described in Appendix Table 1
2	Increased chance of heroin death	25% more likely for SHUD to have overdose or infection death
3	Increased chance of prescription opioid death	25% more likely for SOUD to have overdose death
4	Reduced probability of turning to heroin if there are not enough pills to divert	50% lower chance of opioid addict without access to prescription turning to heroin; 2x chance of enrolling in MAT
5	Reduced MAT effectiveness	No mortality benefit from MAT and chance of recovery in MAT is reduced by half
6	Reduced relative successfulness in getting prescription for SOUD	25% less likely for SOUD without Rx to get prescribed opioids, compared to chronic pain nonuser
7	Increased chance of iatrogenic addiction	Likelihood of iatrogenic addiction is 50% higher
8	Reduced chance of recovery without MAT	Halved chance of recovery without MAT
9	Decreased chance of escalating from SOUD to SHUD regardless of pill supply	75% less likely to escalate to heroin usage regardless of pill supply
10	Increased likelihood of diverting opioid prescription to pain-free nonuser	2x as likely for a prescription holder to divert pills to a pain-free nonuser

MAT, medication-assisted treatment; Rx, prescription; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

Appendix Table 4. Base Case Five-Year Outcomes Under the Status Quo

Set	Parameter Set Brief Description	Discounted Net Present LYs* (Thousands)	Discounted Net Present QALYs* (Thousands)	Addiction Deaths	Rx Pill Addiction Deaths	Heroin Addiction Deaths
1	Reference case	11,236,024	11,056,474	226,592	81,775	144,818
2	Increased chance of heroin death	11,231,795	11,053,007	260,993	81,775	179,218
3	Increased chance of prescription opioid death	11,232,984	11,053,898	246,525	101,947	144,578
4	Reduced probability of turning to heroin if there aren't enough pills to divert	11,236,603	11,057,189	224,434	82,273	142,161
5	Reduced MAT effectiveness	11,231,020	11,051,452	255,041	91,315	163,726
6	Reduced relative successfulness in getting prescription for SOUD	11,235,012	11,055,742	231,475	75,980	155,495
7	Increased chance of iatrogenic addiction	11,232,376	11,051,234	239,216	88,502	150,713
8	Reduced chance of recovery without MAT	11,233,190	11,052,531	236,689	84,745	151,944
9	Decreased chance of escalating from SOUD to SHUD regardless of pill supply	11,237,255	11,058,031	221,349	82,510	138,839
10	Increased likelihood of diverting opioid prescription to pain-free nonuser	11,230,643	11,049,168	246,800	82,771	164,029
Mean		11,233,690	11,053,873	238,911	85,359	153,552

LYs, life years; MAT, medication-assisted treatment; QALYs, quality-adjusted life years; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

[a] Discounted to 2016.

Appendix Table 5. Base Case Ten-Year Outcomes Under the Status Quo

Set	Parameter Set Brief Description	Discounted Net Present LYs* (Thousands)	Discounted Net Present QALYs* (Thousands)	Addiction Deaths	Rx Pill Addiction Deaths	Heroin Addiction Deaths
1	Reference case	12,389,435	12,189,886	479,991	163,324	316,668
2	Increased chance of heroin death	12,383,565	12,185,024	552,146	163,322	388,824
3	Increased chance of prescription opioid death	12,385,735	12,186,716	518,849	203,412	315,438
4	Reduced probability of turning to heroin if there aren't enough pills to divert	12,390,613	12,191,349	471,639	164,935	306,704
5	Reduced MAT effectiveness	12,381,485	12,181,556	549,968	183,910	366,058
6	Reduced relative successfulness in getting prescription for SOUD	12,387,694	12,188,429	495,240	147,177	348,063
7	Increased chance of iatrogenic addiction	12,381,525	12,178,869	530,422	181,841	348,581
8	Reduced chance of recovery without MAT	12,383,140	12,181,355	520,390	171,517	348,873
9	Decreased chance of escalating from SOUD to SHUD regardless of pill supply	12,391,718	12,192,778	462,926	165,188	297,737
10	Increased likelihood of diverting opioid prescription to pain-free nonuser	12,378,303	12,175,155	555,829	165,732	390,097
Mean		12,385,321	12,185,112	513,740	171,036	342,704

LYs, life years; MAT, medication-assisted treatment; QALYs, quality-adjusted life years; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

[a] Discounted to 2016.

Appendix Table 6. Outcomes of Individual Interventions over 5 Years

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
Acute Pain Prescribing	587 *[452, 804]*	-1,244 *[-1,417, -935]*	-1,964 *[-2,370, -1,687]*	70 *[-738, 496]*	-1,894 *[-2,689, -1,429]*
Prescribing for Transitioning Pain	83 *[36, 137]*	194 *[145, 267]*	-837 *[-1,041, -731]*	684 *[334, 908]*	-153 *[-397, 76]*
Chronic Pain Prescribing	-168 *[-783, 533]*	619 *[41, 1,484]*	-8,312 *[-10,331, -6,619]*	10,626 *[6,214, 13,865]*	2,314 *[-1,163, 5,579]*
Drug Rescheduling	-2,845 *[-5,564, 563]*	-70 *[-2,604, 4,089]*	-45,509 *[-55,636, -39,538]*	70,020 *[41,851, 87,917]*	24,511 *[2,313, 43,238]*
PMP	-2,858 *[-4,272, -829]*	-2,054 *[-3,320, 409]*	-19,081 *[-23,413, -16,327]*	34,410 *[20,708, 42,821]*	15,329 *[4,380, 24,001]*
Drug Reformulation	463 *[-609, 1,735]*	2,151 *[1,096, 3,922]*	-15,637 *[-19,384, -12,752]*	16,893 *[8,369, 22,650]*	1,256 *[-5,372, 7,107]*
Excess Opioid Disposal	203 *[3, 656]*	563 *[311, 1,191]*	-2,794 *[-3,468, -2,334]*	2,539 *[922, 3,561]*	-255 *[-1,952, 782]*
Naloxone Availability	1,442 *[1,337, 1,542]*	1,200 *[1,113, 1,281]*	-4,223 *[-5,033, -3,761]*	-5,963 *[-6,900, -5,395]*	-10,186 *[-10,947, -9,479]*
Needle Exchange	355 *[315, 406]*	291 *[258, 332]*	0 *[0, 0]*	-2,718 *[-3,144, -2,460]*	-2,718 *[-3,144, -2,460]*
MAT	907 *[83, 1,109]*	1,364 *[546, 1,625]*	-925 *[-1,313, 453]*	-4,000 *[-5,054, -1,066]*	-4,925 *[-6,109, -612]*
Psychosocial Interventions	530 *[293, 609]*	731 *[408, 815]*	-570 *[-711, -306]*	-1,348 *[-1,708, -729]*	-1,918 *[-2,279, -1,035]*

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years.

[a] Discounted to 2016.

Appendix Table 7. Outcomes of Combined Interventions over 5 Years

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
Drug Rescheduling + Naloxone Availability	-1,445 *[-4,102, 1,794]*	1,088 *[-1,396, 5,112]*	-47,490 *[-57,937, -41,661]*	61,306 *[34,660, 77,588]*	13,816 *[-7,000, 31,064]*
Drug Rescheduling + Needle Exchange	-2,322 *[-5,005, 996]*	359 *[-2,145, 4,444]*	-45,509 *[-55,635, -39,538]*	66,059 *[38,587, 83,222]*	20,550 *[-951, 38,544]*
Drug Rescheduling + MAT	-1,786 *[-4,253, 1,445]*	1,331 *[-1,284, 5,243]*	-45,018 *[-55,112, -39,293]*	63,434 *[36,545, 79,393]*	18,416 *[-2,747, 35,134]*
Drug Rescheduling + Psychosocial Interventions	-2,398 *[-5,028, 936]*	510 *[-1,940, 4,582]*	-45,608 *[-55,751, -39,675]*	68,377 *[40,549, 85,819]*	22,769 *[874, 41,048]*
PMP + Naloxone Availability	-1,390 *[-2,773, 507]*	-835 *[-2,077, 1,522]*	-22,367 *[-27,302, -19,595]*	27,098 *[14,350, 34,253]*	4,730 *[-5,245, 12,310]*
PMP + Needle Exchange	-2,404 *[-3,793, -440]*	-1,682 *[-2,927, 728]*	-19,081 *[-23,413, -16,327]*	31,079 *[17,818, 38,918]*	11,998 *[1,491, 20,098]*
PMP + MAT	-1,787 *[-3,519, 98]*	-585 *[-2,361, 1,676]*	-19,126 *[-23,587, -16,632]*	28,687 *[15,968, 35,863]*	9,561 *[-665, 18,865]*
PMP + Psychosocial Interventions	-2,346 *[-3,668, -390]*	-1,374 *[-2,552, 1,006]*	-19,404 *[-23,810, -16,701]*	32,825 *[19,444, 40,802]*	13,421 *[2,743, 21,664]*
All Prescribing (Acute, Transitioning, Chronic)	571 *[-143, 1,292]*	-385 *[-1,089, 498]*	-10,790 *[-13,294, -8,800]*	10,794 *[5,991, 14,355]*	4 *[-3,644, 3,694]*
All Prescribing + Naloxone Availability	1,957 *[1,261, 2,578]*	766 *[77, 1,586]*	-14,478 *[-17,670, -12,125]*	4,402 *[208, 6,888]*	-10,076 *[-13,019, -7,292]*
All Prescribing + Needle Exchange	958 *[264, 1,635]*	-68 *[-756, 779]*	-10,790 *[-13,294, -8,800]*	7,884 *[3,364, 10,955]*	-2,906 *[-6,270, 295]*
All Prescribing + MAT	1,457 *[216, 2,146]*	923 *[-372, 1,853]*	-11,564 *[-14,365, -9,580]*	6,642 *[2,214, 11,691]*	-4,922 *[-8,358, 1,519]*

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
All Prescribing + Psychosocial Interventions	1,071 *[435, 1,738]*	298 *[-331, 1,123]*	-11,293 *[-13,919, -9,272]*	9,452 *[4,880, 12,652]*	-1,842 *[-5,302, 1,488]*
All Prescribing + Reformulation + MAT + Needle + Naloxone + Psychosocial	4,298 *[2,896, 6,141]*	4,893 *[3,359, 7,420]*	-26,486 *[-32,582, -22,245]*	6,876 *[-2,167, 13,342]*	-19,610 *[-26,370, -12,403]*

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years.

[a] Discounted to 2016.

Appendix Table 8. Outcomes of Individual Interventions over 10 Years

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
Acute Pain Prescribing	1,347 *[1,058, 1,806]*	-411 *[-775, 222]*	-6,096 *[-7,318, -5,086]*	-1,889 *[-5,064, -89]*	-7,985 *[-11,064, -6,051]*
Prescribing for Transitioning Pain	232 *[161, 351]*	425 *[333, 583]*	-2,575 *[-3,137, -2,253]*	1,544 *[656, 2,055]*	-1,031 *[-1,824, -394]*
Chronic Pain Prescribing	235 *[-680, 1,054]*	1,488 *[584, 2,504]*	-24,367 *[-29,954, -19,095]*	28,172 *[17,456, 36,971]*	3,805 *[-4,690, 12,914]*
Drug Rescheduling	-1,782 *[-5,227, 1,842]*	2,059 *[-1,303, 6,475]*	-103,811 *[-125,509, -88,775]*	146,607 *[92,853, 183,847]*	42,796 *[98, 82,935]*
PMP	-4,406 *[-6,395, -1,781]*	-3,605 *[-5,414, -418]*	-47,826 *[-57,967, -40,737]*	90,154 *[58,416, 110,799]*	42,328 *[16,458, 64,117]*
Drug Reformulation	1,907 *[359, 4,603]*	4,547 *[2,702, 8,181]*	-43,254 *[-53,123, -34,426]*	39,365 *[19,593, 54,155]*	-3,889 *[-22,157, 11,500]*
Excess Opioid Disposal	588 *[194, 1,538]*	1,158 *[661, 2,434]*	-7,906 *[-9,743, -6,406]*	5,522 *[-774, 8,344]*	-2,385 *[-8,832, 434]*
Naloxone Availability	1,917 *[1,729, 2,141]*	1,609 *[1,454, 1,793]*	-8,426 *[-9,994, -7,259]*	-12,728 *[-14,616, -11,054]*	-21,153 *[-22,788, -19,200]*
Needle Exchange	505 *[430, 615]*	418 *[356, 508]*	0 *[0, 0]*	-5,863 *[-6,714, -5,102]*	-5,863 *[-6,714, -5,101]*
MAT	1,424 *[78, 1,884]*	2,068 *[662, 2,676]*	-2,869 *[-3,856, 474]*	-9,609 *[-11,898, -1,481]*	-12,478 *[-15,424, -1,007]*
Psychosocial Interventions	1,153 *[667, 1,337]*	1,548 *[903, 1,757]*	-1,555 *[-1,917, -857]*	-5,978 *[-7,436, -3,367]*	-7,533 *[-8,981, -4,224]*

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years.

[a] Discounted to 2016.

Appendix Table 9. Outcomes of Combined Interventions over 10 Years

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
Drug Rescheduling + Naloxone Availability	28 *[-3,361, 3,410]*	3,569 *[255, 7,789]*	-107,151 *[-129,377, -91,680]*	128,261 *[77,805, 162,701]*	21,111 *[-18,530, 58,685]*
Drug Rescheduling + Needle Exchange	-1,090 *[-4,500, 2,413]*	2,632 *[-700, 6,947]*	-103,811 *[-125,508, -88,775]*	138,242 *[86,003, 174,209]*	34,431 *[-6,753, 73,296]*
Drug Rescheduling + MAT	-188 *[-3,292, 3,179]*	4,123 *[736, 8,188]*	-102,616 *[-124,228, -87,751]*	130,369 *[79,599, 163,319]*	27,753 *[-12,445, 63,433]*
Drug Rescheduling + Psychosocial Interventions	-866 *[-4,147, 2,610]*	3,240 *[27, 7,479]*	-103,991 *[-125,714, -88,923]*	140,439 *[87,867, 176,148]*	36,448 *[-5,162, 75,071]*
PMP + Naloxone Availability	-2,434 *[-4,409, -23]*	-1,957 *[-3,752, 1,060]*	-53,923 *[-65,154, -46,010]*	73,987 *[44,699, 92,421]*	20,063 *[-3,337, 39,963]*
PMP + Needle Exchange	-3,762 *[-5,730, -1,240]*	-3,073 *[-4,863, 30]*	-47,826 *[-57,967, -40,737]*	82,738 *[52,148, 102,369]*	34,912 *[10,190, 55,688]*
PMP + MAT	-2,693 *[-5,210, -312]*	-1,329 *[-3,993, 1,526]*	-47,744 *[-58,143, -40,707]*	74,860 *[45,811, 94,987]*	27,116 *[3,366, 50,478]*
PMP + Psychosocial Interventions	-3,312 *[-5,116, -857]*	-2,178 *[-3,818, 811]*	-48,539 *[-58,829, -41,348]*	83,541 *[53,125, 102,543]*	35,002 *[10,295, 55,169]*
All Prescribing (Acute, Transitioning, Chronic)	1,959 *[932, 3,153]*	1,625 *[524, 3,258]*	-31,914 *[-38,926, -25,564]*	25,584 *[14,581, 35,010]*	-6,330 *[-14,576, 3,753]*
All Prescribing + Naloxone Availability	3,759 *[2,726, 5,142]*	3,134 *[1,900, 4,921]*	-38,768 *[-47,008, -31,562]*	11,856 *[2,133, 19,457]*	-26,912 *[-36,085, -18,312]*
All Prescribing + Needle Exchange	2,496 *[1,484, 3,783]*	2,069 *[916, 3,778]*	-31,914 *[-38,926, -25,564]*	19,283 *[9,073, 27,870]*	-12,631 *[-21,178, -3,386]*
All Prescribing + MAT	3,326 *[1,560, 4,796]*	3,562 *[1,629, 5,536]*	-34,093 *[-41,830, -27,568]*	15,481 *[5,393, 30,027]*	-18,612 *[-28,570, -2,138]*

Policy	Mean Change in Discounted Net Present LYs (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs (Thousands) *[Min, Max]*	Mean Change in Pill Addiction Deaths *[Min, Max]*	Mean Change in Heroin Addiction Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*
All Prescribing + Reformulation + MAT + Needle + Naloxone + Psychosocial	8,561 *[6,349, 12,496]*	10,727 *[7,998, 15,945]*	-70,182 *[-85,574, -57,308]*	11,433 *[-15,574, 29,542]*	-58,748 *[-85,363, -41,393]*

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years.

[a] Discounted to 2016.

Appendix Table 10. Base Case Five-Year Threshold Analysis

Policy Name	Policy Change Description	Mean Change in Discounted Net Present LYs[a] (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs[a] (Thousands) *[Min, Max]*	Mean Change in Pill Deaths *[Min, Max]*	Mean Change in Heroin Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*	-10% Deaths Achieved
Acute Pain Prescribing	100% reduction in prescribing opioids for acute pain	2,341 *[1,808, 3,218]*	-4,992 *[-5,677, -3,751]*	-7,978 *[-9,737, -6,748]*	488 *[-2,956, 1,985]*	-7,490 *[-10,760, -5,717]*	No
Prescribing for Persisting Pain	100% reduction in prescribing opioids for acute pain that transitions to chronic	332 *[143, 547]*	776 *[580, 1,070]*	-3,348 *[-4,165, -2,924]*	2,738 *[1,335, 3,632]*	-611 *[-1,589, 302]*	No
Chronic Pain Prescribing	100% reduction in prescribing opioids for chronic pain	3,074 *[912, 5,071]*	7,385 *[5,211, 10,224]*	-35,655 *[-43,789, -29,321]*	34,279 *[19,115, 45,571]*	-1,376 *[-12,794, 10,455]*	No
Drug Reformulation	100% reduction iatrogenic addiction; 30% reduction in addiction by pain-free nonusers (unchanged); 30% reduction in pill-seeking for SOUD w/o Rx (unchanged)	7,587 *[6,384, 10,378]*	12,313 *[10,814, 16,485]*	-29,036 *[-34,641, -24,981]*	5,617 *[1,542, 9,262]*	-23,418 *[-32,910, -18,517]*	No
Excess Opioid Disposal	100% reduction in diversion to pain-free nonusers; 100% reduction in the number of SOUD w/o Rx able to be sustained per non-SOUD Rx holder	1,918 *[-99, 6,365]*	5,413 *[2,919, 11,540]*	-27,935 *[-34,685, -23,347]*	25,685 *[9,374, 35,965]*	-2,249 *[-19,006, 8,166]*	No
Naloxone Availability	12% reduction in overdose mortality	3,505 *[3,247, 3,746]*	2,917 *[2,703, 3,112]*	-10,142 *[-12,091, -9,033]*	-14,353 *[-16,615, -12,984]*	-24,495 *[-26,336, -22,793]*	Yes
Needle Exchange	88% reduction in infection mortality	3,247 *[2,882, 3,715]*	2,660 *[2,360, 3,040]*	0 *[0, 0]*	-24,060 *[-27,874, -21,774]*	-24,060 *[-27,874, -21,774]*	Yes

Policy Name	Policy Change Description	Mean Change in Discounted Net Present LYs[a] (Thousands) *[Min, Max]*	Mean Change in Discounted Net Present QALYs[a] (Thousands) *[Min, Max]*	Mean Change in Pill Deaths *[Min, Max]*	Mean Change in Heroin Deaths *[Min, Max]*	Mean Change in Total Opioid Deaths *[Min, Max]*	-10% Deaths Achieved
MAT	144% increased likelihood of beginning MAT	4,434 *[517, 5,371]*	6,628 *[2,738, 7,843]*	-4,841 *[-7,129, 2,125]*	-19,144 *[-23,570, -5,126]*	-23,985 *[-29,296, -3,000]*	Yes
Psychosocial Interventions	134% increased likelihood of desistance	6,446 *[3,749, 7,337]*	8,944 *[5,217, 9,941]*	-7,339 *[-9,625, -3,937]*	-16,554 *[-20,132, -9,465]*	-23,893 *[-27,790, -13,403]*	Yes
Drug Rescheduling	No level of implementation yielded improvement relative to the status quo over five years.	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	No
PMP	No level of implementation yielded improvement relative to the status quo over five years.	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	No

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

[a] Discounted to 2016.

Appendix Table 11. Base Case Ten-Year Threshold Analysis

Policy Name	Policy Change Description	Mean Change in Discounted Net Present LYs[a] (Thousands) [Min, Max]	Mean Change in Discounted Net Present QALYs[a] (Thousands) [Min, Max]	Mean Change in Pill Deaths [Min, Max]	Mean Change in Heroin Deaths [Min, Max]	Mean Change in Total Opioid Deaths [Min, Max]	-10% Deaths Achieved
Acute Pain Prescribing	100% reduction in prescribing opioids for acute pain	5,386 *[4,234, 7,234]*	-1,660 *[-3,113, 881]*	-24,539 *[-29,583, -20,348]*	-7,302 *[-20,282, -360]*	-31,842 *[-44,295, -24,214]*	No
Prescribing for Persisting Pain	100% reduction in prescribing opioids for acute pain that transitions to chronic	930 *[643, 1,404]*	1,700 *[1,331, 2,333]*	-10,302 *[-12,553, -9,012]*	6,178 *[2,623, 8,222]*	-4,124 *[-7,301, -1,576]*	No
Chronic Pain Prescribing	100% reduction in prescribing opioids for chronic pain	10,662 *[7,402, 15,475]*	18,653 *[14,573, 25,219]*	-103,508 *[-125,376, -84,518]*	60,895 *[29,187, 86,692]*	-42,613 *[-72,876, -13,971]*	No
Drug Reformulation	54% reduction iatrogenic addiction; 30% reduction in addiction by pain-free nonusers (unchanged); 30% reduction in pill-seeking for SOUD w/o Rx (unchanged)	9,461 *[7,496, 12,394]*	14,977 *[12,534, 19,260]*	-61,305 *[-73,498, -50,758]*	9,176 *[-7,494, 20,898]*	-52,129 *[-70,422, -38,675]*	Yes
Excess Opioid Disposal	100% reduction in diversion to pain-free nonusers; 100% reduction in the number of SOUD w/o Rx able to be sustained per non-SOUD Rx holder	5,533 *[1,605, 14,801]*	11,082 *[6,139, 23,484]*	-79,099 *[-97,493, -64,104]*	57,193 *[-4,392, 85,331]*	-21,906 *[-85,034, 6,600]*	No
Naloxone Availability	13% reduction in overdose mortality	5,060 *[4,560, 5,652]*	4,246 *[3,832, 4,731]*	-21,934 *[-26,023, -18,894]*	-33,301 *[-38,219, -28,924]*	-55,235 *[-59,492, -50,126]*	Yes
Needle Exchange	87% reduction in infection mortality	4,572 *[3,889, 5,560]*	3,779 *[3,217, 4,591]*	1 *[1, 1]*	-51,561 *[-58,993, -44,854]*	-51,560 *[-58,992, -44,853]*	Yes

Policy Name	Policy Change Description	Mean Change in Discounted Net Present LYs[a] (Thousands) [Min, Max]	Mean Change in Discounted Net Present QALYs[a] (Thousands) [Min, Max]	Mean Change in Pill Deaths [Min, Max]	Mean Change in Heroin Deaths [Min, Max]	Mean Change in Total Opioid Deaths [Min, Max]	-10% Deaths Achieved
MAT	118% increased likelihood of beginning OST	5,899 *[534, 7,697]*	8,484 *[2,886, 10,846]*	-11,152 *[-15,377, 2,898]*	-40,505 *[-50,015, -8,315]*	-51,657 *[-63,169, -5,417]*	Yes
Psychosocial Interventions	73% increased likelihood of desistance	7,808 *[4,675, 9,037]*	10,489 *[6,334, 11,877]*	-10,733 *[-13,274, -6,060]*	-41,137 *[-51,032, -23,824]*	-51,870 *[-61,678, -29,884]*	Yes
Drug Rescheduling	100% reduction in chance of getting prescription renewed	9,209 *[5,551, 14,510]*	17,692 *[13,201, 24,845]*	-146,645 *[-176,699, -126,074]*	129,170 *[76,765, 169,975]*	-17,475 *[-56,740, 28,047]*	No
PMP	No level of implementation yielded improvement relative to the status quo over ten years.	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	0 *[0, 0]*	No

LYs, life years; MAT, medication-assisted treatment; PMP, prescription monitoring program; QALYs, quality-adjusted life years; SHUD, severe heroin use disorder; SOUD, severe [prescription] opioid use disorder.

[a] Discounted to 2016.

References

1. US Census Bureau. Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2015. 2016; https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk. Accessed Jun 17, 2017.
2. Cullen KA, Hall MJ, Golosinskiy A. *Ambulatory surgery in the United States, 2006.* Hyattsville, MD: National Center for Health Statistics;2009.
3. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. 2006 National Hospital Discharge Survey. *National Health Statistics Reports.* 2008(5):1-20.
4. Sullivan D, Lyons M, Montgomery R, Quinlan-Colwell A. Exploring opioid-sparing multimodal analgesia options in trauma: a nursing perspective. *J Trauma Nurse.* 2016;23(6):361-375.
5. National Center for Injury Prevention and Control. *CDC Injury Fact Book.* Atlanta, GA: Centers for Disease Control and Prevention;2006.
6. Beaudoin FL, Straube S, Lopez J, Mello MJ, Baird J. Prescription opioid misuse among ED patients discharged with opioids. *Am J Emerg Med.* 2014;32(6):580-585.
7. Apfelbaum JL, Chen C, Mehta SS, Gan, Tong J. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg.* 2003;97(2):534-540.
8. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg.* 2017;152(6):e170504.
9. Calcaterra SL, Yamashita TE, Min S-J, Keniston A, Frank JW, Binswanger IA. Opioid prescribing at hospital discharge contributes to chronic opioid use. *J Gen Intern Med.* 2015;31(5):478-485.
10. Mudumbai SC, Oliva EM, Lewis ET, et al. Time-to-cessation of postoperative opioids: a population-level analysis of the Veterans Affairs Health Care System. *Pain Med.* 2016;17(9):1732-1743.
11. Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf.* 2017.
12. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569-576.
13. Hser Y-I, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. Chronic pain among patients with opioid use disorder: results from electronic health records data. *J Subst Abuse Treat.* 2017;77:26-30.
14. Substance Abuse and Mental Health Services Administration. 2015 National Survey on Drug Use and Health: detailed tables. 2016; https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf. Accessed Jun 17, 2017.
15. RAND Corporation. *What America's users spend on illegal drugs: 2000-2010.* Washington, DC: Office of National Drug Control Policy, Office of Research and Data Analysis;2014.
16. Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *Center for Behavioral Health Statistics and Quality Data Review* 2013;

http://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm. Accessed Jun 17, 2017.
17. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry.* 2014;71(7):821-826.
18. Knudsen HK, Abraham AJ, Roman PM. Adoption and implementation of medications in addiction treatment programs. *J Addict Med.* 2011;5(1):21-27.
19. Sullivan LE, Fiellin DA. Office-based buprenorphine for patients with opioid dependence. *Ann Intern Med.* 2008;148(9):662-670.
20. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies -- tackling the opioid-overdose epidemic. *N Engl J Med.* 2014;370(22):2063-2066.
21. Saha TD, Kerridge BT, Goldstein RB, et al. Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *J Clin Psychiatry.* 2016;77(6):772-780.
22. Ruhm CJ. Geographic variation in opioid and heroin involved drug poisoning mortality rates. *Am J Prev Med.* 2017;53(6):745-753.
23. Centers for Disease Control and Prevention. Wide-ranging online data for epidemiologic research (WONDER). 2016; https://wonder.cdc.gov/. Accessed Jun 23, 2017.
24. Schuckit MA. Treatment of opioid-use disorders. *N Engl J Med.* 2016;375(4):357-368.
25. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: National Academies Press; 2011.
26. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain.* 2008;9(10):883-891.
27. Vetter TR. The epidemiology of pediatric chronic pain. *Handbook of Pediatric Chronic Pain*. New York: Springer Publishers; 2011:1-14.
28. Huguet A, Miró J. The severity of chronic pediatric pain: an epidemiological study. *J Pain.* 2008;9(3):226-236.
29. Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend.* 2015;150:112-119.
30. Yokell MA, Delgado MK, Zaller ND, Wang NE, McGowan SK, Green TC. Presentation of prescription and nonprescription opioid overdoses to US emergency departments. *JAMA Intern Med.* 2014;174(12):2034-2037.
31. Kochanek KD, Sl M, Xu JQ, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep.* 2016;65(4):1-122.
32. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006;367(9522):1618-1625.
33. de Leon-Casasola O. A review of the literature on multiple factors involved in postoperative pain course and duration. *Postgrad Med.* 2014;126(4):42-52.
34. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf.* 2009;18(12):1166-1175.
35. Suarez-Almazor ME, Kendall C, Johnson JA, Skeith K, Vincent D. Use of health status measures in patients with low back pain in clinical settings. Comparison of specific, generic and preference-based instruments. *Rheumatology (Oxford).* 2000;39(7):783-790.

36. Goodnough A, Tavernise S. Opioid prescriptions drop for first time in two decades. *NY Times.* May 20, 2016.
37. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
38. Martin BC, Fan M-Y, Edlund MJ, DeVries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP Study. *J Gen Intern Med.* 2011;26(12):1450-1457.
39. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev.* 2010(1).
40. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med.* 2008;9(4):444-459.
41. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194.
42. Dasgupta N, Kramer ED, Zalman M-A, et al. Association between non-medical and prescriptive usage of opioids. *Drug Alcohol Depend.* 2006;82(2):135-142.
43. Marcovitz DE, McHugh RK, Volpe J, Votaw V, Connery HS. Predictors of early dropout in outpatient buprenorphine/naloxone treatment. *Am J Addict.* 2016;25(6):472-477.
44. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA.* 2000;284(13):1689-1695.
45. Volkow ND. How long does drug addiction treatment usually last? *Principles of drug addiction treatment: A research-based guide*: DIANE Publishing; 2011.
46. Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *The Lancet.* 2012;379(9810):71-83.
47. Magura S, Lee SJ, Salsitz EA, et al. Outcomes of buprenorphine maintenance in office-based practice. *J Addict Dis.* 2007;26(2):13-23.
48. Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med.* 2007;22(4):527-530.
49. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis.* 2016;35(1):22-35.
50. Corsi KF, Lehman WK, Booth RE. The effect of methadone maintenance on positive outcomes for opiate injection drug users. *J Subst Abuse Treat.* 2009;37(2):120-126.
51. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11(9):1-171, iii-iv.
52. Banta-Green CJ, Maynard C, Koepsell TD, Wells EA, Donovan DM. Retention in methadone maintenance drug treatment for prescription-type opioid primary users compared to heroin users. *Addiction.* 2009;104(5):775-783.
53. Xu JQ, Murphy SL, Kochanek KD, Bastian BA. Deaths: final data for 2013. *Natl Vital Stat Rep.* 2016;64(2):1-119.

54. Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO Study. *Am J Epidemiol.* 2012;175(4):302-308.
55. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. *Drug Alcohol Depend.* 2008;94(1-3):151-157.
56. Dixon S, Poole CD, Odeyemi I, Retsa P, Chambers C, Currie CJ. Deriving health state utilities for the numerical pain rating scale. *Health Qual Life Outcomes.* 2011;9:96.
57. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372-380.
58. Birke H, Ekholm O, Sjøgren P, Kurita Gp, Højsted J. Long-term opioid therapy in Denmark: a disappointing journey. *Eur J Pain.* 2017;21(9):1516-1527.
59. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015;162(4):276-286.
60. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA.* 2016;315(15):1624-1645.
61. Olson J. Minneapolis VA study challenges wide use of opioids. *Star Tribune.* May 14, 2017.
62. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol.* 2008;16(5):405-416.
63. Barnett PG, Zaric GS, Brandeau ML. The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. *Addiction.* 2001;96(9):1267-1278.
64. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med.* 2013;158(1):1-9.
65. Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. *Am J Public Health.* 2000;90(7):1100-1111.
66. Dhawan A, Chopra A. Does buprenorphine maintenance improve the quality of life of opioid users? *Indian J Med Res.* 2013;137(1):130-135.
67. Lipscomb J. The Proper Role for Discounting: Search in Progress. *Med Care.* 1996;34(12):DS119-DS123.
68. Arias E. United States life tables, 2011. *Natl Vital Stat Rep.* 2015;64(11):1-63.
69. Severtson SG, Ellis MS, Kurtz SP, et al. Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone. *Drug Alcohol Depend.* 2016;168:219-229.
70. Egan KL, Gregory E, Sparks M, Wolfson M. From dispensed to disposed: evaluating the effectiveness of disposal programs through a comparison with prescription drug monitoring program data. *Am J Drug Alcohol Abuse.* 2017;43(1):69-77.
71. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol.* 2015;2(1):10.
72. Bohnert ASB, Tracy M, Galea S. Characteristics of drug users who witness many overdoses: implications for overdose prevention. *Drug Alcohol Depend.* 2012;120(1-3):168-173.

73. Kaplan EH, O'Keefe E. Let the needles do the talking! Evaluating the New Haven needle exchange. *Interfaces.* 1993;23(1):7-26.
74. Lewis N, Ockerman E, Achenbach J, Lowery W. Fentanyl linked to thousands of urban overdose deaths. *Washington Post.* Aug 15, 2017.
75. Ganim S. China's fentanyl ban a 'game-changer' for opioid epidemic. *CNN.* 2017/02/16/, 2017.
76. Vestal C. *Diverse Medicaid Rules Hurt in Fighting Addiction.* The Pew Charitable Trusts; 2016/10/14/ 2016.