Supplementary Materials for:

Reducing Opioid Use Disorder and Overdose in the United States: Model Development and Estimation

Note to program chairs & reviewers

This model is still under embargo from the FDA and not yet cleared for full publication, but we have obtained permission to share it at this conference. As such:

1) Please keep this material confidential.
2) Please exclude the full version of this paper and/or its supplement from the conference website, proceedings, or any other publicly accessible venue, and share only the title and abstract for now.
3) Unfortunately, we are unable to share the actual model and data files or the online code repository at this time, though we have tried to document the model as fully as possible in the Supplement.
4) Finally, a few of the proprietary data sources we use have not given authorisation for release yet, so we have had to redact a handful of data points from tables and text.

Contents

S1) Glossary

S1.a) Definitions of key terms

Prescription opioids: Prescription (Rx) opioids are analgesic medications, used primarily to treat pain. Examples include natural opiates such as morphine or codeine; semi-synthetic opioids such as hydrocodone and oxycodone; and synthetic opioids such as tramadol and licit fentanyl (see also **fentanyl** below). They most commonly come in pill form, though other forms (e.g. liquid, film, etc.) exist as well. Prescription opioids are pharmaceutical products, though illicitly manufactured counterfeit prescription pills, often containing fentanyl, are a growing concern (see S2.d.i.(2)). We use the term 'prescription opioids' to any pharmaceutically produced opioid analgesic, regardless of how it is obtained or used (e.g. whether prescribed by a medical provider or diverted; whether used to treat pain as prescribed or for other purposes).

Heroin: Heroin is an illicit semi-synthetic opioid that comes in several forms (e.g. black tar, brown or powder). It is consumed in several ways, including oral intake, snorting, smoking, and injection. As an illicit drug, the production, distribution, and sale of heroin is illegal. Heroin is often contaminated with various adulterants, and increasingly with **fentanyl** (see below).

Fentanyl: Fentanyl is a highly potent synthetic opioid with many analogues (e.g. carfentanil, sufentanil, etc.). While licit, pharmaceutically produced prescription fentanyls exist, they are relatively uncommon; the majority of fentanyl in circulation now is illicitly manufactured fentanyl (IMF). IMF is increasingly common in the supply of **heroin** and other illicit drugs (see S2.d.iii.(3)). Other, non-fentanyl synthetic opioids exist as well, though they are generally less potent and far less common in the illicitly-manufactured fentanyl supply, which includes both basic fentanyl and numerous analogues. In this model, we do not distinguish between them, and use the terms 'synthetic[s]' and 'fentanyl' interchangeably to refer to illicitly manufactured fentanyl and its analogues, unless otherwise specified. We specifically use the terms 'prescription synthetics' or 'prescription fentanyl' to refer to the licit form (see **prescription opioids**).

Misuse: Prescription opioid misuse includes any use of Rx opioids prescribed for someone else, or use of Rx opioids solely 'for the feeling [they] caused' (see S3.a.i)). As an umbrella term, 'misuse' can also include 'low-intensity' use of heroin that does not rise to the level of **use disorder** (see below), which we also term 'non-disordered heroin use' (NDHU; see S3.a.iii)).

Use disorder: Substance use disorder is a clinically-diagnosable psychiatric disorder defined in the DSM-5 (see S3.a.ii)). Use disorder of varying degrees of severity is defined by endorsement of an increasing number of criteria identifying problems associated with drug use. Substance use disorder is associated with use of a particular substance; we distinguish between 'Rx opioid use disorder' and 'heroin use disorder' (see S3.a.iv)).

Remission: Remission is the reduction or disappearance of symptoms of **use disorder**. An individual who formerly qualified as having use disorder and now no longer meets the criteria for use disorder is in remission. While the term 'recovery' is used more generally to refer to the process of going from use disorder to a normal state of functioning and quality of life (see S3.c.v)), we focus on 'remission' as defined relative to use disorder. Note that remission does not necessarily entail complete abstinence from substance use.

Medication for Opioid Use Disorder (MOUD): Medication[s] for opioid use disorder [MOUD] refers to one or more of a set of three FDA-approved medications used to treat OUD – buprenorphine, methadone, and Vivitrol®. Treatment with MOUD is sometimes referred to as medication-assisted treatment (MAT) or opioid agonist therapy (OAT). There are many forms of treatment for use disorder, e.g. psychosocial therapy, community support groups, 12-step programs, etc. in addition to treatment with MOUD. However, our model explicitly represents MOUD but not other forms of treatment (see S2.b)); we therefore sometimes use 'MOUD' and 'treatment' interchangeably in the context of the model to refer to treatment involving MOUD.

S1.b) List of acronyms

ADF	Abuse-deterrent formulation
BAU	Business as usual
Bup / Bupe	Buprenorphine
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
DEA	Drug Enforcement Administration
DSM (DSM-IV / DSM-5)	Diagnostic and Statistical Manual of Mental Disorders (Fourth / Fifth edition)
EMS	Emergency medical services
FDA	Food and Drug Administration
H	Heroin
HHS	Department of Health and Human Services
HUD	Heroin use disorder
ICD (ICD-9 / ICD-10)	International Classification of Diseases (9^{th} / 10^{th} edition)
IMF	Illicitly manufactured fentanyl
MME	Milligrams morphine equivalent
MMT	Methadone maintenance therapy
MOUD	Medications for opioid use disorder
NASEM	National Academies of Science, Engineering and Medicine
NCHS	National Center for Health Statistics
NDHU	Non-disordered heroin use
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NFLIS	National Forensic Laboratory Information System
NSDUH	National Survey on Drug Use and Health
NSDUH RDAS	NSDUH Restricted-use Data Analysis System
N-SSATS	National Survey of Substance Abuse Treatment Services
NVSS	National Vital Statistics System
Nx	Naloxone
OD	Overdose
OSM	Opioid systems model
OUD	Opioid use disorder
Rx	Prescription / prescription opioid[s]
Rx OUD	Prescription opioid use disorder
SAMHSA	Substance Abuse and Mental Health Services Administration
STRIDE	System to Retrieve Information from Drug Evidence
SUD	Substance use disorder
TEDS	Treatment Episode Data Set
Tx	Treatment (for use disorder)
UNODC	United Nations Office on Drugs and Crime
Viv	Vivitrol® (naltrexone)

S2) FULL MODEL STRUCTURE

S2.a) Overview of structure

[OSM] is a continuous-time differential equations model, developed using a systems approach that emphasises endogenous feedback processes within a broad model boundary that drive changes over time. The model simulates the movement of people through different states of opioid use, with endogenous influences on initiation and transition rates, as well as more detailed representations of prescribing, treatment, and overdose-related processes. The model is parametrised to represent the opioid-using population in the US at a national level. Here we present key equations and structures in each of its sectors, with a complete listing of model equations in S7). Data sources for each sector are detailed in S3).

S2.b) Stock & flow structure

The opioid system includes people in various stages of use of both prescription opioids (*Rx*) and illicit opioids like heroin (*H*). For all disorder and remission definitions, we use the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria >. **Figure 1** provides an overview of the key population groups and the transitions among them (for more detailed definitions of these states and corresponding data sources, see S3.a)).

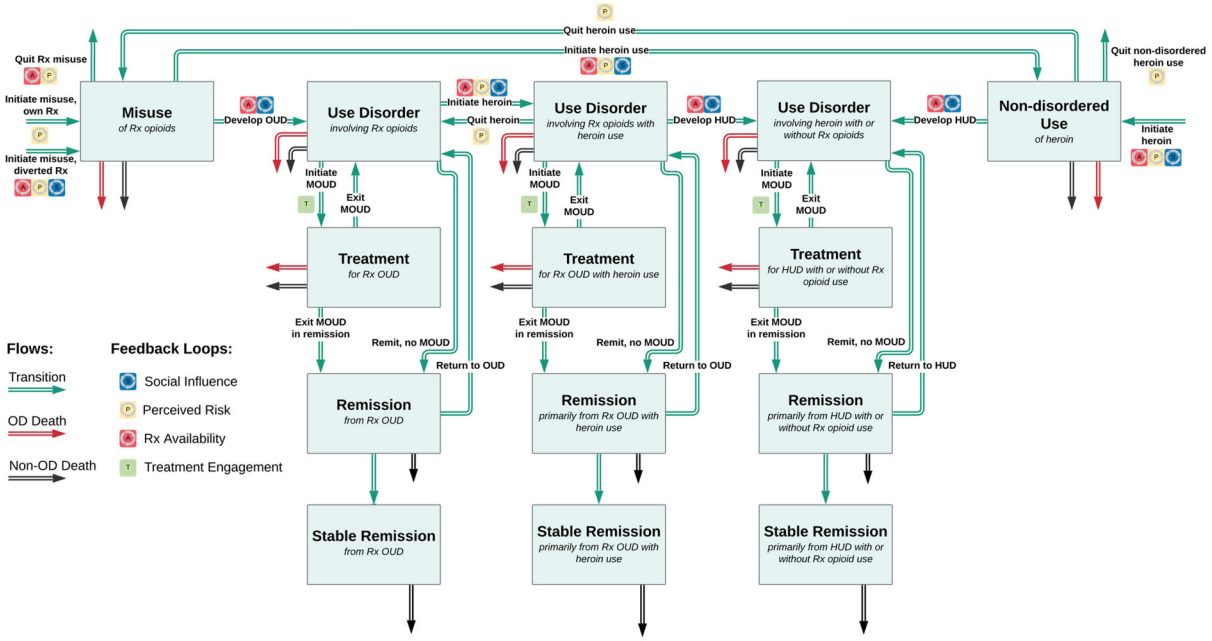

Figure 1. *Overview of model use states (stocks) and transitions (flows). Treatment states are further separated by MOUD type.*

People enter the opioid system by either initiating prescription opioid misuse – with their own prescription (*initiating Rx misuse own Rx*, r_{MI}), or with others' (*initiating Rx misuse diverted*, r_{MD}) – or by initiating heroin use without prior Rx opioid misuse (*initiating heroin no Rx*, r_{ND}). Definitions of opioid misuse vary; we follow the 2002-2014 NSDUH definition, to include *any* use of someone else's opioid prescription, *or* use of Rx opioids solely 'for the feeling [they] caused' >.

People who initiate Rx opioid misuse enter the stock of people with *Rx misuse* (M), while people who initiate heroin use without prior Rx misuse enter the stock of people with *non-disordered heroin use* (N). People misusing opioids can also initiate heroin (*initiating heroin with Rx misuse*, r_{MN}) and enter *N.* Once people transition from *M* to *N*, they are no longer distinguished from people who transitioned directly into *N* without first using Rx opioids. People in *M* and *N* can quit use in a given year, but also later resume use, with net flows (*net quitting Rx misuse*, r_{MQ}; *net quitting NDHU*, r_{NQ}) reflecting the combined total of quits and resumptions of use (but not new initiations) at any given time.

From Rx misuse, *M*, people can develop opioid use disorder (OUD) (*developing Rx OUD*, r_{MU}), thereby entering a disordered state involving Rx opioids only (*Rx OUD no PY heroin*, U_R). From the non-disordered heroin use state, they can develop an OUD involving heroin (*developing HUD no Rx OUD*, r_{NU}). For clarity, we call this state *heroin use disorder* or HUD (U_H). We also distinguish a third use disorder state, *Rx OUD with PY heroin* (U_O), which encompasses people with Rx OUD who have also used heroin in the past year, but whose heroin use does not rise to the level of a use disorder. While relatively uncommon, this is an important transitional state, which we therefore represent explicitly. People enter this state from U_R by *initiating heroin with Rx OUD* (r_{UO}). Once in this state, people can also develop HUD (*developing HUD with Rx OUD*, r_{OH}).[1]

Once in the use disorder states (U), people enter remission (*… in remission*, $R_{(.)}$) through one of two pathways: via remission without use of medications for opioid use disorder (*remitting… no MOUD*, $r_{UR(.)}$), which could include psychosocial or behavioural treatment or no treatment at all; or through treatment with MOUD (*… in MOUD Tx*, $T_{(.)}$). Remission occurs after no longer meeting criteria for a DSM-5 disorder for at least one year. Once in remission, the probability of relapse (*relapsing…*, $r_{RU(.)}$) or remaining in remission is the same regardless of the pathway by which remission was achieved, with or without MOUD.

After some time in the remission states, people transition to a more durable state of stable remission (*… in stable remisison*, $R_{S(.)}$), from which we assume they are no longer at risk of relapse. This transition (*stabilizing remission…*, $r_{RS(.)}$) takes place after an average of four additional years (*time to stabilize remission*, τ_{RS}) in the base remission state (see S3.c.v)).

Treatment engagement can involve any of the three FDA-approved MOUDs: buprenorphine, methadone, and Vivitrol (subscripts $_{B, M, V}$ respectively). *Treatment engagement* flows ($r_{UT(.)}$) are limited by both demand and capacity for each of these medications separately, as explained further in S2.d.ii). Once in treatment, people can leave treatment before remitting, thereby returning to use disorder (*Tx exit with UD*, $r_{TU(.)}$), or leave in remission (*Tx exit in remission*, $r_{TR(.)}$). Throughout the use disorder-treatment-remission chain, stocks are separated by drugs of use (subscripts $_{R, O, H}$) and by medication used (subscripts $_{B, M, V}$) as appropriate.

Each stock in the model also has two additional outflows (one for remission states, $R_{(.)}$) – death from non-overdose causes (*nonOD death*, $n_{(.)}$), as well as opioid-caused *overdose death* ($o_{(.)}$) for all states except remission. Overdose death rates are significantly impacted by naloxone availability and fentanyl penetration into the Rx opioid and heroin markets, as detailed in S2.d.iii).

[1] Note that the distinction between use disorder states is based on substance[s] of use and use behaviours, not the sources of those substances. See S3.a) for details.

The vast majority of transition rates or flows in the model are formulated as fractional annual hazard rates ($\rho_{(.)}$) multiplied by source populations, sometimes further multiplied by additional coefficients, e.g.:

$$\mathrm{r_{MN}} = (\rho_{MN}\mathrm{M})S_{MN}P_{MN}A_{MN} \quad (2.1)$$

Where $S_{(.)}$, $P_{(.)}$, and $A_{(.)}$ are coefficients for various endogenously generated effects, elaborated on in S2.c). Different transition rates are subject to different effects and coefficients, while treatment entry/exit and overdose death flows are subject to additional influences as well. In most cases, the base rates (ρ) are estimated model parameters; in a few cases they are derived from extant literature.

In the case of the three entry flows into the system (r_{MI}, r_{MD}, r_{ND}), source populations are not explicitly represented in the model. For misuse starting with one's own prescription (r_{MI}), we calculate the number of medical users of Rx opioids (*patients with current opioid Rx*, m_C) based on exogenous input data as the source population, without representing them as a stock, as their numbers are very large and relatively static compared to the populations in the model. Details of this calculation are included in S3.b). For the other two inflows (r_{MD}, r_{ND}), we simply estimate an absolute base rate in place of a fractional hazard rate, which implicitly accounts for the source population size.

Table 1. *Main states, transitions, and feedback coefficients*

State variables		
M	Rx misuse no heroin	Prescription opioid misuse
N	Nondisordered heroin use	Non-disordered heroin use
U_R	Rx OUD no PY heroin not in MOUD Tx	Prescription opioid use disorder, no past-year heroin use
U_O	Rx OUD with PY heroin not in MOUD Tx	Prescription opioid use disorder, past-year heroin use
U_H	HUD not in MOUD Tx	Heroin use disorder
T_R	Rx OUD no heroin by MOUD	Prescription opioid use disorder, no past-year heroin use, in medication for opioid use disorder treatment
T_O	Rx OUD with heroin by MOUD	Prescription opioid use disorder with past-year heroin use, in medication for opioid use disorder treatment
T_H	HUD by MOUD	HUD in medication for opioid use disorder treatment
R_R	Rx OUD no heroin in remission	Remission from prescription opioid use disorder, no heroin use in the year prior to quitting
R_O	Rx OUD with heroin in remission	Remission from Rx OUD with heroin use in the year prior to quitting
R_H	HUD in remission	Remission from heroin use disorder
R_{SR}	Rx OUD no heroin in stable remission	> 5 years in remission from prescription opioid use disorder, no heroin use in the year prior to quitting
R_{SO}	Rx OUD with heroin in stable remission	> 5 years in remission from Rx OUD with heroin use in the year prior to quitting
R_{SH}	HUD in stable remission	> 5 years in remission from heroin use disorder
Flows		
r_{MI}	Initiating Rx misuse own Rx	Initiating prescription opioid misuse with one's own prescription opioid
r_{MD}	Initiating Rx misuse diverted	Initiating prescription opioid misuse with someone else's prescription opioid

r_{ND}	Initiating heroin no Rx	Initiating non-disordered heroin use without having misused prescription opioids
r_{MN}	Initiating heroin with Rx misuse	Initiating non-disordered heroin use after having misused prescription opioids
r_{MQ}	Net quitting Rx misuse	Quitting prescription opioid misuse
r_{NQ}	Net quitting NDHU	Quitting non-disordered heroin use
r_{MU}	Developing Rx OUD	Developing opioid use disorder from prescription opioid use
r_{NU}	Developing HUD no Rx OUD	Developing opioid use disorder from heroin use without having had opioid use disorder from prescription opioid use
r_{UO}	Initiating heroin with Rx OUD	Initiating heroin use after having had opioid use disorder from prescription opioid use
r_{OH}	Developing HUD with Rx OUD	Developing opioid use disorder from heroin after having had opioid use disorder from prescription opioid use
$r_{UR(.)}$	Remitting… no MOUD	Remitting from (…) without medication-based treatment for opioid use disorder
$r_{RU(.)}$	Relapsing…,	Returning to opioid use disorder from remission from (…)
$r_{UT(.)}$	Treatment engagement	Engaging in medication-based treatment for opioid use disorder from (…)
$r_{TU(.)}$	Tx exit with UD	Exiting medication-based treatment for opioid use disorder from (…) with opioid use disorder from (…)
$r_{TR(.)}$	Tx exit in remission	Exiting medication-based treatment for opioid use disorder for (…) in remission from (…)
$n_{(.)}$	*NonOD death*	Dying from a non-opioid-related cause from (…)
$o_{(.)}$	*Overdose death*	Dying from an opioid-related cause from (…)
Feedback effects		
$S_{(.)}$	*Social influence coefficient*	
$P_{(.)}$	*Perceived risk coefficient*	
$A_{(.)}$	*Rx availability / H price / Rx vs. H price coefficient*	

S2.c) Major feedback effects

The model contains three main sets of endogenous influences (i.e. feedback loops or effects) on transition rates ($r_{(.)}$) between use states, shown in **Figure 2**:

1) Social influence reinforcing feedbacks, whereby existing users increase initiation and people with UD accelerate disorder development among existing users;

2) Risk perception balancing feedbacks, whereby opioid overdoses, especially overdose mortality, discourage initiation;

3) Availability balancing feedbacks, whereby the availability and/or price of Rx opioids fluctuates with the balance of supply and demand, influencing initiation, development of use disorder, transitions between Rx opioid and heroin use, and potentially quitting.

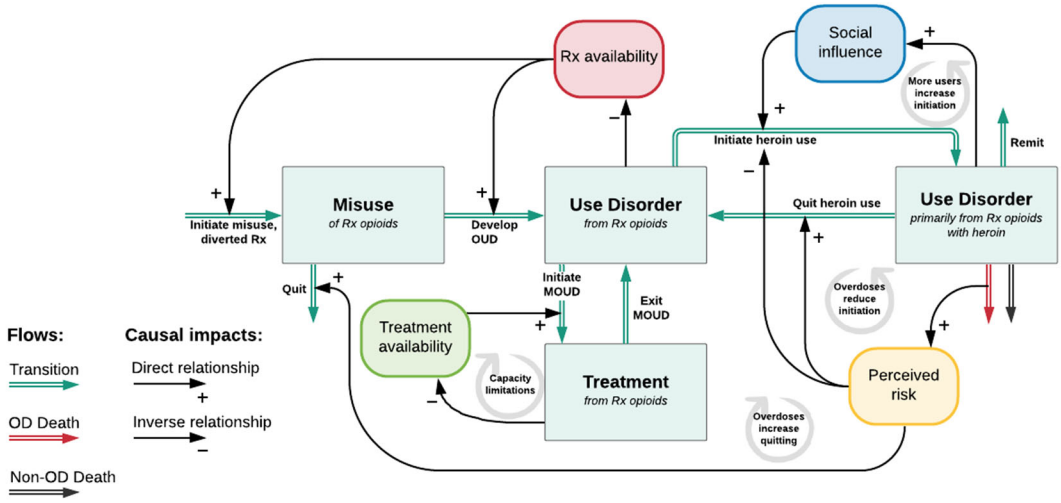

Figure 2. *Overview of key feedback effects in model.*

These feedback effects are all formulated with the same basic structure:

$$C_{(.)} = \left(D_{C(.)}\right)^{\varepsilon_{(.)}} \tag{2.2}$$

Where $C_{(.)} \in \{S_{(.)}, P_{(.)}, A_{(.)}\}$ is the *social influence coefficient*, *perceived risk coefficient*, or *Rx availability / H availability / Rx vs. H availability coefficient* for a given transition rate respectively; $D_{C(.)}$ is the relevant driver of the effect (*relative social influence*, *relative perceived risk*, *relative availability*); and $\varepsilon_{(.)} \in \{\psi_{(.)}, \pi_{(.)}, \alpha_{(.)}\}$ is the *social influence strength*, *perceived risk strength*, *availability strength* for that particular transition rate. These effect strengths are model parameters, estimated through the model estimation process (see S4)).

Specifics on the drivers of each effect are in the following sections; in all cases, the driver is a time-varying quantity normalized by its initial value. Normalizing allows coefficients on transition rates to vary with changes in their drivers without needing to tease apart baseline transition rates from the endogenous effects present at the start of the simulation time period.

In addition to these three main sets of feedbacks, treatment capacity limitations create a fourth, balancing feedback process, whereby as new patients enter treatment, the limited number of available treatment spots if filled, reducing or preventing further treatment engagement until existing patients leave (see S2.d.ii.(2)).

S2.c.i) Social influence

Drug use behaviour has an element of social contagion [3–>]. As more people use a substance, its use becomes increasingly normalised, and relevant knowledge about its use (e.g. methods of administration, sources of supply, etc.) becomes more widespread and accessible [4,7]. Access to the substance in social networks grows as people seek the substance or become suppliers to others (especially in the case of prescription opioids). Collectively, these processes increase initiation of drug use, creating a self-reinforcing growth process. (These processes can also work in reverse as use declines.) Similarly, social

space-driven ratcheting effects can drive increasingly heavy drug use [8,9], which we operationalise as social influence on the UD development process.

We operationalize social influence separately for Rx misuse (r_{MI}, r_{MD}) and heroin initiation (r_{ND}, r_{MN}, r_{UO}) flows, as well as for initiation vs. development of use disorder (r_{MU}, r_{NU}, r_{OH}). The *relative social influence* ($D_{S(.)}$) for a given transition depends on the fraction of the total population (see S3.a.viii)) engaging in the relevant drug use behaviours. Essentially, 1) only users of a given substance class (Rx vs. heroin) exert social influence on initiation or development of use disorder for that substance, and 2) heavier users exert influence on lighter users, but not vice-versa, such that people with use disorder affect initiation rates, but those without use disorder do not affect use disorder development rates (see **Figure 3** for details).

Note that while network effects on the accessibility of drugs in social networks are captured in this social influence process, the aggregate effect of a changing user base on the demand-supply balance is represented separately in the availability effects detailed below.

Flow Symbol	Flow Name	Population exerting social influence				
		Rx misuse no heroin (M)	Rx OUD no PY heroin not in MOUD Tx (U_R)	Rx OUD with PY heroin not in MOUD Tx (U_O)	HUD not in MOUD Tx (U_H)	Nondisordered heroin use (N)
r_{MD}	Initiating Rx misuse diverted	■	■	■		■
r_{ND}	Initiating heroin no Rx			■	■	■
r_{MN}	Initiating heroin with Rx misuse			■	■	■
r_{MU}	Developing Rx OUD		■	■		
r_{NU}	Developing HUD no Rx OUD				■	
r_{UO}	Initiating heroin with Rx OUD			■	■	■
r_{OH}	Developing HUD with Rx OUD				■	

Figure 3. *Use state populations driving each social influence effect. Initiating Rx misuse from diverted opioids is influenced by the fraction of people in the non-disordered heroin use state who also misuse Rx opioids.*

S2.c.ii) Perceived risk

Perceived risk coefficients $P_{(.)}$ reflect the deterrent effect that adverse outcomes like death can have on drug use behaviour. As overdoses and especially overdose mortality become more common, the perceived risk associated with a drug increases, dissuading potential initiates (reducing r_{MI}, r_{MD}, r_{ND}, r_{MN}, r_{UO}) and possibly encouraging current misusers (but not people with a disorder) to quit use (r_{MQ}, r_{NQ}), creating a balancing feedback process.

The perceived risk associated with use of a drug (D_{PR}, D_{PH}) adjusts with some lag to an underlying *indicated perceived risk* (D^*_{PR}, D^*_{PH}). The lag is asymmetric, i.e. the *perceived risk increase time* (τ_{PI}) is significantly shorter than the *perceived risk decrease time* (τ_{PD}), reflecting that deaths, overdoses, etc.

tend to get more attention than the lack of them, and a dangerous reputation for a drug fades slowly [10,1]>. The indicated perceived risk is operationalized as a weighted sum of the fatal and nonfatal overdoses associated with that drug, with a lower relative weight (*perceived risk weight NFOD*, w_n) given to non-fatal overdoses in users' or potential users' perceptions of risk:

$$\frac{dD_P}{dt} = \frac{D_P^* - D_P}{\tau_P} \tag{2.3}$$

$$D_P = \sum_{(.)} o_{(.)} + w_n n_{(.)}, \quad (.) \in \{R, H\} \tag{2.4}$$

Nonfatal overdoses are far more common and receive far less attention (especially for people not already using drugs) than fatal overdoses, so we assume a value of 0.1 for w_n, i.e. nonfatal overdoses carry 10% the risk perception impact of fatal overdoses.

S2.c.iii) Availability

Availability coefficients $A_{(.)}$ represent the effects of market forces and drug supply on initiation, use disorder development, and quit rates. The availability of Rx opioids (*Rx availability for misuse*, D_{ARM}) affects initiation of Rx misuse and development of Rx OUD (r_{MD}, r_{MU}, r_{MQ}).

Rx availability is in part a function of demand for Rx opioids, which in turn depends on the number of users. It thus exerts a balancing effect whereby more people using reduces the relative availability, in turn reducing initiation. Numerous other factors also influence availability, as detailed in S2.d.i).

Similarly, the availability of heroin (*heroin availability index*, D_{AH}) can exert an effect on heroin initiation and use disorder development flows (r_{ND}, r_{NU}, r_{NQ}), with greater availability facilitating initiation and UD development and discouraging quitting. Note, however, that we model heroin availability exogenously (see S2.d.i.(3)), so this is not, strictly speaking, a feedback process.

In addition to the separate availabilities of Rx opioids and heroin, we also consider their comparative availability, which affects transitions between Rx and heroin use. For purposes of this comparison, we use separate Rx availability constructs for prescription opioid misuse vs. use disorder (D_{ARM} vs. *Rx availability for UD*, D_{ARU}), as detailed in S2.d.i.(2) below. The ratio of the respective Rx availability construct to heroin availability yields the *Rx vs heroin availability index misuse* (D_{ACM}), which drives heroin initiation from Rx opioid misuse (r_{MN}), or the *Rx vs heroin availability index UD* (D_{ACU}), which drives initiation or escalation of heroin use with Rx OUD (r_{UO}, r_{OH}).

S2.c.iii.(1) ADF effects on heroin initiation

In addition to availability and price effects, we allow for one additional supply-related effect on transitions – an effect of abuse-deterrent formulations (ADFs) on heroin initiation with Rx OUD (r_{UO}). Like heroin price effects, this is not strictly speaking a feedback process, but operates in a similar way, driven by the *ADF fraction of Rx street supply* (F^{AS}) (see S2.d.i.(2)).

ADF prescription opioids are specially formulated to impede physical or chemical modification (e.g. crushing or dissolving), which makes them less amenable to non-oral routes of administration (e.g. snorting or injecting) [1]>. In principle, the intended effect of ADFs is to deter escalation from oral to non-

oral misuse of prescription opioids. We do not explicitly distinguish between routes of administration in this model, and therefore cannot represent this effect directly. However, non-oral misuse of opioids is a marker of OUD severity and a significant predictor of heroin initiation [13,14]. We therefore approximate the potential effect of ADFs on reducing non-oral misuse as an effect on the subsequent transition to heroin use instead.

S2.c.iv) Inclusion & exclusion of specific feedback effects

The feedback processes explained above are all plausible influences on opioid use transitions, with some evidence for their effects. However, the magnitude of each effect and its impact on e.g. initiation rates is difficult to discern with precision from available evidence. For instance, surveys of attitudes toward drug use among young people indicate an increase in the perceived risk associated with Rx opioids and heroin over the last decade[2], but do not associate those changing attitudes with changing likelihoods of initiating drug use. We therefore need to ascertain the impact of each process from the aggregate data, through model estimation.

Flow Symbol	Flow Name	Social influence	Percieved risk	Availability effects		
				Rx availability	Heroin availability	Rx vs. heroin availability
r_{MI}	Initiating Rx misuse own Rx		■			
r_{MD}	Initiating Rx misuse diverted	■	■	■		
r_{ND}	Initiating heroin no Rx	■	■		■	
r_{MN}	Initiating heroin with Rx misuse	■	■			■
r_{MO}	Net quitting Rx misuse		■	■		
r_{NO}	Net quitting NDHU		■		■	
r_{MU}	Developing Rx OUD	■		■		
r_{NU}	Developing HUD no Rx OUD	■			■	
r_{UO}	Initiating heroin with Rx OUD	■	■			■
r_{OH}	Developing HUD with Rx OUD	■				■

Figure 4. *Feedback effects actively or potentially influencing each transition. Initiating heroin with Rx OUD (r_{UO}) also includes a potential effect from ADFs (see S2.c.iii.(1))*

[2] Specifically, among Monitoring The Future respondents aged 18-30, the fraction perceiving 'great risk' of taking narcotics other than heroin just once or twice has risen from approximately 40% in 2011 (when the question was first asked) to 46% in 2018 [180]. The fraction reporting the same for trying heroin once or twice has risen from 60% in 1999 to 66% in 2018. In NSDUH, among those with an Rx OUD who had not yet used heroin, the fraction perceiving "great risk" in using heroin once or twice rose from 70% in 2011 to 81% in 2018 [181].

In order to allow the potential impact of each feedback to emerge from the data, we include all the aforementioned plausible feedbacks in the model structure during the estimation process. Some of the resultant estimated effect strengths show no significant effect for a given feedback on a given rate ($\varepsilon_{(.)} \sim 0$); those specific feedbacks are then removed in the final model. In some cases, the lack of effect is likely due to under-determination. For instance, the effect of perceived risk on initiating and quitting heroin use (r_{ND} and r_{NQ}) is similar, and given the absence of any reliable data on quit rates, cannot be distinguished. Additional data would allow re-estimation and potentially re-inclusion of these effect strengths. **Figure 4** summarises which feedback effects were allowed to potentially operate on which transitions in the estimation process, and in the final model.

S2.d) Additional model sectors

S2.d.i) Opioid supply, availability, & price

S2.d.i.(1) Prescribing and supply

Opioid prescribing practices influence both the number of medical users of opioids (m_C) who may initiate opioid misuse (r_{MI}), and the availability and street price of Rx opioids.

The number of medical users of Rx opioids (*patients with current opioid Rx*, m_C) is very large relative to others in the model, and their average 'residence time' fairly short. As such, the population of medical users is close to stable at any given time. We therefore represent them not as an explicit state variable, but with an analytic approximation:

$$\mathrm{m_C} = \mathrm{m_P m_N} \tau_M \tag{2.5}$$

Where $\mathrm{m_P}$ is the total number of *patients receiving opioid prescription* each year, $\mathrm{m_N}$ is the number of *prescriptions per person*, and τ_M is the *average prescription duration*, as detailed in S3.b.i). The number of medical users at any given time is thus in effect the product of the rate of people receiving prescriptions and their average duration of medical use, per Little's Law [1]>. Note that unlike most actual stocks in the model, $\mathrm{m_C}$ does not represent medical use *within the past year*, but rather currently ongoing use. As such, the transition rates reflecting hazard of misuse initiation from prior medical use (ρ_{MI}) or overdose death for medical users ($\mathrm{o_{mc}}$) should be interpreted as hazard rates per person-year of medical use of prescription opioids.

The *Rx supply* (q_S) represents the total supply that could be made available for potential misuse and can be thought of as 'excess' pills not used as prescribed within the time period of the prescription, which therefore present potential opportunities for misuse. Supply is fundamentally a function of total amount of prescription opioid medications dispensed each year, but is potentially influenced by more granular prescribing practices. We distinguish several aspects of prescribing that contribute to total amount prescribed, analogous to the Kaya identity [1]> – in its basic form, total supply in morphine milligrams equivalent (MME) is the product of patients receiving prescriptions each year ($\mathrm{m_P}$), prescriptions per patient ($\mathrm{m_N}$), and MME per prescription ($\mathrm{m_M}$):

$$\mathrm{q_S} = \mathrm{m_P} \times \mathrm{m_N} \times \mathrm{m_M} \tag{2.6}$$

These different aspects of prescribing patterns do not necessarily have equal weight in determining the effective supply of Rx opioids, as usage and consumption patterns differ. Simply put, giving twice as many people half as many opioids each vs. giving half as many people twice as many prescriptions each

vs. giving the same number of people half the prescriptions of twice the amount, and so on, will not necessarily have the same effect on supply. To allow for this possibility, we operationalise supply with a number of *sensitivity of Rx supply* exponents ($s_{S(.)}$), representing the relative contribution of each factor to overall supply. Specifically:

$$\mathrm{q_S} = \mathrm{m_P}^{s_{SP}} \times \mathrm{m_N}^{s_{SN}} \times \mathrm{m_M}^{s_{SM}} \tag{2.7}$$

Where each factor $\mathrm{m}_{(.)}$ is normalised to its initial value, and the sensitivity exponents $s_{S(.)}$ are normalised to have a mean of 1. In the absence of more specific evidence, we assume a baseline value of 1 for each exponent, giving equal importance to number of patients, number of prescriptions, and size of prescriptions, though the relative contributions of each factor could be adjusted to test different possibilities. In addition, other aspects of prescribing such as duration of prescriptions or number of pills (units) could potentially be incorporated into an expanded formulation for supply.

S2.d.i.(2) Availability and street supply

The availability of Rx opioids for potential misuse (*Rx availability for misuse*, D_{ARM}) is driven by the ratio of *Rx supply* to *Rx demand for misuse* ($\mathrm{q_D}$):

$$D_{ARM} = \frac{\mathrm{q_S} + w_C \mathrm{q_{SC}}}{\mathrm{q_D}} \tag{2.8}$$

$$\mathrm{q_D} = \sum_S S_{(.)} \mathrm{q_{DS(.)}}, \qquad S \in \{\mathrm{M, N, U, T}\} \tag{2.9}$$

Where the supply side is the sum of Rx supply ($\mathrm{q_S}$) and *counterfeit supply* ($\mathrm{q_{SC}}$), downweighted by some *counterfeit supply weight* (w_C). The presence of counterfeit Rx opioids in the street supply is a growing concern [17–2]>, but there are no estimates presently available of their actual prevalence. As such, we allow for the possibility of their contributing to supply, potentially downweighted to reflect lower desirability, but set their quantity to 0. Rx demand ($\mathrm{q_p}$) depends on the sizes of the populations in each drug use state and the expected average demand for individuals in that state (see S3.b.ii)).

The *Rx availability for UD* (D_{ARU}) likewise depends on Rx supply, potential counterfeit supply, and demand, as well as an additional *Rx street supply disruption* factor (Z):

$$D_{ARU} = \frac{\mathrm{q_S} + w_C \mathrm{q_{SC}}}{\mathrm{q_D}} (1 - \mathrm{Z}) = D_{ARM}(1 - \mathrm{Z}) \tag{2.10}$$

Rx street supply disruption (Z) is a state variable reflecting short-term perturbations, beyond the longer-term dynamics of supply and demand, which affect the street market for Rx opioids:

$$\frac{d\mathrm{Z}}{dt} = \mathrm{q_Z} - \frac{\mathrm{Z}}{\tau_Z} \tag{2.11}$$

The degree of disruption increases as *Rx street supply shocks* ($\mathrm{q_Z}$) occur. We include a single such shock – the 2010 withdrawal of the crushable form of OxyContin from production. OxyContin was by far the single most widespread formulation in the prescription opioid street supply at the time (see S3.b.i.(5)), and although it was replaced with an abuse-deterrent formulation, the withdrawal of the non-ADF form nonetheless represented a substantial disruption of available supply, as the crush-resistant ADF form is not a perfect substitute. Disruptions fade as suppliers find new sources and consumers adjust their

consumption preferences to available alternatives; this is a gradual process, taking *time to readjust Rx street supply* (τ_Z).

We separate Rx availability for people with misuse vs. use disorder (D_{ARM} vs. D_{ARU}) in order to allow these street supply disruptions to affect the latter but not the former. People with OUD consume far more opioids than those only misusing; they are much more likely to obtain at least some of their drugs from the 'street' or black market, including purchasing drugs through monetary or equivalent transactions [24,2]>; and they are more likely to have specific preferences for higher-dosage units or pills they can modify for non-oral routes of administration (e.g. crushing or dissolving) [26]. As such, they are more vulnerable or sensitive to potential disruptions in prescription opioid availability, particularly as compared to the availability of alternatives like heroin.

We calculate the *ADF fraction of Rx street supply* (F^{AS}) as a function of the *ADF fraction of prescribed Rx opioids* (F^{AR}):

$$F^{AS} = (F^{AR})^{s_{af}} \quad (2.12)$$

Where s_{af} is the *ADF substitutability factor*, representing the ability of the street supply to preferentially take up or avoid ADFs, shifting the composition of the street supply to include disproportionately high or low amounts of ADFs compared to what is prescribed (F^{AR}). While we allow for this possibility of differential uptake, in the absence of evidence indicating a strong skew one way or the other, we set s_{af}=1 by default, resulting in ADFs being as prevalent in the street supply as in the prescribed supply. We treat prescribed ADF supply (F^{AR}) as exogenous (see S3.b.i.(4)).

S2.d.i.(3) Heroin availability

As described in S2.c.iii), heroin availability can influence heroin initiation or UD development. In reality, heroin availability depends not only on street price but also features such as convenience, reliability, purity, and safety of obtaining supply [2]>. However, to our knowledge, there are no reliable data on availability or a suitable proxy thereof, besides price. We therefore operationalise heroin availability as simply the inverse of normalised heroin price, as calculated in S3.b.iii).

There is some evidence that heroin supply chains benefit from learning or improving returns to scale [28,2]>, as producers, traffickers, distributors and dealers improve the efficiency of their practices or overwhelm law enforcement efforts. These learning effects may be partly responsible for the decline in heroin prices particularly from the mid-2000s onward [30,31]. However, the dynamics of the heroin supply chain and market are outside the scope of this model. As such, we do not represent these dynamics explicitly, instead treating heroin price as exogenous.

S2.d.ii) Treatment

S2.d.ii.(1) Treatment seeking, demand, and engagement

The process by which people receive addiction treatment can be thought of as a continuum of care (**Figure 5**), with some portion of patients lost to care at each step of the continuum upstream of actual *treatment engagement* ($r_{UT(.)}$). We represent this continuum with multiple variables, replicated as appropriate for each use disorder and/or MOUD type.

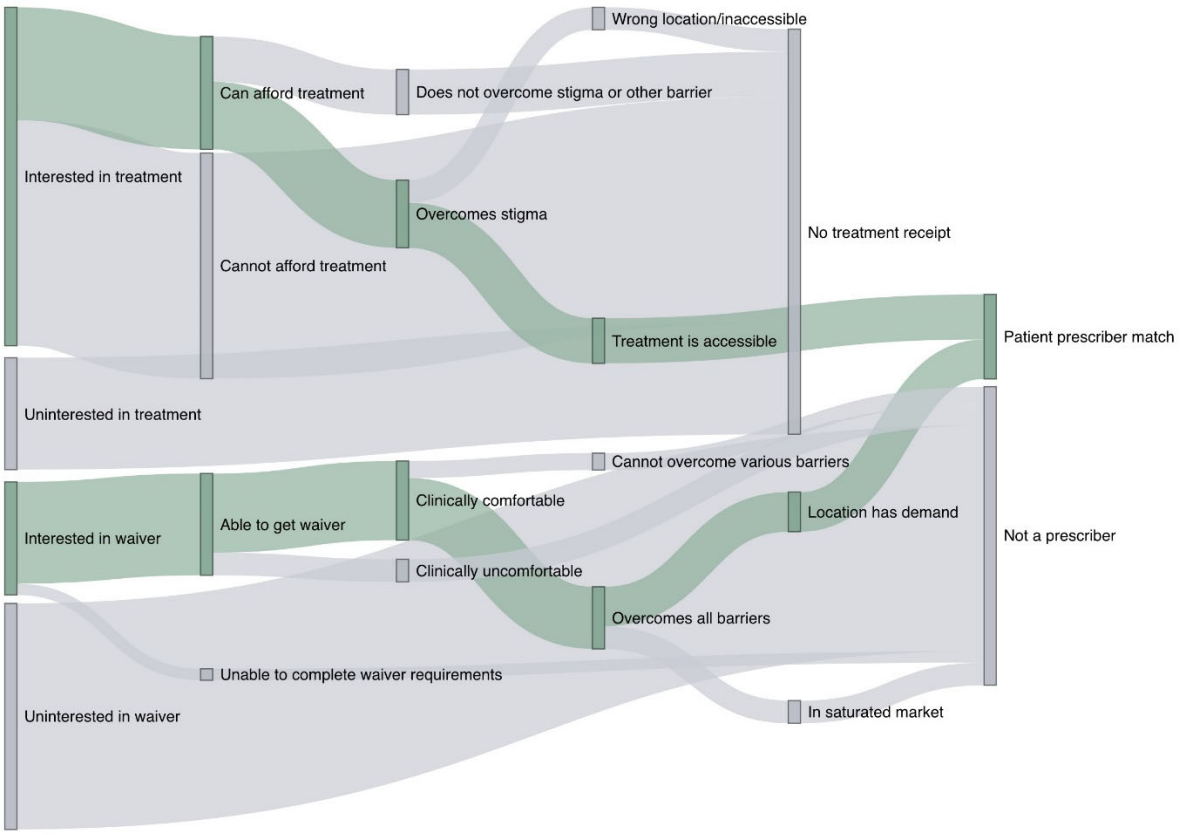

Figure 5. *Treatment engagement as a dual continuum of care. Demand (treatment seekers) and supply (treatment providers) need to match in space and time for successful treatment entry, but both providers and seekers face numerous barriers along the way.*

We assume that only people with use disorder will engage in MOUD treatment, as those without use disorder can simply voluntarily cease their drug use. Not all people with use disorder perceive a need for treatment or are interested in MOUDs. The hazard rate for people with use disorder making an effort to seek MOUD treatment is the *Tx seeking rate…* ($\rho_{T(.)}$). Treatment-seeking can be thought of as attempting to inquire with a provider or program about receiving MOUD, regardless of whether MOUD is ultimately received.

Of those thus seeking treatment, some fraction will fail to receive it due to barriers such as affordability, acceptability, or stigma (*Tx seeking barrier loss fraction*, F^L). Estimates of this loss fraction are detailed in S3.c.ii.(2). The remainder are those who will engage in treatment as long as they have access to it (*Tx demand…*, $\mathrm{r}^*_{\mathrm{UT}(.)}$):

$$\mathrm{r}^*_{\mathrm{UT}(.)} = \rho_{T(.)}(1 - F^L)\mathrm{U}_{(.)} \qquad (2.13)$$

Treatment demand is then compared with treatment capacity to determine what fraction of demand can actually be met. We represent treatment capacity explicitly in the model, detailed below. If capacity is insufficient, that means some people will be unable to access treatment despite facing no other barriers to engagement:

$$\mathrm{r}_{\mathrm{UT}(.)} = \mathrm{MIN}\left(\mathrm{r}^*_{\mathrm{UT}(.)}, K_{I(.)}\right) \qquad (2.14)$$

Where $K_{I(.)}$ is the *Tx intake capacity* at any given time, detailed below.

S2.d.ii.(2) Treatment capacity

Treatment capacity reflects the total number of patients nationwide who could be actively receiving a given treatment at any given time (*Tx capacity effective*, $K_{(.)}$). We calculate $K_{(.)}$ separately for each MOUD (subscripts $_{B}$, $_{M}$, $_{V}$), but not each disorder type.

The maximum number of people who can be *in* treatment at a given time is distinct from the maximum number who can *enter* treatment, i.e. the maximum rate of treatment engagement (*Tx intake capacity*, $K_{I(.)}$); the latter depends on how much of existing capacity is already utilised, the rate of patients leaving treatment ($r_{TR(.)}$ and $r_{TU(.)}$), and the processing time required for someone seeking treatment to start receiving it (*Tx intake delay*, $\tau_{I(.)}$), which for simplicity we estimate at 1 month (0.083 years) for all MOUDs:

$$K_{I(.)} = \mathrm{MAX}\left(0, \frac{K_{(.)} - \sum_u \mathrm{T}_{u(.)} + \sum_u \left(\mathrm{r}_{\mathrm{TR}u(.)} + \mathrm{r}_{\mathrm{TU}u(.)}\right)}{\tau_{I(.)}}\right), \qquad u \in \{\mathrm{R}, \mathrm{O}, \mathrm{H}\} \qquad (2.15)$$

National-level data on treatment capacity are unfortunately and surprisingly very sparse (see S3.c.iii)). The limitations of data availability significantly constrain the level of detail with which we can represent treatment capacity, particularly for methadone and Vivitrol treatment. For these two MOUD types, we calculate effective treatment capacity $K_{(.)}$ as a fraction (*Tx effective capacity fraction*, $F^{T}_{(.)}$) of estimated nominal or theoretical treatment capacity ($K^{*}_{(.)}$):

$$K_{(.)} = K^{*}_{(.)} F^{T}_{(.)}, \qquad (.) \in \{\mathrm{M}, \mathrm{V}\} \qquad (2.16)$$

The effective capacity fraction captures a number of possible reasons why treatment capacity may not be fully utilised even in the face of demand, such as imperfect matching between demand and capacity due to geographic and temporal heterogeneity, or possibly treatment providers' and facilities' preferences for maintaining some capacity buffer.

We represent effective buprenorphine treatment capacity (K_B) in more detail, using data on the number of providers waivered to prescribe buprenorphine (see S3.c.iii)). While the DATA 2000 buprenorphine waiver requirement and its different levels[3]> create a certain theoretical maximum number of patients who could be receiving buprenorphine nationwide, in practice, providers face numerous other barriers to prescribing buprenorphine besides the waiver requirement, and rarely prescribe up to their full waivered capacity [33,34]. We do not disaggregate these barriers, but they include factors like low reimbursement, lack of training, stigma, or lack of coordinating providers for e.g., mental health services[35].

Empirical evidence indicates diminishing marginal returns to effective capacity from additional waivered providers (see S3.c.iii)). This pattern likely arises for two main reasons. First, there is self-selection among providers in who gets waivered first[3]>. Those providers who got waivered early on (in the order of waiver receipt) were more likely to be those for whom addiction treatment was a major focus of their practice, or those with many patients who showed a need for treatment, and therefore more likely to dedicate more time and effort to prescribing. Conversely, those waivered later on are less likely to be focused on addiction treatment and less likely to make much time and effort available for buprenorphine prescribing. Second, there is some geographic mismatch between supply of waivered

providers and demand for buprenorphine treatment [37,38], which tends to worsen with more waivered providers. Initial waivered providers in any geographic location would likely have found some local demand for buprenorphine, whereas a growing fraction of later-waivered providers are in areas where capacity is plentiful demand is already saturated, even while other locales still have unmet demand. To reflect these diminishing returns, we model K_B as the integral of an exponential decay function representing each additional provider's diminishing contribution to capacity ($\widehat{K}$):

$$K_B = \int \widehat{K}\, dB \tag{2.17}$$

$$\widehat{K} = \widehat{K}_0 e^{-\lambda_B B} \tag{2.18}$$

$$K_B = \frac{\widehat{K}_0 e^{-\lambda_B B} + \widehat{K}_0}{-\lambda_B} \tag{2.19}$$

Where B is the number of waivered *Bup providers*, $\widehat{K}_0$ is the initial or base effective capacity per provider (*Bup effective capacity per provider base*), and λ_B is a decay constant (*Bup effective capacity decay constant*) indicating the rate at which capacity added per additional provider diminishes. The effect of these parameters on the marginal effective capacity per new provider $\widehat{K}$ is shown in **Figure 6**.

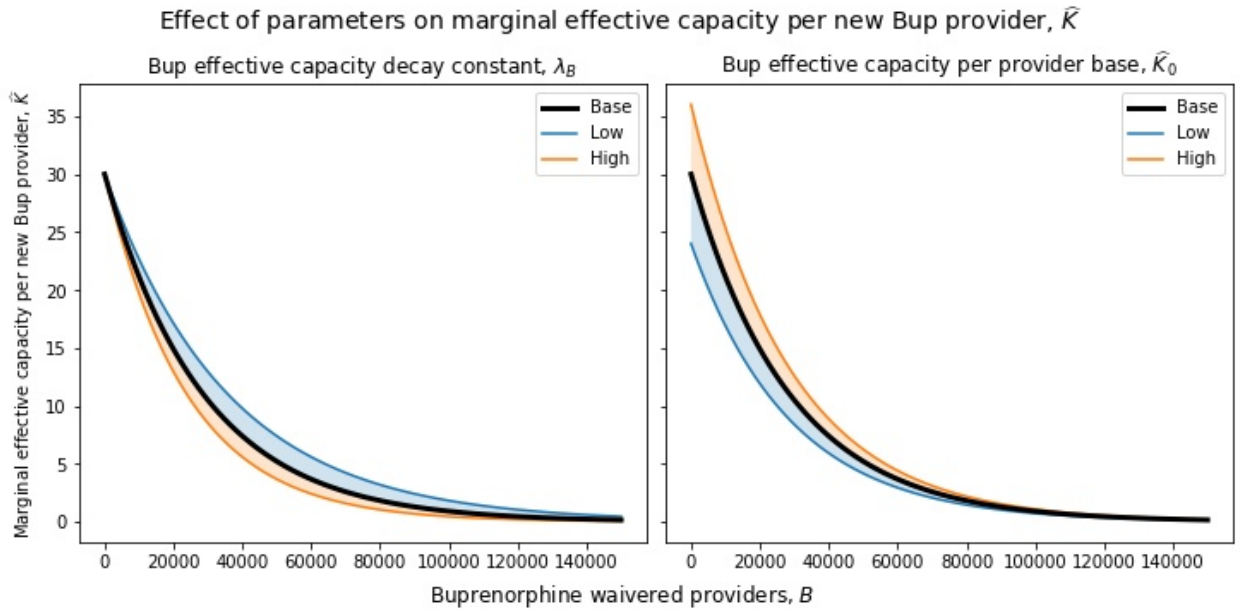

Figure 6. *Functional relationship between buprenorphine-waivered providers and marginal effective capacity added per new waivered provider, showing effect of each parameter. Note that while* marginal *capacity declines rapidly with additional providers,* average *capacity per provider never declines, as additional marginal providers only ever add capacity, never reduce it (see S3.c.iii)).*

S2.d.ii.(3) Treatment effects and outcomes

Patients in treatment will exit that state after a certain *Tx average duration* ($\tau_{T(.)}$) for each treatment type. Weighted averages for each MOUD were derived from an extensive review of literature; see S3.c.iv.(1).

Following treatment, patients exit to either a remission state ($r_{TR(.)}$), or back to use disorder ($r_{TU(.)}$). The proportion exiting to remission rather than back to use disorder (*Tx success fraction*, $p^R_{(.)}$), is itself a function of duration in treatment:

$$p^R_{(.)} = \frac{r_{TR(.)}}{r_{TR(.)} + r_{TU(.)}} = f(\tau_{T(.)}) \tag{2.20}$$

$$f(\tau_T) = \begin{cases} \left(\frac{{\kappa_R}^2}{1+{\kappa_R}^2}\right) e^{\left(\frac{\lambda_R}{\kappa_R}\right)(\tau_T - m_R)} p^{RM}, & \tau_T \le m_R \\ \left(1 - \left(\frac{1}{1+{\kappa_R}^2}\right) e^{(-\lambda_R \kappa_R (\tau_T - m_R))}\right) p^{RM}, & \tau_T > m_R \end{cases} \tag{2.21}$$

The duration-success function, based on an asymmetric Laplace function, creates an asymmetric S-shaped curve (see **Figure 7**), whose shape and scale are based on a combination of expert judgment and existing studies (see S3.c.iv.(1)). The *Tx success fraction* function takes four parameters – the *inflection* point (m_R), scale parameter *lambda* (λ_R), asymmetry parameter *kappa* (κ_R), and the *max* possible success fraction (p^{RM}).

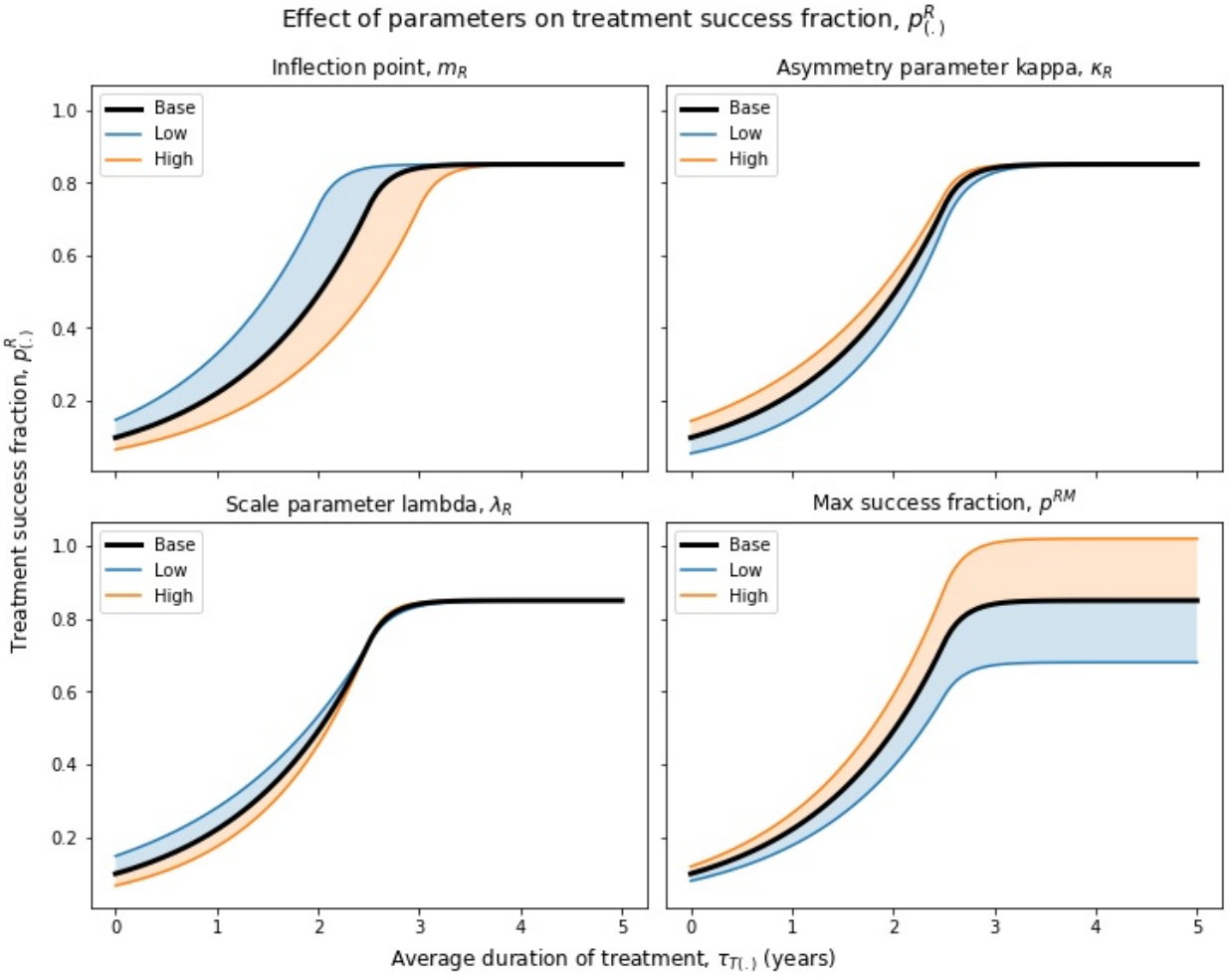

Figure 7. *Functional relationship between duration of treatment and treatment success fraction, showing effect of each parameter.*

Patients in the treatment stocks $T_{(.)}$ include a mix of people in one-year remission and people with ongoing use disorder. Transitions in and out of remission while in treatment are not uncommon, but to our knowledge there has been no attempt made to quantify these transition rates. For each treatment type, therefore, we specify a *remission fraction in Tx* ($F^R_{(.)}$), which is the average proportion of patients in that type of treatment whose use disorder is in remission. The fraction of treatment patients who are *not* in remission count towards the total number of people with use disorder, even though they are not in the $U_{(.)}$ stocks. For simplicity, we assume the remission fraction in each treatment type is equal to the current success fraction for that type:

$$F^R_{(.)} = p^R_{(.)} \tag{2.22}$$

Overdose and non-overdose death rates for treatment stocks ($\omega_{T(.)}$ and $n_{T(.)}$) are weighted by this fraction, with the portion of treatment patients in remission experiencing non-overdose deaths at the same rate as people in remission stocks ($R_{(.)}$) rather than use disorder stocks ($U_{(.)}$), and experiencing no overdose deaths. For those in treatment but not yet in remission, being in treatment nonetheless has beneficial effects on overdose and non-overdose death rates (*effect of MOUD Tx on OD death rate / non-OD death rate*, $w^{TO}_{(.)}$ / $w^{TN}_{(.)}$). Magnitudes of these effects are based on extant literature (see S3.c.iv.(2)). The net overdose death rate for a given stock of people in treatment is thus:

$$\omega_{T(.)} = \omega_{U(.)}\left(1 - F^R_{(.)}\right)w^{TO}_{(.)} \tag{2.23}$$

While the non-overdose death rate is:

$$n_{T(.)} = n_{U(.)}\left(1 - F^R_{(.)}\right)w^{TN}_{(.)} + n_{R(.)}F^R_{(.)} \tag{2.24}$$

Treatment also reduces opioid consumption for patients in treatment not yet in remission (*effect of MOUD Tx on Rx consumption*, $w^{Tq}_{(.)}$), thereby reducing their influence on demand for Rx opioids:

$$q_{DT(.)} = q_{DU(.)}\left(1 - F^R_{(.)}\right)w^{Tq}_{(.)} \tag{2.25}$$

S2.d.iii) Overdoses, naloxone, and synthetics

S2.d.iii.(1) Basic overdose death structure

The hazard rates of overdose and overdose death ($o_{(.)}$) differ based on drug use state. Overdose death data identify overdoses by the drug[s] involved (see S3.d.i)), but to keep the model estimation tractable, we instead allocate overdose deaths to user populations based on the populations' primary drug of use (Rx opioids vs. heroin), with further allocation of synthetic-opioid-involved deaths as detailed in S3.d.ii) below.

Not all overdoses result in death; sometimes death is averted through intervention, and sometimes an overdose is inherently less than lethal. For simplicity, we assume that the inherent lethality of an overdose and the probability that intervention occurs (or at least is attempted) are independent; many attempted interventions occur for overdoses that may not have resulted in death in the first place. In its basic form, therefore, we represent the overdose death rate ($\omega_{(.)}$) as:

$$\omega_{(.)} = \beta_{(.)}\left(1 - p_{S(.)}\right)p_{D(.)} \tag{2.26}$$

The overall overdose rate ($\beta_{(.)}$) is multiplied by the complement of some base probability that overdoses are nonlethal, differentiating between Rx opioid and heroin overdoses (*base survival probability Rx OD / H OD*, p_{SR} / p_{SH}), and the probability that some lifesaving intervention does not successfully occur (*probability OD death not averted Rx / heroin*, p_{DR} / p_{DH}). We assume $p_{S(.)}$ is on average constant for a given substance, reflecting its inherent lethality given its usual modes of use; $p_{D(.)}$ is detailed further below.

Each use state (M, N, U_R, U_O, U_H) has its own base overdose rate parameter $\beta^*_{(.)}$, reflecting the combined effects of not only the substance involved and its usual modes of use, but also of frequency and patterns of use for that use state. For Rx OUD without heroin use (U_R), we also estimate a baseline (i.e., pre-illicitly manufactured fentanyl) synthetic-involved overdose rate (*overdose rate synth baseline*, β^S_R). We use the synthetic-involved overdose rate to help distinguish the effects of illicitly manufactured fentanyl from that of misused prescription fentanyl on overdose deaths, as detailed in S2.d.iii.(3) and S3.d.ii). Base overdose rates ($\beta^*_{(.)}$ / β^S_R) and survival probabilities (p^*_{SR} / p^*_{SH}) are estimated model parameters.

S2.d.iii.(2) Intervention probability structure & naloxone probabilities

For a death to not be averted, none of the potential interventions that could prevent it can occur. An intervention can only occur if an overdose is first witnessed by someone who could intervene. For simplicity, we treat potential interventions as independent conditional on an overdose being witnessed, such that $p_{D(.)}$ is the joint probability that none of them occur:

$$p_D = 1 - p_W p_I \tag{2.27}$$

$$p_I = 1 - \prod_j \left(1 - p_{Ij}\right) \tag{2.28}$$

Here p_W is the *probability OD witnessed* and p_{Ij} is the probability that intervention *j* successfully occurs, given that an overdose is witnessed. The value of p_W is derived from existing studies; see S3.d.v).

We represent two types of intervention, each with distinct probabilities of occurrence – bystander naloxone administration or calling emergency services. The *probability of calling emergency services* (p_{IE}) is a constant value estimated from literature (see S3.d.v)), which we assume results in a life-saving response by emergency medical services (EMS). If an EMS responder arrives, they have the ability to avert death for the overdose victim regardless of naloxone availability, by for instance using rescue breathing or mechanical ventilation during an ambulance ride to the hospital (A. Walley 2020, pers. comm., 1 Jul). While in reality naloxone improves the chances of successful EMS intervention somewhat [3]>, for simplicity, we assume that the success of the EMS intervention is not dependent on the availability of naloxone.

The probability of bystander naloxone administration (*probability Nx bystander…*, $p_{IB(.)}$) depends on the amount of naloxone distributed. Specifically, we represent $p_{IB(.)}$ using as a cumulative exponential distribution function of the density of naloxone kits distributed in the population:

$$p_{IB(.)} = 1 - e^{\lambda_N \nu_{(.)}} \tag{2.29}$$

Where λ_N is the *Nx kit distribution efficiency*, reflecting how effectively kits distributed end up in the times and places where they are needed, and $\nu_{(.)}$ is the number of *Nx kits per 100k population* for heroin

or Rx users. λ_N is an estimated parameter; the effect of varying efficiency on $p_{IB(.)}$ can be seen in **Figure 8**.

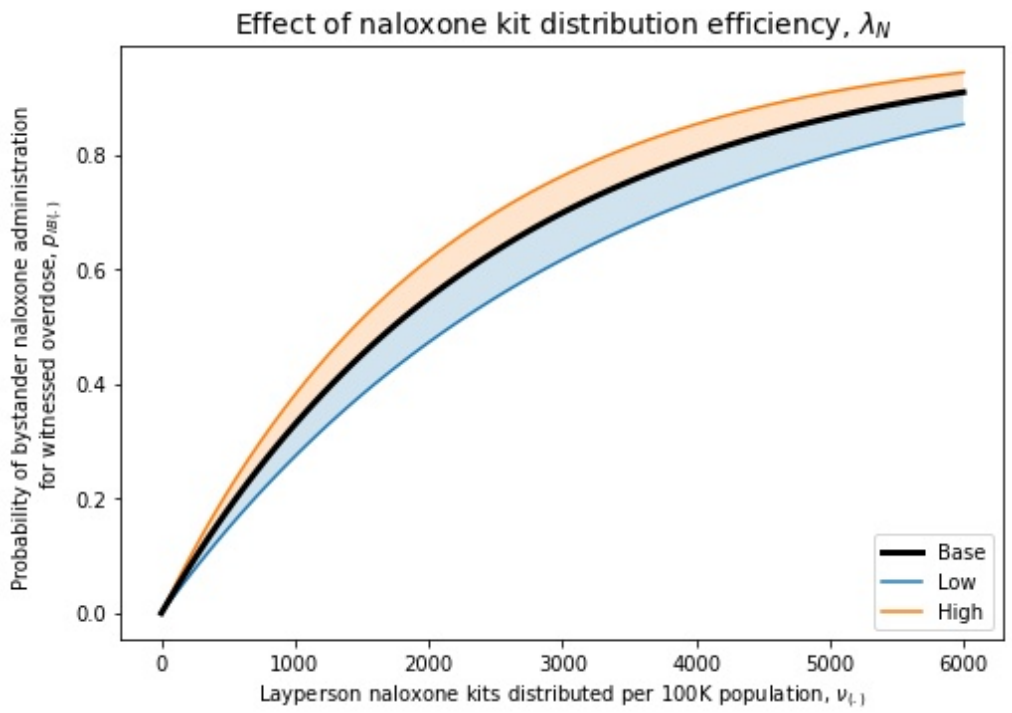

Figure 8. *Functional relationship between naloxone kits distributed and probability of naloxone administration in the event of witnessed overdose, as dependent on naloxone kit distribution efficiency parameter.*

Note that $\nu_{(.)}$ is normalised per 100,000 *total* people, rather than just people who use Rx opioids or heroin. The distinction between ν_R and ν_H depends on the channels by which naloxone is distributed and the populations such distribution focuses on (see S3.d.iv.(3)). The total amount of naloxone distributed is an exogenous time-series input, which is apportioned between Rx and heroin users based on an estimated parameter, the *fraction Nx kits to H users* (F^{NH}) (see S3.d.iv.(2)).

S2.d.iii.(3) Fentanyl effects on OD rates, survival rates, intervention probabilities

The prevalence of illicitly manufactured fentanyl in the illicit drug supply has increased rapidly since around 2013 [40,4]>. Fentanyl is far more potent than other Rx opioids or even heroin [42], and has substantially affected overdose risks. We operationalise the effects of fentanyl on each stage of the overdose process based on its prevalence in the drug supply. Specifically, we drive the underlying growth in fentanyl prevalence with exogenous data (*fentanyl penetration curve*, ϕ; see S3.d.iii)), representing the penetration of illicitly manufactured fentanyl in the heroin supply.

Note that while there is some evidence of fentanyl in counterfeit prescription opioids, especially on the west coast [17,19,21,2]>, to our knowledge no quantitative data tracking counterfeit prevalence exists. We therefore cannot quantitatively account for illicit fentanyl in the Rx supply at this time, nor the effects of counterfeit prescription pills containing fentanyl on the street availability of Rx opioids.

Fentanyl penetration ϕ can be thought of as the average probability of exposure to fentanyl for users of heroin in any given instance of drug use. We can therefore approximate the average effects of fentanyl

on overdose rates and survival probabilities as averages weighted by ϕ_H of their baseline heroin values and their corresponding values for fentanyl overdoses:

$$\beta_{(.)} = \beta^*_{(.)}(1-\phi) + w_{\beta F}\beta^*_{(.)}\phi \quad (2.30)$$

$$p_{SH} = p^*_{SH}(1-\phi) + p_{SF}\phi \quad (2.31)$$

Where $w_{\beta F}$ is the *fentanyl effect on OD rate H max*, i.e. how many times more likely overdose events are for fentanyl use relative to heroin use, and p_{SF} is the *base survival probability* of a fentanyl-involved overdose. These parameters, as well as the fentanyl penetration scaling factor ($s_{\phi H}$), are estimated in the main model calibration process.

Comparing overdose death rates against the counterfactual base death rates calculated using the base overdose rates and survival probabilities that exclude the effect of fentanyl allows us to attribute a certain portion of heroin-user deaths to the effects of illicit fentanyl (*overdose death rate synth…*, $o_{(.)F}$):

$$\omega_{(.)F} = \beta_{(.)}(1-p_{SH})p_{DHJ} - \beta^*_{(.)}(1-p^*_{SH})p_{DH} \quad (2.32)$$

We use this calculated death rate to estimate the contribution of illicit fentanyl penetration to overall overdose deaths.

S2.d.iii.(4) Nonfatal overdoses

We explicitly track nonfatal overdoses for each of the five main use states (M, N, U_R, U_O, U_H). The nonfatal overdose rate for each use state ($n_{(.)}$) is simply the difference between the overdose rate and overdose death rate for that state:

$$n_{(.)} = \beta_{(.)} - \omega_{(.)} \quad (2.33)$$

S3) Data Sources

S3.a) Main drug use states & transitions

Most data on drug use states and transitions in the model are drawn from the National Survey on Drug Use and Health (NSDUH). NSDUH allows us to distinguish individuals by the substances they have used in the past year (Rx opioids vs. heroin), as well as the degree of use associated with each substance (non-use vs. misuse / non-disordered use vs. use disorder). With two substances with three use states each, this creates a 3 x 3 matrix with 9 cells, of which 8 (excluding non-use of both) collectively map on to the 5 main drug use states in the model (M, N, U_R, U_O, U_H; see **Figure 9** and **Table 7**), in combination with the fraction of people in treatment not in remission (see S2.d.ii.(3)). Broadly, we aggregated matrix cells based on what substance is associated with the highest severity of use disorder and/or risk of overdose.

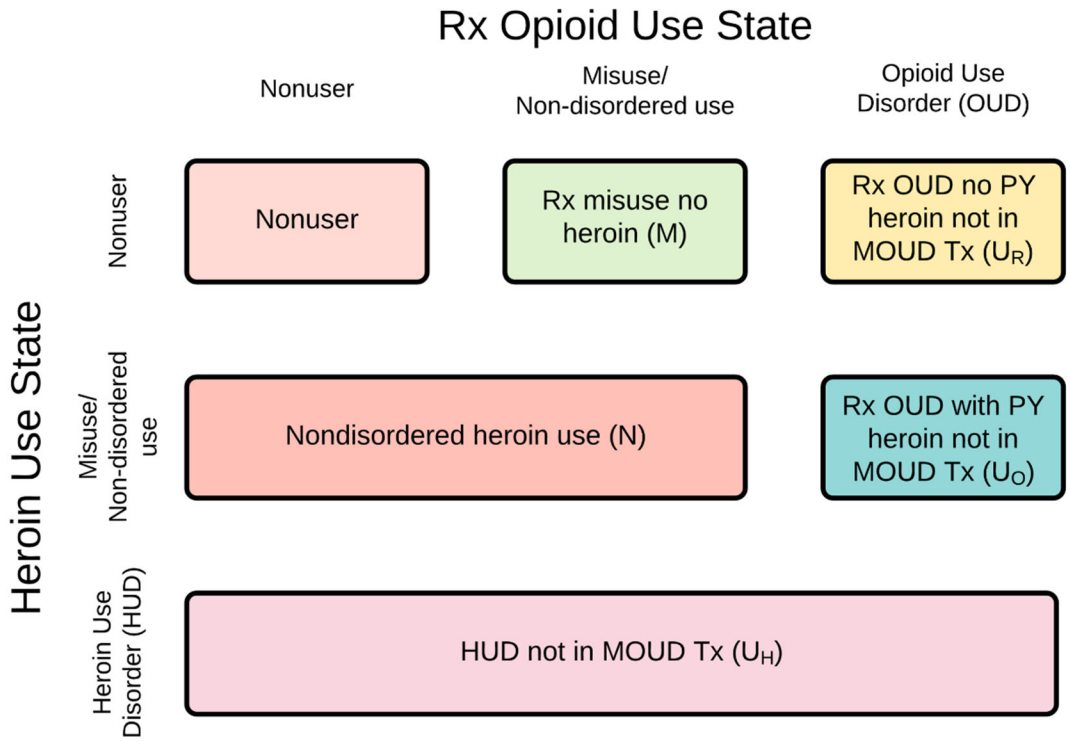

Figure 9. *Prescription opioid / heroin use state matrix with corresponding NSDUH data variables or model states*

S3.a.i) Prescription opioid misuse

We define Rx opioid misuse as including *any* use of someone else's opioid prescription *or* use of Rx opioids solely "for the feeling [they] caused." This definition matches the pre-2015 question wording in NSDUH >.

Our definition of Rx opioid misuse excludes people sometimes called "medical misusers," i.e., people who 1) used Rx opioids that were prescribed to them; 2) used them in ways other than as directed by their medical care providers; but 3) did so to treat pain (which is the intended therapeutic use of Rx

opioids) and not for any other reason. This can include, for instance, using Rx opioids prescribed to oneself, in therapeutic doses, to treat pain, of the same kind for which they were originally prescribed, but without first consulting a medical professional regarding the repeat use.

S3.a.i.(1) Adjustments for NSDUH question change

From 2015 onward, NSDUH defines misuse more broadly, in a way that includes "medical misusers" or more specifically anyone who has used Rx opioids in *any* way not as directed by their medical care providers >.

We account for this definitional change, which SAMHSA considers a trend break >, using a fixed effect for the percentage increase in reporting of misuse due to the definitional change (*NSDUH misuse redefinition fixed effect*, F^M). This fixed effect parameter is estimated as part of the model calibration process (see S4)). From 2015 onward, we adjust the time series on Rx misuse and misuse initiation (see S3.a.v)) accordingly:

$$\mathrm{M}_{adj}^{y} = \frac{\mathrm{M}^{y}}{1 + F^{M}} \tag{3.1}$$

$$\mathrm{r}_{\mathrm{MI}}{}_{adj}^{y} = \frac{\mathrm{r}_{\mathrm{MI}}^{y}}{1 + F^{M}} \tag{3.2}$$

This adjustment reduces the number of people misusing after 2015 by approximately a third.

S3.a.ii) Prescription opioid use disorder

We define use disorder states according the DSM-5 criteria; however, NSDUH does not use the DSM-5 definition. Instead, we approximate the DSM-5 definition from NSDUH using the count of DSM-IV criteria for substance abuse or substance dependence that they meet. We ignore reported legal problems, which is no longer a DSM-5 criterion for disorder, and we are unable to include craving, which was added to the DSM-5 criteria but is not queried in NSDUH (see **Table 2**) [4]>. Note that our use of NSDUH's DSM-IV criteria to approximate DSM-5 criteria differs from how NSDUH commonly reports 'use disorder' – NSDUH typically reports the union of DSM-IV substance abuse and substance dependence as 'use disorder', even though that more accurately reflects DSM-IV diagnoses rather than DSM-5 use disorder. This difference results in our calculated estimates for use disorder, particularly Rx OUD, being higher than what NSDUH reports as "use disorder."

We separate people with Rx OUD who have not used heroin in the past year vs. those who have (U_R vs. U_O, see **Figure 9**). We adjust all NSDUH heroin-use estimates, including the count of people with Rx OUD with past-year heroin use ($\mathrm{U}_{\mathrm{O}}^{y}$), to account for systematic under-reporting (see S3.a.vii)).

The NSDUH counts of people with past-year use disorder also include that fraction of people in treatment states in the model ($T_{(.)}$) who are not yet in remission, who by definition have qualified for use disorder within the past year (see **Table 7**).

Table 2. *DSM-5 criteria for substance use disorder, with comparison to DSM-IV substance abuse & substance dependence criteria*

DSM-IV	Diagnostic criterion
*	Craving or a strong desire to use opioids
A	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home
A	Continued opioid use despite having persistent or recurring social or interpersonal problems caused or exacerbated by the effects of opioids
A	Recurrent opioid use in situations in which it is physically hazardous
D	Opioids are often taken in larger amounts or over a longer period of time than intended
D	There is a persistent desire or unsuccessful efforts to cut down or control opioid use
D	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
D	Important social, occupational or recreational activities are given up or reduced because of opioid use
D	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
D	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
D	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms
DSM-IV column indicates DSM-IV diagnosis corresponding to DSM-5 criteria: A = substance abuse; 1 or more needed; 4th criterion (legal problems) removed from DSM-5 D = substance dependence; 3 or more needed in 12-month period * Craving is a DSM-5 criterion not included in DSM-IV diagnoses and not queried in NSDUH Source: [4]>	

S3.a.iii) Non-disordered heroin use

Approximately one-quarter of the people who report heroin use in the past year in NSDUH do not meet use disorder criteria for their heroin use. Anyone who reports past-year heroin use in NSDUH who does not qualify for HUD is counted either as having non-disordered heroin use (N^{y}) if they do not qualify for Rx OUD (or Rx OUD with past-year heroin use ($\mathrm{U}_{\mathrm{O}}^{y}$) if they do; see **Figure 1**). We adjust all NSDUH heroin-use estimates, including the count of people with NDHU (N^{y}), to account for systematic under-reporting (see S3.a.vii)).

S3.a.iv) Heroin use disorder

As with Rx OUD, we approximate the DSM-5 use disorder definition using NSDUH criteria (see above). Note that substance use disorder associated with Rx opioid use vs. heroin use are sometimes both collectively referred to as 'opioid use disorder', since heroin is an opioid substance. However, NSDUH queries each UD criterion for each substance separately, allowing us to identify whether UD is associated with use of Rx opioids, heroin, or both. For clarity, we use 'Rx OUD' to refer to UD associated with use of Rx opioids, and 'HUD' to refer to UD associated with use of heroin or both.

We adjust all NSDUH heroin-use estimates, including the count of people with HUD ($\mathrm{U}_{\mathrm{H}}^{y}$), to account for systematic under-reporting (see S3.a.vii)).

The NSDUH counts of people with past-year use disorder also include that fraction of people in treatment states in the model ($T_{(.)}$) who are not yet in remission, who by definition have qualified for use disorder within the past year (see **Table 7**).

S3.a.iv.(1) Caveat regarding HUD data

NSDUH's 2018 data on HUD prevalence and heroin use initiation show a downward trend from previous years, and 2019 data continue this downward trend, showing a sharp decline. The drop is large and rapid enough that several subject-matter experts expressed concern about the accuracy of the data. Changes in overdose mortality and MOUD treatment engagement are insufficient to explain the drop, but without specific data on remission (and relapse), we cannot conclusively demonstrate the physical impossibility or inconsistency of the reported numbers.

In consultation with our subject-matter experts, we have considered several plausible explanations for the decline – increased under-reporting due to growing fear or stigma, possibly associated with fentanyl; increasing self-identification as a fentanyl rather than heroin user (e.g. in regions where fentanyl has almost completely displaced heroin); and decreasing relapse due to 'older' cohorts of former heroin users attaining an increasingly durable state of remission. We found no evidence for the first two of these explanations, and our subject-matter expert team considered them less likely than there being issues with the NSDUH data.

Increasing durable or sustained remission was the only other explanation supported by our subject-matter experts as well as existing literature. We modified the model's remission structure (see S2.b) and S3.c.v)) to more accurately reflect this effect, which improved model performance but was insufficient to produce the observed decline.

We have inquired directly with SAMHSA several times about the 2019 HUD and heroin initiation data, and received no explanation beyond reiteration that they believe the 2019 data are in no way anomalous as no methodological changes occurred that may account for the difference.

With no further explanation or justifiable alternative, we have estimated the model on the assumption that the NSDUH 2019 HUD and heroin initiation data are no less accurate than in other years. This has several implications for the model's estimates, behaviour and projections.

Most importantly, the rapid drop in initiation indicates the risk response feedback (see S2.c.ii)) is very strong, exerting a dominant effect on the system in the last few years as the sharp rise in overdose mortality due to illicit synthetics deters new heroin initiates. Similarly, the fall in HUD prevalence indicates relatively high rates of remission vs. relapse, absent new initiations or use disorder development. With sustained high overdose mortality, this strong behavioural response results in a substantial projected decline in opioid use and mortality over the next decade.

If the 2019 heroin use data turn out to be, for whatever reason, a substantial under-estimate, then our model will have over-estimated the strength of this risk response feedback, as well as rates of HUD remission vs. relapse. A weaker risk response and lower remission / higher relapse rates will result in persistently higher levels of opioid use and overdose mortality than we are currently projecting, with a much slower decline.

S3.a.v) Initiating prescription opioid misuse

We derive data on annual initiation rates of Rx opioid use from NSDUH's Restricted Data Analysis System (RDAS), which allows identification of past-year initiates. The data do not directly distinguish between initiation of use with vs. without a prescription (r_{MI} vs. r_{MD}). To make that distinction, we use the fraction of past-year initiates who report that the source of Rx opioids for their *most recent* instance of misuse was one or more of their own prescriptions (vs. other sources), averaged over time, as a proxy for the fraction initiating misuse from a prescription. Due to the trend break in misuse reporting in 2015, we use separate fractions before 2015 and from 2015 onward.

S3.a.vi) Initiating heroin use

We derive data on annual initiation rates of heroin use from NSDUH's Restricted Data Analysis System (RDAS) as well, using it to identify whether individuals are initiating heroin with no past-year Rx opioid use (r_{ND}), with past-year Rx opioid misuse (r_{MN}), or with past-year Rx OUD (r_{UO}). These data were then adjusted to address under-reporting, as outlined below.

S3.a.vii) Heroin use adjustments

NSDUH estimates of the number of people who use heroin are notoriously low [44–4]. This under-reporting is due in part to exclusion of incarcerated populations where heroin use is disproportionately common, and in part to the strong stigma associated with heroin use. To correct for this under-estimation, we adjust all NSDUH data on prevalence and initiation of heroin use (N^y, U_O^y, U_H^y, r_{ND}^y, r_{MN}^y, r_{UO}^y) as follows.

No adjustment to empirical data should ever be undertaken lightly. We make this change noting that 1) the systematic problems with the data are well-known, and 2) the alternative of not adjusting the data would be worse, forcing skewed estimates of various parameters and creating errors that would propagate throughout the model (due to its enforced internal consistency and conservation of matter). Our adjustments are based on extensive literature review as well as discussions with subject matter experts (J. Caulkins 2020, pers. comm., 28 May; J. Mcaninch 2020 pers. comm., 24 Jul; R. Pacula 2020, pers. comm., 31 Jul) .

We base the adjustment on estimates of chronic heroin users (CHU) from the RAND Corporation report "What America's Users Spend on Illegal Drugs, 2006-2016" [47,5]. The report estimates number of CHUs for 2006-2016. We compare the RAND CHU population against the total NSDUH reported population of heroin users year by year ($N_t^y + U_{Ot}^y + U_{Ht}^y$), yielding an average ratio of 3.15. We then multiply each NSDUH heroin use population and initiation flow by this ratio. Note that the actual ratios of RAND to corresponding NSDUH estimates in the data decline over time, but for simplicity, we use a single average figure for each population group, meaning the temporal trends in the data are driven by NSDUH. This may result in some underestimation of heroin users in our adjusted data in earlier years, and some overestimation in later years.

S3.a.viii) Total population

As great a problem as the opioid crisis may be, the total US population is orders of magnitude larger. We therefore represent total population – or more accurately, the NSDUH survey population of non-institutionalised individuals aged 12 and older – as exogenous.

Total population figures for 1999-2019 are taken directly from NSDUH reports. For future years, projected total population is estimated by simple linear trend extrapolation of NSDUH data.

S3.b) Opioid prescribing, supply, and price data

S3.b.i) Prescription opioid supply

We draw most data regarding prescribing patterns, as detailed in S2.d.i.(1), from several proprietary IQVIA datasets – the National Sales Perspective®(NSP), National Prescription Audit® (NPA), and Total Patient Tracker® (TPT). NPA and TPT are national-level projected services designed to estimate the total number of unique (non-duplicated) prescriptions dispensed and patients receiving prescriptions respectively, across all drugs and therapeutic classes. NPA captures prescriptions dispensed in the outpatient setting at US retail and mail-order pharmacies, while TPT projects patient counts based on prescriptions dispensed from US retail pharmacies. NPA and TPT use prescription activity as part of their projections and integrate information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills. IQVIA has 92% coverage and a sample of about 48,700 retail pharmacies and captures about 3.5 billion transactions annually. NPA and TPT are projected to the known universe of retail pharmacies.

NSP estimates the volume of prescription drug products moving from distributors and manufacturers into various retail and non-retail outlets, in terms of sales dollars and product quantities. Retail outlets include various pharmacy settings, including mail-order; non-retail outlets include clinics, hospitals, long-term care facilities, and other such settings. NSP captures 86% of sales in the retail channel and 97% of the sales in the non-retail channel, or about 90% of the US pharmaceutical market in total. It includes sales from 388 indirect suppliers and direct sales reported from around 100 manufacturers, totaling about 1.5 billion transactions per year.

S3.b.i.(1) Total prescriptions and MMEs

For the total number of opioid analgesic prescriptions dispensed annually (*total prescription opioid Rx*), we use IQVIA NPA® data on the total number of prescriptions for all opioid analgesic products dispensed from US outpatient pharmacies (retail and mail-order) as well as long-term care facilities.

We calculate the total annual MMEs (*total Rx MME prescribed*) by multiplying the opioid units (e.g. pills, patches, vials) reported in IQVIA NPA by the appropriate MME conversion factors [5]>.

Note that neither total prescriptions nor total MMEs is used directly in the model; instead they are combined to calculate the *avg MME per opioid Rx* ($\mathrm{m_M}$). They are also used to derive a number of other prescribing-related time series as explained below.

S3.b.i.(2) Prescriptions per person and average duration

For the average number of *prescriptions per person* ($\mathrm{m_N}$) over time, we use data from Symphony Health Integrated Dataverse®. The Symphony Health data record total numbers of opioid analgesic prescriptions dispensed and patients receiving prescriptions each year, and group the patients by whether they receive 1, 2, 3, 4, and 5+ prescriptions within a calendar year. The data cover the period from 2009-2016.

We calculate *prescriptions per person* ($\mathrm{m_N}$) over time using the average of the proportions of the total Symphony Health sample receiving different numbers of prescriptions, weighted by the number of

prescriptions received. We assume here that patients in the 5+ prescriptions per year group receive an average of 8 prescriptions. This value has declined steadily from 2009-2016; for years outside this period, we therefore extrapolate $\mathrm{m_N}$ with a simple linear trend.

To calculate the *average prescription duration* (τ_M), on the advice of the FDA Office of Surveillance and Epidemiology (OSE), we make the further assumption that patients receiving 5+ prescriptions per year are more likely long-term opioid users whereas those receiving 1-4 prescriptions are more likely short-term users. For long-term users we assume a prescription duration of 1 month / 30 days, as long-term users typically require continuous daily use; for short-term users we assume a prescription duration of 0.5 months / 15 days. Using these distinctions, we calculate the overall average duration for each prescription based on the proportions of prescriptions received by presumptive short-term vs. long-term users, yielding τ_M=0.047 years.

S3.b.i.(3) Total patients receiving prescriptions

We calculate the total number of *patients receiving opioid prescription* each year ($\mathrm{m_P}$) using a combination of IQVIA NPA data on total prescriptions dispensed annually and Symphony Health data on the average number of prescriptions per patient each year. Symphony Health's data, while a large and nationally representative sample, is *not* projected to the full set of pharmacies, prescriptions, or patients nationally. However, it specifically focuses on identifying unique patients and patients receiving multiple prescriptions, making it a more accurate reflection of the *distribution* of prescriptions among patients (FDA Office of Surveillance and Epidemiology 2020, pers. comm., 24 Feb). We therefore combine that distribution with the projected national totals from IQVIA NPA to arrive at $\mathrm{m_P}$.

S3.b.i.(4) ADF fraction of prescribed supply

We calculate a time series for the *ADF fraction of prescribed Rx opioids* (F^{AR}) (see S2.d.i.(2)) using the same IQVIA NPA data and MME conversion factors [5]> used to calculate total annual MMEs above. We use a list of all FDA-approved ADF opioids currently marketed in the United States (see **Table 3**) to identify the total annual MMEs prescribed for ADF products and divide that by *total Rx MME prescribed* to arrive at the ADF fraction (of MMEs prescribed) for each year.

Table 3. *FDA-approved abuse-deterrent formulation opioids currently marketed in the US, by product name and active ingredient*

FDA-approved ADF opioids			
Product name	**Active ingredient**	**Product name**	**Active ingredient**
Arymo™ ER	Morphine	OxyContin®	Oxycodone
Embeda®	Morphine	RoxyBond™	Oxycodone
Hysingla® ER	Hydrocodone	Xtampza® ER	Oxycodone
MorphaBond ER™	Morphine		

S3.b.i.(5) OxyContin withdrawal street supply shock

We include a single historical Rx street supply shock (see S2.d.i.(2)), representing the August 2010 withdrawal of non-ADF OxyContin. To estimate the magnitude of this shock, in terms of the proportion of the street supply impacted, we used StreetRx, a crowdsourced database of street prices paid for illicit substances. StreetRx reports include information on substance, quantity, and price. We set the magnitude of the shock at 0.45 (where 100% of street supply = 1), equal to the fraction of total MMEs reported in StreetRx for 2010 consisting specifically of OxyContin (excluding other oxycodone).

S3.b.ii) Prescription opioid demand

To calculate the *Rx demand for misuse* (q_D), we use the number of people in each opioid use state multiplied by the per-person demand for opioid use for that use state, expressed in MMEs per year. We calculate per-person demand based on NSDUH data on average number of days of se per year, rounded to the nearest 10 days, reported over the 2010-2018 period: 50 days for M, 120 days for U_R, 170 days for U_O, 110 days for N, and 130 days for U_H. (The latter two categories are modified by the average fraction over 2010-2018 of people in those states who also use Rx opioids.) Note that these reported days of use are likely underestimates, particularly for the U_R and U_O groups. We multiply the days of use by assumed MME per day values of 40 MME/day for non-disordered groups (M and N), and 100 MME/day for use disorder (U_R, U_O, U_H). We believe these are conservative estimates, and actual use quantities are likely higher.

S3.b.iii) Heroin price

We calculate a normalised index of heroin price using data from two sources – US wholesale prices for heroin from the UN Office on Drugs and Crime [5]>, and heroin retail prices from the DEA System to Retrieve Information from Drug Evidence (STRIDE), as used in [53]. These two sources cover different years (2007-2018 vs. 2002-2011, 2013 & 2015 respectively). To combine them, we first normalised each price series to its 2007 value. We combined the two 2007-normalised indices, taking the mean in years where both were available and using whichever was available otherwise. Finally, we re-normalised the combined index to 2002, the year of model initialisation.

S3.c) Treatment & remission

[OSM] explicitly represents use of the three FDA-approved MOUDs – buprenorphine, methadone, and Vivitrol. Other forms of treatment (e.g., psychosocial, mutual aid group, etc.) are not explicitly represented; their effects are incorporated into non-MOUD remission pathways ($r_{UR(.)}$). Note that in contrast to drug use states, which represent *past-year* use, the treatment states in the model represent current, ongoing treatment receipt.

S3.c.i) Treatment receipt

We represent buprenorphine treatment receipt using IQVIA Total Patient Tracker® (TPT) data, which reports estimated total people receiving buprenorphine each year. This total includes only people receiving buprenorphine products designated for use as opioid antagonists (i.e. as MOUD), and not for pain. We multiply the TPT estimates by the average duration of buprenorphine treatment (τ_{TB}) to yield estimated total patients receiving buprenorphine at any point in time (T_B^y).

Methadone maintenance treatment (MMT) receipt (T_M^y) is estimated using N-SSATS point-in-time counts as of March 31 for each year from 2002-2019, with data interpolated for missing years.

For Vivitrol receipt, we use IQVIA National Sales Perspective®, which reports annual injections of Vivitrol. Because Vivitrol can also be used for alcohol use disorder (AUD), and IQVIA does not report the indication for use, we subtracted the average number of injections from 2006-2010 (prior to Vivitrol's approval for OUD treatment) from subsequent years, to arrive at estimates for Vivitrol injections for OUD. These estimates were then divided by 12, as injections are usually given monthly, to arrive at point-in-time counts for patients receiving Vivitrol (T_V^y).

S3.c.ii) Treatment-seeking and barriers

S3.c.ii.(1) Treatment seeking rates

We estimate a single base treatment-seeking rate in the model, which is the total treatment-seeking rate across MOUD types for people with Rx OUD without heroin use ($\rho_{TR} = \rho_{TRB} + \rho_{TRM} + \rho_{TRV}$), as part of the model calibration process. This base rate provides an anchor for all other treatment-seeking rates in the model.

In the absence of more detailed data to distinguish the states, we assume people with Rx OUD with heroin use seek treatment at the same rate as those without heroin use ($\rho_{TO(.)} = \rho_{TR(.)}$). Most literature on treatment does not distinguish between these two groups; indeed, most literature on treatment focuses on people with HUD rather than Rx OUD.

We express total HUD treatment seeking rate (ρ_{TH}) as a multiple of the base rate:

$$\rho_{TH} = m_{TRH}\rho_{TR} \tag{3.3}$$

Where m_{TRH} is the *Tx seeking rate HUD relative to Rx OUD no H*. We set m_{TRH} = 4.85 based on consistent data from NSDUH showing that a much higher proportion of all HUDs report seeking or receiving treatment compared to people with Rx OUD.

Treatment-seeking rates for each MOUD type are expressed as fractional multipliers of the total base rate, differing for Rx OUD vs. HUD:

$$\rho_{Tij} = m_{Tij}\rho_{Ti}, \qquad i \in \{\mathrm{R}, \mathrm{H}\}, j \in \{\mathrm{B}, \mathrm{M}, \mathrm{V}\} \tag{3.4}$$

The values of each of these fractions are based on expert estimates on relative patient preferences for each treatment type (see **Table 4**). For instance, while buprenorphine treatment is generally the most popular [54,5]>, people with HUD are much more likely to seek MMT than people with Rx OUD.

Table 4. *Relative rates of treatment-seeking by use disorder and MOUD type, compared to total Tx-seeking rate for OUD (r_{UTR})*

	Total MOUD Tx-seeking rate	Buprenorphine	Methadone	Vivitrol
Opioid use disorder	1	0.625	0.05625	0.31875
Heroin use disorder	4.85	2.6675	1.746	0.4365

Note that we do not account for people switching between medications within a given treatment episode, though it is possible for someone who receives one MOUD during one treatment episode to subsequently receive a different one later. We also assume patients seek a specific MOUD during a given treatment-seeking attempt, as the three available medications are generally viewed as quite different.

S3.c.ii.(2) Barriers to treatment receipt

We calculate the *Tx seeking barrier loss fraction* (F^L), i.e. the fraction of people seeking treatment who fail due to barriers such as affordability, acceptability, or stigma, based on data from NSDUH. Specifically, for people who make an effort to get treatment but do not receive it, NSDUH offers 15 potential reasons for non-receipt. We divide these reasons into three categories (see **Table 5**) – 1) affordability, e.g., lack of health insurance or insurance that doesn't cover treatment; 2) accessibility, e.g. lack of transportation to get to a treatment provider or providers not having space available for new

patients; and 3) stigma and other non-affordability issues, e.g. fear of potential negative opinions or belief that treatment will not help.

Since the model explicitly represents treatment capacity constraints, which captures the loss of potential treatment patients due to accessibility reasons, we do not include those people who report non-receipt exclusively for accessibility reasons in F^L. Instead, we include only those who report at least one of affordability and stigma or other non-affordability issues as reasons for treatment non-receipt:

$$F^L = \frac{Treatment\ seekers\ not\ receiving\ due\ to\ affordability\ or\ stigma\ barriers}{Total\ treatment\ seekers, receiving\ or\ not} \qquad (3.5)$$

Table 5. *Barriers to treatment engagement queried in NSDUH (with variable codes) and corresponding overarching categories used in model*

Need treatment but no health coverage or cannot pay	NDTRNNOCOV	Affordability
Need treatment but insurance doesn't cover substance use treatment	NDTRNNOTPY	
Need treatment but transportation posed a difficulty	NDTRNTSPHR	Accessibility
Need treatment but the type desired is not available	NDTRNWANTD	
Need treatment but the treatment centers had no open spaces	NDTRNPFULL	
Need treatment but don't know where to get it	NDTRNDKWHR	
Need treatment but afraid neighbors would have a negative opinion	NDTRNNDRNG	Stigma & other
Need treatment but afraid job will have a negative opinion	NDTRNJOBNG	
Need treatment but afraid others would find out	NDTRNFNDOU	
Need treatment but not ready to stop using	NDTRNNSTOP	
Don't think you need treatment	NDTRNNONED	
Need treatment but think you can handle the problem without it	NDTRNHANDL	
Need treatment but don't think that it will help	NDTRNNOHLP	
Need treatment but don't have time	NDTRNNTIME	
Some other reason	NDTRNMIMPT	

We capture the effect of accessibility barriers through the treatment capacity constraint. The *Tx demand fulfilment ratio* reflects how much of treatment demand, after accounting for non-accessibility barriers, can be met given the available capacity:

$$DFR = \frac{\mathrm{r}_{\mathrm{UT(.)}}}{\mathrm{r}^*_{\mathrm{UT(.)}}} = \frac{\mathrm{MIN}\left(\mathrm{r}^*_{\mathrm{UT(.)}}, K_{I(.)}\right)}{\mathrm{r}^*_{\mathrm{UT(.)}}} \qquad (3.6)$$

We calculate a prior (see S4.a.ii)) for this value for buprenorphine in 2018 ($\frac{\mathrm{r}_{\mathrm{UTB}}}{\mathrm{r}^*_{\mathrm{UTB}}}$) based on a recent audit study [5]>, which tracked treatment-seeking attempts and the success rate at obtaining an appointment for buprenorphine treatment. Specifically, we use the number of appointments offered as a proxy for $\mathrm{r}_{\mathrm{UTB}}$, and the sum of appointments offered and attempts failed due to access or capacity barriers as a proxy for $\mathrm{r}^*_{\mathrm{UTB}}$, yielding a calculated demand fulfilment ratio of 58.7% in 2018.

S3.c.iii) Treatment capacity

We calculate total buprenorphine-waivered providers (B), used to calculate effective buprenorphine capacity (K_B) as described in S2.d.ii.(2), using multiple literature sources (see S3.e)). These studies have

reported the estimated number of buprenorphine (i.e., DATA 2000) waivered providers each year since 2003, when buprenorphine was first approved for OUD treatment.

Comparing the number of patients receiving buprenorphine against the number of waivered providers shows that the average number of patients per waivered providers has been dropping as more providers get waivered (**Figure 10**). Combined with evidence that capacity continues to be a binding constraint on receipt of buprenorphine treatment (see above), we infer from this that the marginal contribution of each new waivered provider to effective capacity is diminishing, as explained in S2.d.ii.(2) above. We estimate the *Bup effective capacity decay constant* (λ_B) and base capacity per provider ($\widehat{K}_0$) at 3.5e-05 and 30 respectively, to match the empirically observed pattern (**Figure 10**; see also **Figure 6**).

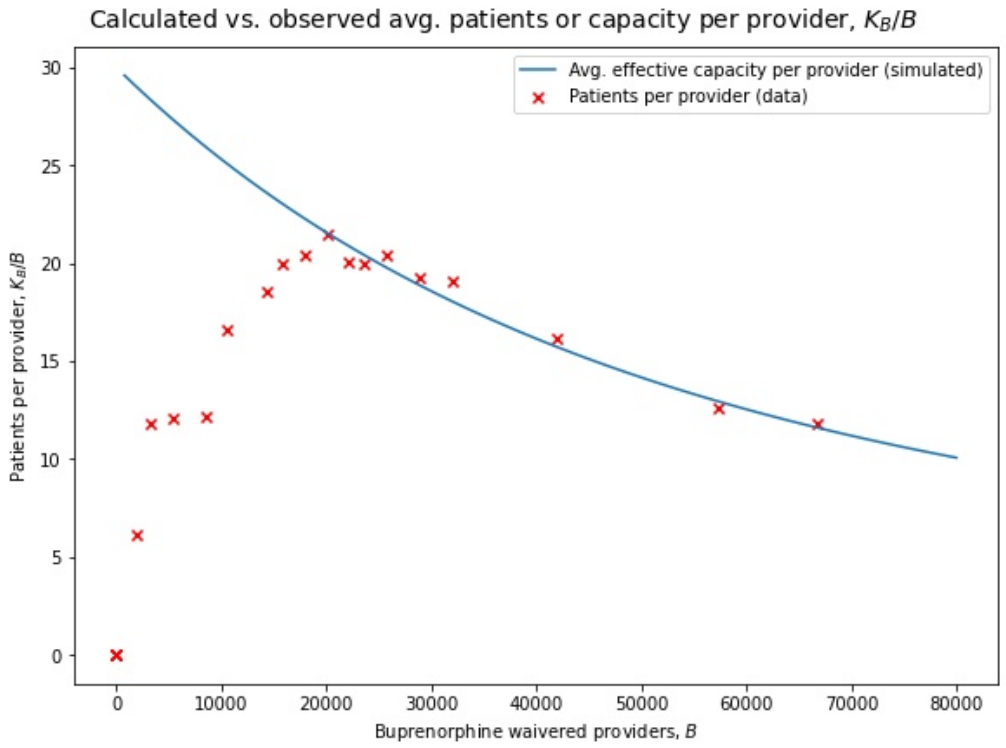

Figure 10. *Observed patients per provider against number of waivered providers in historical data, compared with calculated average effective capacity per provider in model. The calculated function for effective capacity over-estimates patients per provider for initial waivered providers, in part due to the lower initial waiver limits, but reproduces the declining average well for larger numbers of providers (which is more relevant for policy projections).*

To our knowledge, there are no time series data available for methadone (MMT) and Vivitrol capacity (including from national treatment surveys such as N-SSATS). As such, we estimate theoretical capacity ($K^*_{(.)}$) based on the number of patients receiving each of these types of treatment (see S3.c.i)) divided by the capacity utilization percentages ($F^{TU}_{(.)}$) reported for each in N-SSATS:

$$K^*_{(.)} = \frac{\mathrm{T}^{\mathcal{Y}}_{\mathrm{M}}}{F^{TU}_{(.)}}, \qquad (.) \in \{\mathrm{M}, \mathrm{V}\} \tag{3.7}$$

Absent additional data, we assume the effective capacity fraction is equal to the capacity utilization percentage ($F^{T}_{(.)} = F^{TU}_{(.)}$ = 0.866 for methadone and 0.88 for Vivitrol). Note that this creates a circularity –

effective treatment capacity ($K_{(.)}$) will be *exactly* equal to the number of patients receiving treatment $T_{(.)}^{y}$, resulting in an artificially perfect fit between simulated patient numbers and data as long as capacity is the binding constraint on treatment receipt in the model. This circularity can only be resolved with additional data on treatment capacity.

S3.c.iv) Treatment duration, outcomes, and effects

S3.c.iv.(1) Average treatment duration and outcomes

Average durations for buprenorphine, methadone, and Vivitrol treatment ($\tau_{T(.)}$) are calculated from mean or median reported durations of treatment, weighted by sample size, in multiple studies over two decades (see S3.e)), at 0.61, 1, and 0.23 years respectively. Where studies reported only medians but not means, we approximated the mean using the approach from [5]> based on either the interquartile range or minimum and maximum.

While a positive relationship between duration of retention in treatment and 'successful' treatment outcomes (i.e. sustained remission either in or after leaving treatment) is well-established [5]>, we identified only one study that actually reports 1) what fraction of treatment patients leave treatment 'successfully' vs. return to use disorder, 2) at various durations of treatment, and 3) how long on average each subgroup of patients remains in treatment [59].[3]

As such, we also drew on expert estimates to quantify the relationship between duration and outcomes of treatment. Our expert panel stipulated a sigmoidal relationship, estimating a very low success rate for durations < 4 months, approximately 25-40% success at 1 year, depending on medication, and a maximum success rate of approximately 75-80% by about 5 years. Consistent with these estimates and those of [5]>, we parametrise the function for *Tx success fraction* ($p_{(.)}^{R}$) to match these estimates, with m_R= 1, λ_R= 3.5, κ_R= 0.85, and p^{RM}= 0.8 (see S2.d.ii.(3)). Note that this results in higher success rates for treatment durations < 4 months than the near-zero rates that our experts estimated; however, there is evidence that *some* success with treatment is possible even after short durations [60].

S3.c.iv.(2) Effects of treatment on mortality

We express the *effect of MOUD Tx on OD death rate / non-OD death rate* ($w_{(.)}^{TO}$ / $w_{(.)}^{TN}$) as multipliers of the respective mortality rates for people with HUD or OUD not receiving MOUD treatment.

For non-OD mortality, we calculate an average aggregate non-OD mortality rate for untreated HUD and OUD groups of 1.43 people per 100 person-years. Based on reported hazard ratios, we calculate the effect of MOUD treatment ($w_{(.)}^{TN}$) at 0.54 for buprenorphine, 0.37 for MMT, and 0.93 for Vivitrol (see S3.e)).

For the effect on OD mortality ($w_{(.)}^{TO}$), several studies report no significant difference between hazard ratios for buprenorphine and methadone. As our calculated averages for each were very close (0.301 and 0.289 respectively), we instead use a combined average effect for buprenorphine and MMT of 0.295, with an effect of 0.439 for Vivitrol (see S3.e)). Note that for simplicity, we apply these multipliers to the overdose death rate, without modifying the base overdose rate. Insofar as the reductions reflect

[3] Specifically, [59] records that 28.8% of patients are successful, 36% drop out, and 18% are unsuccessfully transferred after median treatment durations of 39.5 weeks, 22.9 weeks, and 32.4 weeks respectively.

greater likelihood of resuscitation in the event of overdose, this is accurate; insofar as they may reflect reductions in baseline overdose rates, it likely means that non-fatal overdoses are being somewhat overestimated for people in MOUD treatment. This overestimation is, however, very small in absolute terms.

S3.c.v) Remission

Remission from disorder is a critical part of recovery, which ideally encompasses a return to functioning, health, and quality of life [6]>, though clinical remission is more narrowly defined as people who have had no symptoms of a substance use disorder for at least one year [1]. The estimated millions of people who are in opioid use disorder remission [62] reflect the history of the crisis. They are both a potential role model and source of hope for others, and also remain at risk of relapse themselves.

We found no reliable time series data on size of populations in remission, and so remission is excluded from our panel of time-series data used in model estimation. Nevertheless, their inclusion in the model is important, and indeed model performance is improved when this group is retained rather than allowed to disappear from the system.

Initial values for remission stocks (R_R, R_O, R_H, R_{RS}, R_{OS}, R_{HS}) are estimated using findings from various papers analysing NESARC Waves I and II (see S3.e)). Once people enter remission, they are no longer distinguished by their treatment history. This distinction could be made in future iterations of the model, if data become available that report the rates of relapse after remission by treatment history and type.

Note that though remission does not require abstinence, NSDUH does not identify people who report non-disordered use who are in remission from use disorder. Due to this lack of data, and to reduce model complexity, we do not represent non-abstinent remission (which would entail non-disordered use) as a separate state, nor do we capture flows of people from UD states into non-disordered use states. As a result, NSDUH respondents who report non-disordered use while in remission will be counted in the corresponding non-disordered use population counts (M^y or N^y).

Remission via MOUD is a function of duration in treatment (see S2.d.ii.(3)). We calculate the hazard rate of remission without MOUD (*remission rate… no MOUD Tx*, $\rho_{UR(.)}$) at 0.068 based on previous systematic reviews [61,6]>, as well as our own analysis of remission in several long-term studies (see S3.e)).

After four years on average in the remission stocks, people transition to stable remission (R_{SR}, R_{SO}, R_{SH}), after which they are no longer at risk of relapse or overdose death. Evidence indicates that the risk of return to use disorder typically drops considerably after an average total of five years in remission [64,6]>. We therefore set the *time to stabilize remission* (τ_{RS}) at 4 years (4 + 1 year already in remission by definition for the remission stocks = 5 years total).

S3.d) Overdoses, naloxone, and synthetics

S3.d.i) Overdose mortality data

We use annual multiple cause of death mortality data from CDC's National Vital Statistics System (NVSS) to estimate overdose death flows ($o_{(.)}$). The records in the NVSS microdata provide information on all deaths occurring within the United States, and each underlying cause of death is coded according to the International Classification of Diseases (ICD) classification system, Tenth Revision (ICD-10) [6].

We identified all drug-related fatal overdoses in NVSS mortality data using the following ICD-10 underlying cause of death codes: X40–X44, X60–X64, X85, or Y10–Y14. Among these records, we identified opioid-involved fatal overdoses by type[s] of opioid, using the following ICD-10 codes: prescription opioids or methadone (T40.2 or T40.3), heroin (T40.1), synthetic opioids other than methadone (T40.4), and unspecified opioids (T40.6) [6]. We group these records into a set of mutually exclusive and collectively exhaustive combinatorial categories, which we then aggregate into four streams of annual deaths (see **Figure 11**) involving:

1) Prescription opioids or methadone, but *not* heroin or synthetics
2) Heroin but *not* synthetics, possibly involving prescription opioids or methadone
3) Synthetics but *not* heroin, possibly involving prescription opioids or methadone
4) Synthetics *and* heroin, possibly involving prescription opioids or methadone

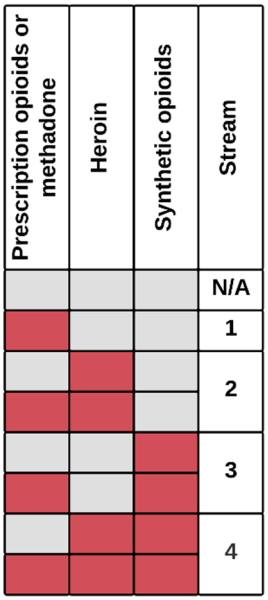

Figure 11: *Allocation of overdose mortality by MECE categories to model data streams. Red indicates that a drug class is reported as involved in a death, and grey*

Deaths involving only unspecified opioids are allocated in proportion to the size of these four categories each year. These four death data streams are read into the model to estimate overdose death flows.

The NVSS data identify overdose deaths by the substance[s] involved, e.g., Rx opioids only, Rx opioids + heroin, heroin + synthetic opioids, synthetic opioids only, and so on. This creates a fundamental limitation – deaths are identified by the substance[s] involved in the last use episode[s] before death, not by the use *behaviour* that the decedent primarily engaged in, but [OSM] classifies people by use behaviour (e.g., Rx OUD vs. HUD). We allocate deaths involving a given substance to the user group[s] which primarily use that substance, recognising that this is a substantial simplifying assumption. People with Rx misuse or Rx OUD with or without heroin use (M, U_R, U_O) are assumed to contribute to Rx overdose deaths, while people with non-disordered heroin use or HUD (N, U_H) contribute to heroin deaths.

S3.d.ii) Synthetic death allocation structure

Synthetic-involved deaths present an additional challenge. We do not explicitly identify synthetic users. Most synthetic use, especially since ~2013, involves illicitly manufactured synthetics that have entered the drug supply, whether as an adulterant in or replacement for heroin, or possibly in the form of

counterfeit prescription pills. Unfortunately, the CDC data (or any overdose death data to our knowledge) do not distinguish between prescription and illicitly manufactured synthetics.

Prior to ~2013, the vast majority of synthetic-involved deaths involved *only* synthetics, without other Rx opioids or heroin. All available evidence indicates that widespread fentanyl contamination of both pill and powder drug supplies only occurred after 2013 [27,40,4]>. We therefore assume that a small fraction of synthetic-involved deaths pre-2013 (specifically, those with co-reported heroin + synthetics) may have been due to low-level penetration of fentanyl in the illicit/powder drug supply (including a small but notable spike in 2005-2006 [68,69]), but that the vast majority of synthetic-involved deaths at the time (i.e. those with no co-reported heroin) were due to intentional misuse of prescription fentanyl. This separation allows us to estimate the baseline rate of overdose due to prescription fentanyl (β_R^S), which we assume affects people with Rx OUD [70,71].

Using β_R^S based on pre-2013 data, we can then separate synthetic-involved overdose deaths after 2013 into two streams:

1) a 'base' stream driven by intentional prescription synthetic use (without co-reported heroin), and
2) an 'excess' stream that combines
    a. synthetic deaths without co-reported heroin, less the projected base stream, presumably driven by largely unintentional use of illicitly manufactured fentanyl, with
    b. all synthetic deaths with co-reported heroin, driven by contamination of the heroin supply.

The latter two streams collectively account for the excess deaths attributable to fentanyl penetration through its effects on the process of overdose death (see S2.d.iii.(3)), which allows estimation of the effect sizes involved.

Note that we combine heroin deaths and excess synthetic deaths into a single stream for purposes of model estimation (see S4.b) for details).

S3.d.iii) Fentanyl penetration

We calculate a time series of fentanyl prevalence (*fentanyl penetration curve*, ϕ) used data from the National Forensic Laboratory Information System (NFLIS). NFLIS aggregates the number of reports of various drugs from forensic analyses of substances seized by law enforcement. We calculate ϕ as the fraction of reports involving fentanyl or its analogues out of the total reports of heroin or fentanyl & analogues each year:

$$\phi = \frac{Reports\ of\ fentanyl\ \&\ analogues}{(Reports\ of\ heroin + \ Reports\ of\ fentanyl\ \&\ analogues)} \quad (3.8)$$

Note that some portion of the reports of fentanyl & analogues may actually involve prescription fentanyl rather than illicitly manufactured fentanyl, as well as fentanyl pressed into counterfeit prescription pills as opposed to in powder form (see S2.d.iii.(3)). NFLIS data do not disambiguate reports by form or source, only substance. Because we cannot exclude these reports, ϕ is almost certainly an overestimate of powder-form, illicitly manufactured fentanyl as a fraction of heroin + fentanyl *reports*. However, several studies point to fentanyl exposure among heroin users being at least as great as indicated in

NFLIS, if not much higher – at least 50% by 2017 [72–7]>. We therefore do not think the overestimation of ϕ due to prescription fentanyl or counterfeit prescription pills is of substantial concern.

S3.d.iv) Naloxone distribution

S3.d.iv.(1) Total kits distributed

We approximate total naloxone distributed using two data sources, corresponding to the two main channels by which naloxone kits enter the community – distribution through harm reduction and other community programs, and pharmacy purchases.

We calculate the former using the only published national data on naloxone kit distribution through community programs [78–8]>. These reports provide annual estimates of kits distributed for three years (2009, 2013, 2019). We extrapolate to other years from these data points using the annual percentage growth in programs and estimates reported in these three years. Note that after mid-2014, the only publicly available data are on *injectable* naloxone kits (i.e., not Narcan®) distributed by the OSNN naloxone buyer's club [80], a different sample of harm reduction programs than is reported on in 2012 and 2015.

For naloxone purchased in pharmacies, we use IQVIA NPA® data (see S3.b.i)) on prescriptions for naloxone filled in outpatient pharmacies (retail and mail-order).

S3.d.iv.(2) Naloxone kit allocation

Kits are not distributed equally between people who use prescription opioids vs. heroin (D. Raymond 2020, pers. comm., 20 Aug), though we do not have a direct estimate of what fraction of kits go to heroin users (F^{NH}) vs. prescription opioid users, or more precisely, to people most likely to witness heroin user overdoses vs. prescription opioid user overdoses (e.g. including friends & family).

In order to estimate F^{NH}, we calculate the fraction of naloxone utilisation events involving heroin vs. prescription opioid overdoses, based on the total overdoses of each type multiplied by $p_W p_{IB(.)}$. We anchor the estimate of F^{NH} using a prior value (see S4.a.ii)) for the fraction of utilisation events involving heroin overdoses. We calculate at this fraction at 86% based on the fraction of naloxone reversals reported to harm reduction programs involving heroin or something other than prescription opioids [7]>.

S3.d.iv.(3) Naloxone distribution efficiency

We derive the functional form for *probability Nx bystander…*, $p_{IB(.)}$ (see S2.d.iii.(2)) based on data from [8]>, which is the only estimate to our knowledge of how naloxone distribution affects probability of utilisation in the event of overdose. [81] reports the probability of naloxone utilisation in witnessed overdoses across 12 US states as a function of naloxone kits distributed per 100,000 population. It also reports partial data on how probability of naloxone utilisation varies by distribution channel (standing order vs. prescription vs community distribution, though these data are insufficient to derive separate functions. An exponential function fits well with both the aggregated and disaggregate data reported.

Note that given the data available on total naloxone kits distributed (see above), this function results in naloxone kit utilisation fractions consistent with existing estimates from literature, which finds that 6-13% of all kits distributed are used (see S3.e)).

S3.d.v) Intervention Probabilities

We calculated *probability OD witnessed* (p_W) as the weighted average of the proportion of nonfatal overdoses that have been reported as witnessed (76.4%) across six studies (see S3.e)). Note that most of the data for this estimate come from older studies, as newer studies tend to report only the fraction of fatal overdoses that are witnessed. Conditioning on overdose fatality skews the reported probability compared to the unconditional probability (p_W), as whether an overdose is witnessed changes the net probability of death. Because the vast majority of overdoses are nonfatal, conditioning on overdoses being non-fatal results in less skew than conditioning on fatal overdoses, which are less likely to have been witnessed (41.1% weighted average; see S3.e)). In the absence of studies reporting aggregate witnessing probabilities for both fatal and nonfatal overdoses, we therefore use those with samples limited to the latter.

We calculated *probability of calling emergency services* (p_{IE}) in the event of a witnessed overdose using the weighted average from 31 studies that reported the fraction of all events witnessed during which the witness or someone else present called emergency services, yielding p_{IE} = 42.4% (see S3.e)). Most studies included people who use drugs, though some also included, e.g., friends and family members. Note that several studies were of people who had been trained in the use of naloxone, but at witnessed overdoses they reported only using naloxone and not also calling emergency services. Some evidence suggests possession of naloxone reduces the likelihood of calling emergency services [8], but we do not account for this potential interaction effect.

S3.e) Literature sources for parameter estimates

Various parameters in the model are synthesised from multiple studies following extensive literature searches. As a general rule, we sought to use multiple and diverse sources to compensate for the potential non-representativeness of study populations. Calculations and explanations for each parameter are described in the relevant sections above. Literature sources used are summarised in **Table 6**.

Table 6. *Literature sources for parameter estimates*

Parameter name	Parameter symbol	Parameter value	Sources
Average duration for buprenorphine		222.3 days, 0.61 years	[83,84,93–102,85,103,104,86–9]
Average duration for methadone		365 days, 1 year	[83,88,107–109,90,92,97,98,101,104–10]
Average duration for injectable naltrexone (Vivitrol)		82.4 days, 0.23 years	[87,102,110–11]
Average aggregate non-OD mortality rate for untreated OUD and HUD groups		1.43 per 100 person-years	[114–11]
Buprenorphine-waivered providers	B		[120–12]

Effect of MOUD treatment on non-OD mortality	w_B^{TN}	0.54	[115–119,125–12]
Effect of MOUD treatment on non-OD mortality	w_M^{TN}	0.37	[115–119,125–12]
Effect of MOUD treatment on non-OD mortality	w_V^{TN}	0.93	[115–119,125–12]
Effect of MOUD treatment on OD mortality	w_B^{TO}, w_M^{TO}	0.295	[115–119,125–12]
Effect of MOUD treatment on OD mortality	w_V^{TO}	0.439	[115–119,125–12]
Initial value for remission stocks	R_R, R_O, R_H, R_{RS}, R_{OS}, R_{HS}		[128–13]
Naloxone kit utilization fraction		6-13%	[78,133,142,143,134–14]
Probability OD witnessed	p_W	76.4%	[144–14]
Probability fatal OD witnessed		41.1%	[150–15]
Probability of calling emergency services	p_{IE}	42.4%	[133,135,151,155–163,136,164–173,137,174,139,141,143,147–14]

S4) Model Estimation

S4.a) Overview

[OSM] is a nonlinear and complex model, which makes finding an estimation framework with clean, closed-form analytical solutions highly challenging and unlikely. Instead, we estimate the model by maximum likelihood [17]>, using a Gaussian likelihood function to fit simulated time series to historical data, as well as a penalty term on a small number of point observations of certain key ratios. The model can be thought of as a deterministic system of ordinary differential equations, with some set of unknown parameters (as well as known ones specified based on literature, expert estimates, etc., and exogenous time-series inputs). To avoid over-fitting, we do not use any time-varying parameter inputs. The maximum likelihood estimation framework identifies the most likely value for each unknown parameter, given the historical data. We combine this with a Markov Chain Monte Carlo (MCMC) simulation approach [176,177] to identify the credible regions of parameter space and quantify uncertainties in parameter estimates and projections. We describe a number of validation procedures aimed at building confidence in the estimation framework in S4.e).

S4.a.i) Likelihood function for historical data

The model generates simulated expected values for several time series variables, such as populations in several use states various transition flows between states (see **Table 7** for full listing of time series used in estimation). Let μ_{it} represent simulated values for variable i at time t, while y_{it} represents the corresponding observed historical data points. With $\boldsymbol{\theta}$ as the vector of unknown model parameters, we can summarise the model as a function *f* that yields predicted values for μ_{it} given $\boldsymbol{\theta}$ as well as a set of exogenous time-series inputs x_{jt} (for variables *j* e.g. prescribing rates, naloxone distribution; see **Table 7** and S3) for details):

$$\mu_{it} = f(\boldsymbol{\theta}, x_{jt}) \tag{4.1}$$

We use a Gaussian (log-) likelihood function to specify the likelihood of observing y values given $\boldsymbol{\theta}$ and x (which result in predictions μ):

$$LT(y_{it}|\boldsymbol{\theta}, x_{it}) = \sum_{it} -\frac{(\mu_{it} - y_{it})^2}{2{\omega_i}^2} - \ln(\omega_i) \tag{4.2}$$

Summing the log-likelihood function over variables i and times t yields the full log-likelihood for observed data given a specific parameterisation and set of time-series inputs. The Gaussian function includes a set of scale parameters or calibration weights for each i variable (ω_i), which we estimate as the standard deviations of the corresponding observed time series y_{it}. These weight variables account for differences in the underlying magnitude and variability of the different time series used.

S4.a.ii) Penalty terms for key point observations

In addition to the likelihood value for observing historical data series, we also calculate a penalty term for certain key ratios and other point observations k. These penalty terms represent priors derived from literature estimates, expert judgment, or limited datasets, which we incorporate to provide some constraint on the estimation process:

$$LP(y_{kt}|\boldsymbol{\theta}, x_{jt}) = -\sum_{kt} \frac{(\mu_{kt} - y_{kt})^2}{2{\omega_k}^2} \quad (4.3)$$

Here y_{kt} represents the prior expected values for k defined over specified time periods, which are compared against the model-generated values μ_{kt}. The scaling parameter ω_k represents the pre-specified allowable deviation of k values from their prior expected values.

While the selection of key observations k and their prior expected values y_{kt} and allowable variance ω_k are guided by existing data, there is inevitably an element of subjectivity in their selection. Such subjectivity, however, is not disqualifying. There is a degree of subjective judgment involved in any modelling endeavour, from problem definition to model specification to the estimation process, and indeed in all scientific endeavour in the first place. Incorporating priors in this manner allows us to inject valuable information into the estimation process without constraining it more than the quality of said information warrants. Absent the use of priors, we would either have to discard the informational value of these data points, or build them into hard constraints on parameters or fixed assumptions, neither of which seems like a desirable alternative. Instead, therefore, we aim to present the use of these assumed priors in a transparent manner while also validating the estimation procedure where possible (see S4.e)).

S4.b) Data used in estimation

Table 7 summarises the panel of time series data used in model estimation, whether as observed targets for model fitting y_{it} or as exogenous input variables x_{jt}. Sources and adjustments for these data are detailed in S3).

Table 7. *Panel of time-series data used in model estimation*

Time series		Source	Model variable[s]
Observed data / calibration targets y_{it}	Rx misuse no PY heroin	NSDUH	M
	Nondisordered heroin use	NSDUH	N
	Rx OUD no PY heroin	NSDUH	$\sum_{(.)} \mathrm{U_R} + (1 - F^R_{(.)})\mathrm{T_{R(.)}}, \quad (.) \in \{B, M, V\}$
	Rx OUD with PY heroin	NSDUH	$\sum_{(.)} \mathrm{U_O} + (1 - F^R_{(.)})\mathrm{T_{O(.)}}, \quad (.) \in \{B, M, V\}$
	HUD	NSDUH	$\sum_{(.)} \mathrm{U_H} + (1 - F^R_{(.)})\mathrm{T_{H(.)}}, \quad (.) \in \{B, M, V\}$
	Total buprenorphine patients	Various	$\sum_{(.)} \mathrm{T_{(.)B}}, \quad (.) \in \{R, O, H\}$
	Initiating Rx misuse own Rx	NSDUH	$\mathrm{r_{MI}}$
	Initiating Rx misuse diverted	NSDUH	$\mathrm{r_{MD}}$
	Total heroin initiation	NSDUH	$\mathrm{r_{ND} + r_{MN} + r_{UO}}$
	Initiating heroin no Rx	NSDUH RDAS	$\mathrm{r_{ND}}$
	Initiating heroin with Rx misuse	NSDUH RDAS	$\mathrm{r_{MN}}$
	Initiating heroin with Rx OUD	NSDUH RDAS	$\mathrm{r_{UO}}$
	Total overdose deaths base Rx	NVSS	$\mathrm{o_{mc} + o_M + o_{UR} + o_{UO} + o_{TR} + o_{TO}}$
	Total overdose deaths synth base	NVSS	$\mathrm{o_{URS}}$
	Total overdose deaths heroin & excess synthetics	NVSS	$\mathrm{o_{UN} + o_{UH} + o_{UNF} + o_{UHF} + o_{TH}}$
	Total overdose deaths	NVSS	$\sum_{(.)} \mathrm{o_{(.)}}$
Exogenous inputs x_{it}	Patients receiving opioid prescription	IQVIA, Symphony Health	$\mathrm{m_P}$
	Prescriptions per person	Symphony Health	$\mathrm{m_N}$
	Average opioid MME per prescription	IQVIA	$\mathrm{m_M}$
	ADF fraction of prescribed opioids	IQVIA	F^{AR}
	Buprenorphine-waivered treatment providers	Various	B
	Methadone maintenance treatment capacity*	N-SSATS	K_M
	Vivitrol® treatment capacity*	IQVIA	K_V
	Naloxone kits distributed	IQVIA, various	ν_T
	Heroin price index («StartYear» = 1)	UNODC, STRIDE	$1/D_{AH}$
	Fentanyl penetration	NFLIS	ϕ

S4.c) Iterative estimation procedure

With [#] parameters, the model is sizeable, but not so large as to make searching the full parameter space computationally impractical. Nonetheless, to speed up the estimation process, we use a multi-step iterative procedure, estimating partial models first [17]> in order to converge on the most likely region of parameter space before estimating the full parameter vector simultaneously. All steps prior to [STEP] use the Powell direction search method implemented in Vensim™ simulation software.

1) We split the parameter vector $\boldsymbol{\theta}$ and the set of data variables used in calibration y_{it} into a few subsets. Specifically, we define $\boldsymbol{\theta}_{\mathrm{o}}$ as the subset of parameters that directly affect overdose death risks (as explained in S2.d.iii)), with y_{ot} being the data variables directly tracking overdose deaths; we also define $\boldsymbol{\theta}_{\mathrm{S}}$ as the subset of *initial stock correction* parameters ($m_{0(.)}$), explained further below. Remaining parameters (excluding $\boldsymbol{\theta}_{\mathrm{o}}$ and $\boldsymbol{\theta}_{\mathrm{S}}$) we define as $\boldsymbol{\theta}_{\mathrm{m}}$.
2) We first estimate only the subset of parameters $\boldsymbol{\theta}_{\mathrm{o}}$ that directly affect overdoses, to maximise the likelihood of observing y_{ot}, holding all other parameters constant at their previous best-estimate values. The first time we perform this step during each estimation process, overdose deaths are calculated using exogenous data values $y_{(.)t}$ for all drug user stocks; subsequently, we use endogenously generated stock values. This is in effect a partial model calibration aimed at matching just the overdose death data using only overdose-related parameters. With 11 overdose-related parameters included in this step out of 63 estimated parameters total, it helps to narrow down the plausible range of parameter space.
3) Next we estimate only $\boldsymbol{\theta}_{\mathrm{m}}$, using the full set of target data y_{it}, holding $\boldsymbol{\theta}_{\mathrm{o}}$ constant at the values estimated in step (2).
4) Next we estimate only the initial stock correction parameters $\boldsymbol{\theta}_{\mathrm{S}}$, using the full set of target data y_{it}, holding $\boldsymbol{\theta}_{\mathrm{o}}$ and $\boldsymbol{\theta}_{\mathrm{m}}$ constant at previously estimated values. The initial stock corrections modify the baseline initial stock values ($\mathrm{S}^{*}_{(.)0}$), which are derived from values of data at the initialisation of the run in [#]:

$$\mathrm{S}_{(.)0} = m_{0(.)}\mathrm{S}^{*}_{(.)0} \tag{4.4}$$
$$\mathrm{S}^{*}_{(.)0} = y_{(.)0} \tag{4.5}$$

   The correction parameters are necessary to allow initial stock values to differ from the first observed data points. These first data points ($y_{(.)0}$) are not inherently any more accurate than any other values for these stocks observed in the data ($y_{(.)t}$), and are equally subject to random variation like process noise and measurement error. The estimation process accounts for such randomness over time; however, using the first data points directly as the initial stock values would effectively over-weight those first points, asserting that the random variation contained in their values is of zero magnitude. The initial stock corrections ($m_{0(.)}$) provide a means to avoid this problem, giving the first data points the same importance as any others.
5) We iterate through steps (2)-(4), each time holding constant the parameter subsets ($\boldsymbol{\theta}_{\mathrm{o}}$, $\boldsymbol{\theta}_{\mathrm{S}}$, $\boldsymbol{\theta}_{\mathrm{m}}$) not being estimated in the current step at their last-estimated values, until the iterations cease to offer significant improvement (approx. 0.05% of total log-likelihood) when compared at step (3). At that point, we assume the estimation has converged to close to the optimal parameter set, speeding the subsequent steps. Step (4) is repeated one more time before moving on.

6) We conduct a full optimization using the complete parameter vector $\boldsymbol{\theta}$ and comparing the full set of time-series data y_{it}, starting from the parameter values estimated in the last iteration in step (5). This full optimization locates the exact peak in the full likelihood landscape, which corresponds to the best-fit maximum likelihood parameter set $\widehat{\boldsymbol{\theta}}$ for the full model.
7) Finally, we carry out an MCMC simulation to explore the likelihood surface in parameter space around $\widehat{\boldsymbol{\theta}}$. We use an MCMC algorithm designed for exploring high-dimensional parameter spaces using differential evolution with self-adaptive randomised subspace sampling [17]>. We use an extensive burn-in period of 1.5 million MCMC samples, by which point the MCMC chains yield stable outcomes; we then continue the MCMC to sample a further 1 million outcomes, and then randomly take a subsample of 2500 of those 1 million sampled points to use for sensitivity analyses and projections (see S6)). We also use this subsample to derive 90% credible intervals for parameter estimates.

This process is automated using a Python script that controls the simulation software (Vensim). We conduct the analysis using a parallel computing feature of Vensim on a multi-core Windows machine. Full analysis code is available online at [LINK].

S4.d) Quantifying uncertainties

S4.d.i) Credible intervals for parameter estimates

Estimated parameters can have interacting effects on the total likelihood and overall fit of the model to observed data. Maximum likelihood parameter estimates are therefore not independent, but should be thought of as a parameter set $\widehat{\boldsymbol{\theta}}$. Similarly, the MCMC simulation explores the high-likelihood credible *region* of parameter space, producing a sample or subsample of credible parameter *sets*. This credible region provides a more meaningful quantification of uncertainty in parameter estimates than univariate ranges, which are in effect the projections of the credible region onto each parameter's axis. We therefore utilise the MCMC subsample of credible parameter sets for projections and sensitivity analyses, detailed below.

However, reporting a high-dimensional credible region is impractical and difficult to present meaningfully. For transparency, we report here the univariate 90% credible intervals for each parameter (**Table 9** in S5.a)), with the caveat that they should be interpreted with care. The full MCMC subsample that defines this region is available online at [LINK].

S4.d.ii) Estimating measurement error

The estimation procedure identifies the region of parameter space that results in the highest likelihood of observing the data y_{it} given the model f. The model, however, is deterministic, and does not account for random process noise nor measurement error. Model-generated predictions based on the maximum-likelihood parameter set, $\hat{\mu}_{it}$, therefore represent expected values for observed variables y_{it}, rather than predictions or projections of the exact unobserved realisations of variables i, which will include process noise, or of observed variables y_{it}, which will include measurement error as well. Similarly, projections based on the credible region of parameter space around $\widehat{\boldsymbol{\theta}}$ capture uncertainty in the expected values of observed variables, rather than the full range of uncertainty in possible trajectories for those variables, which includes the aforementioned sources of randomness.

In order to make projections that better express the range of possible trajectories, therefore, we need to account for such randomness. We do this by injecting random noise into model projections for variables i, with a unique realisation of this noise stream for each parameter set in the credible region used in projections or sensitivity analyses.

To parametrise the distribution of this noise term, we fit a multivariate Normal distribution to the residuals from the main model estimation process. Use of a multivariate rather than independent univariate Normal distributions is important as many of the observed variables draw on the same few data sources (e.g. NSDUH, NVSS), so there is likely to be substantial covariance in their measurement errors. On the other hand, while autocorrelation is a common issue with time-series data, the long interval between data points (1 year) relative to the speed of underlying processes means there is little autocorrelation in the residuals, with most sources of inertia in the data accounted for by model mechanisms. We therefore use noise terms without autocorrelation.

S4.e) Synthetic data validation

To build confidence in our estimation framework, we conducted a synthetic data experiment to better assess its accuracy. We generate synthetic data representing artificial 'parallel universes' by simulating the model with known parameter values combined with simulated measurement noise. We then attempt to recover those parameter values from the simulated data using our exact estimation framework. We can then assess how well the estimated parameters and credible intervals correspond to the known, true values.

S4.e.i) Data generation and estimation

To generate the synthetic data, we first randomly draw «SynSets» parameter sets $\boldsymbol{\theta^s}$ from the MCMC subsample generated in the main model estimation process as described in S4.b). Since these parameters sets are drawn from the credible region of parameter space, they provide plausible alternatives similar but not identical to the model's estimated most-likely parameter set $\widehat{\boldsymbol{\theta}}$. We then simulate the model using these parameter sets, injecting 'measurement' noise into simulated model outputs to create realistic 'observed' values for data, y_{it}^s. The noise stream for each synthetic data set is randomly drawn from the same multivariate Normal distribution estimated for the residuals from the main model estimation process, as described in S4.d.ii).

The synthetic data sets thus generated are available online at [LINK].

We then estimate the model using each synthetic data set y_{it}^s in turn, in place of observed data. We use the same set of exogenous time-series inputs x_{jt} for each estimation. Estimation follows the same procedure as for the main model, described in S4.b). As with the main estimation, we start with uninformed priors on all parameters (uniform distributions with large ranges).

S4.e.ii) Synthetic data estimation results

The percentage of parameter values estimated from synthetic data falling within varying credible intervals is shown in **Table 8**. Generally, the percentage of parameters within each theoretical CI is somewhat smaller than expected by definition. This is largely as expected, as the model's structure does not capture all possible sources of random variation nor indeed all possible structural drivers of the observed phenomena; too high a percentage within each CI level would indicate possible over-fitting. In

addition, the results are skewed slightly by a handful of data series for which some systematic bias was present; see **Table 10** in S5.b).

Table 8. *Proportion of synthetic data parameter estimates falling within various theoretical credible intervals*

Perc	0
50%	0.307534
80%	0.54726
90%	0.636986
95%	0.687671
98%	0.739726

S5) Full results

S5.a) Full parameter estimates

Table 9 shows most likely values $\widehat{\boldsymbol{\theta}}$ as well as medians and 90% credible intervals for all 63 estimated parameters and 20 initial stock value adjustments $\boldsymbol{\theta}$. In some cases, the most likely value falls outside the 90% credible interval. While uncommon, this is not inherently erroneous – it could for instance indicate a 'cliff-shaped' likelihood surface, shallow-sloped on one side of its highest point and dropping off steeply on the other.

Table 9. *Complete list of estimated parameter values & credible intervals*

	Value	0.05	0.5	0.95
ADF effect strength initiating heroin with Rx OUD	0.01	0.01	0.110668	0.519019
Base survival probability H OD relative to Rx	0.977961	0.970388	0.980138	0.990074
Base survival probability Rx OD	0.971674	0.964591	0.970939	0.975765
Developing HUD rate no Rx OUD	0.203679	0.11341	0.194221	0.256677
Developing HUD rate with Rx OUD	0.726097	0.607029	0.720052	0.82174
Developing Rx OUD rate	0.032924	0.026935	0.032893	0.042293
Fentanyl effect on base survival max relative to H	0.631458	0.584376	0.647227	0.705156
Fentanyl effect on OD rate H max	2	2	2.01633	2.084197
Fraction Nx kits to H users	0.943129	0.89941	0.933174	0.95
Heroin price strength developing HUD	0.01	0.01	0.053412	0.23096
Heroin price strength initiating NDHU no Rx	0.01	0.01	0.028798	0.09067
Heroin price strength net quit NDHU	1.78721	1.390608	1.749765	1.998201
Initial stock correction[RXM]	1.2	1.134158	1.182655	1.2
Initial stock correction[NDH]	1.2	1.156902	1.191566	1.2
Initial stock correction[OUB]	1.16703	0.8	1.003207	1.2
Initial stock correction[OUM]	0.8	0.8	0.942563	1.180828
Initial stock correction[OUV]	1.07504	0.815409	1.02441	1.2
Initial stock correction[OUT]	1.18248	0.981645	1.148652	1.2
Initial stock correction[OUR]	1.2	0.889505	1.105895	1.2
Initial stock correction[OUS]	1.02538	0.81685	1.05075	1.2
Initial stock correction[OHB]	0.999731	0.835233	1.073869	1.2
Initial stock correction[OHM]	0.8	0.8	1.01016	1.2
Initial stock correction[OHV]	1.18934	0.801128	0.987831	1.192506
Initial stock correction[OHT]	1.2	0.85435	1.090929	1.2
Initial stock correction[OHR]	0.8	0.8	0.967487	1.191232
Initial stock correction[OHS]	0.920384	0.8	0.979872	1.193875
Initial stock correction[HUB]	1.18152	0.803806	1.015715	1.2
Initial stock correction[HUM]	1.2	1.058131	1.167882	1.2
Initial stock correction[HUV]	0.822524	0.8	0.934168	1.172224
Initial stock correction[HUT]	0.8	0.8	0.810098	0.839248
Initial stock correction[HUR]	1.2	0.805578	1.031807	1.2

Initial stock correction[HUS]	1.18852	0.802021	1.012567	1.2
Initiating heroin no Rx base	120886	115187.3	120448	125566.2
Initiating Rx misuse diverted base	1902070	1816559	1922883	2060031
Initiation rate heroin with Rx misuse	0.016411	0.014415	0.015984	0.017524
Initiation rate heroin with Rx OUD relative to Rx misuse	3.52071	3.304415	3.68319	4.169408
Initiation rate Rx misuse own Rx	0.045356	0.040581	0.047097	0.053816
Net quit rate heroin with Rx misuse	0.01	0.01	0.021246	0.076589
Net quit rate heroin with Rx OUD	0.01	0.01	0.016138	0.039382
Net quit rate NDHU	0.386108	0.292719	0.372976	0.461236
Net quit rate Rx misuse	0.152422	0.115689	0.147615	0.175928
NSDUH misuse redefinition fixed effect	0.469162	0.411582	0.462558	0.499073
Nx kit distribution efficiency	0.000397	0.000333	0.0004	0.000466
Overdose rate base HUD	0.143863	0.126405	0.148128	0.175758
Overdose rate NDHU relative to HUD	0.25	0.25	0.259222	0.293583
Overdose rate base Rx misuse	0.001	0.001	0.003283	0.008744
Overdose rate base Rx OUD	0.256004	0.187575	0.238179	0.298544
Overdose rate synth baseline	0.005355	0.005	0.005648	0.006667
Perceived risk strength initiating heroin with Rx use	0.911213	0.766158	0.918979	1.069379
Perceived risk strength initiating NDHU no Rx	0.187885	0.145434	0.239278	0.346726
Perceived risk strength initiating Rx misuse diverted	0.614648	0.494515	0.664996	0.93921
Perceived risk strength initiating Rx misuse own Rx	0.734844	0.503027	0.785909	1.059356
Perceived risk strength net quit heroin with Rx OUD	0.01	0.01	0.156371	0.454153
Perceived risk strength net quit NDHU	0.01	0.01	0.023319	0.085392
Perceived risk strength net quit NDHU with Rx	0.01	0.01	0.07765	0.273504
Perceived risk strength net quit Rx misuse	0.904099	0.613554	0.856874	1.122377
Relapse rate HUD	0.084448	0.01	0.122835	0.381061
Relapse rate Rx OUD relative to HUD	0.999999	0.756658	0.943467	1
Remission rate HUD no MOUD Tx	0.076531	0.061153	0.085477	0.128422
Remission rate Rx OUD relative to HUD	1.82341	1.233973	1.759135	2
Rx availability strength developing Rx OUD	0.621204	0.031794	0.800911	1.571838
Rx availability strength initiating Rx misuse	0.305049	0.059621	0.450163	1.023364
Rx availability strength net quit Rx misuse	2	1.493907	1.858442	2
Rx vs H price strength developing HUD with Rx OUD	1.37918	0.864429	1.338025	1.840282
Rx vs H price strength initiating heroin with Rx OUD	0.01	0.01	0.062872	0.178506
Rx vs H price strength initiating NDHU with Rx	1.12079	0.784512	1.081241	1.378596
Social influence strength developing HUD	0.01	0.01	0.030567	0.106982
Social influence strength developing Rx OUD	0.480384	0.01	0.370332	0.884969
Social influence strength initiating heroin with Rx OUD	2	1.878457	1.972562	2
Social influence strength initiating NDHU no Rx	0.01	0.01	0.088733	0.251881
Social influence strength initiating NDHU with Rx	1.38971	1.212988	1.418183	1.620755

Social influence strength initiating Rx misuse	0.778242	0.377553	0.722274	0.986793
Tx seeking rate Rx OUD no H total	0.565016	0.369303	0.65196	1

S5.b) Fit to historical data

Figure 12 shows fit between simulated model output μ_{it} and historical data y_{it} for all time-series data used in model estimation (see **Table 7** in S4.b)), spanning 1999-2019.

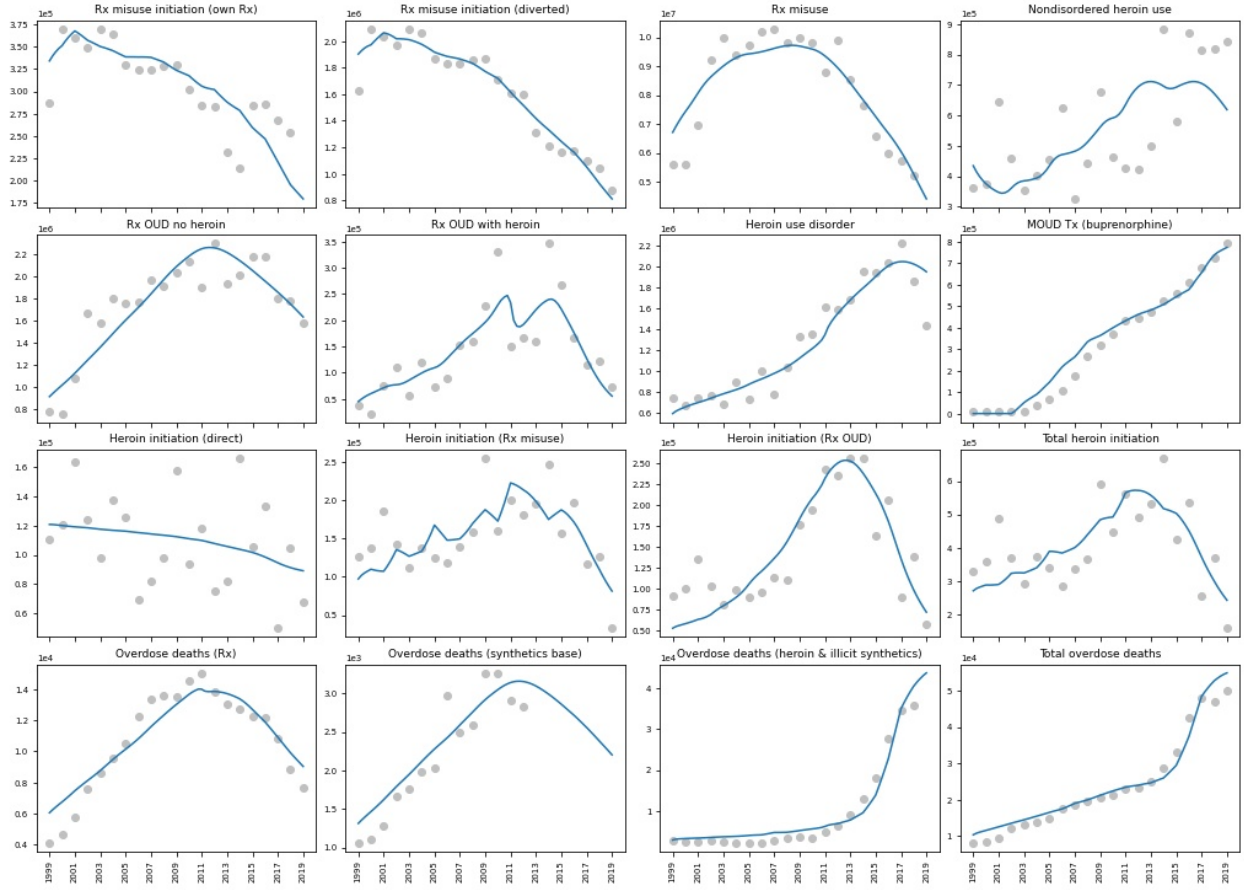

Figure 12. *Comparison of simulated model output (blue) to historical data (grey) for all time-series data used in estimation.*

Table 10 reports full quality-of-fit metrics for each estimated time series. Most of the time series fit well, with the majority of error stemming from unequal covariance (U_c), indicating an unbiased estimation [15,17].

In a few cases there is substantial unequal variance (U_s) or bias (U_m). For buprenorphine patients (TxBp), this bias arises from our decision not to model lower waiver limits in the initial years of buprenorphine availability (see S3.c.iii)), which results in overestimation of treatment capacity and patients early on but does not affect projections.

For overdose flows (ODRB, ODSB, ODRT) there is some degree of systematic skew. The most likely reason for this is cohort effects on the likelihood of overdose which we do not incorporate in our model.

Table 10. *Goodness of fit statistics for each estimated time series*

	MAEoM	MAPE	R2	MSE	Um	Us	Uc
RMis	0.070313	0.078717	0.886501	5.37E+11	0.011494	0.465571	0.522934
ROUD	0.086151	0.097424	0.797805	3.64E+10	0.003069	2.82E-05	0.996902
ROUH	0.251135	0.321806	0.71457	2.17E+09	0.001748	0.203849	0.794403
NDHU	0.238148	0.243244	0.318449	2.44E+10	0.006773	0.119071	0.874156
HUD	0.094341	0.102824	0.896416	2.79E+10	0.008473	0.000481	0.991046
TxBp	0.106906	0.580456	0.977951	2E+09	0.170386	0.110431	0.719183
InRM	0.083519	0.093831	0.572403	1.01E+09	0.006645	0.005128	0.988227
InRD	0.045483	0.049392	0.94067	8.78E+09	0.0028	0.000821	0.996379
InHT	0.182969	0.201695	0.516317	7.39E+09	0.001494	0.05343	0.945075
InHD	0.224498	0.254358	0.120827	8.63E+08	0.000663	0.554484	0.444853
InHR	0.188083	0.23344	0.455279	1.31E+09	0.003406	0.079889	0.916704
InHO	0.181383	0.221638	0.780462	1.02E+09	0.003821	0.030842	0.965336
ODRB	0.081588	0.11063	0.933253	1161247	0.019161	0.526565	0.454274
ODHC	0.204031	0.372609	0.9566	5258599	0.046329	0.018767	0.934905
ODSB	0.115385	0.133415	0.893173	79306.72	0.123621	0.241916	0.634463
ODTo	0.083349	0.104087	0.964727	6579699	0.098675	0.000177	0.901148
ROUT	0.081289	0.094772	0.817881	4.33E+10	0.003622	0.000955	0.995423
InRT	0.048326	0.052939	0.910412	1.41E+10	0.008809	2.84E-05	0.991163
ODRT	0.088369	0.124402	0.961887	1851866	0.000659	0.702696	0.296645

S6) Sensitivity analyses

S6.a) Sensitivity of projections to exogenous input assumptions

[OSM] makes projections of potential future trajectories of the opioid crisis using some baseline assumptions about future trends in exogenous inputs x_{jt}. By default, we include two main sets of baseline assumptions about [OSM]'s inputs (see **Table 11**): 1) a 'constant' case where exogenous inputs do not change after their last data points in «EndYear», and 2) a 'business-as-usual' (BAU) case where present trends continue at decelerating rates, stabilising at plausible levels by «ProjEndTime». Alternative sets of baseline assumptions can be specified by model users.

Table 11. *Exogenous inputs with alternative base case assumptions for projections*

Input	Source	2019	BAU 2031
Patients receiving opioid prescription	IQVIA, Symphony Health	«ITS19Patients»	«ITS31Patients»
Prescriptions per person	Symphony Health	«ITS19RxPP»	«ITS31RxPP»
Average opioid MME per prescription	IQVIA	«ITS19MMEs»	«ITS31MMEs»
ADF fraction of prescribed opioids	IQVIA	«ITS19ADFs»	«ITS31ADFs»
Buprenorphine-waivered treatment providers	Various**	«ITS19Bup»	«ITS31Bup»
Methadone maintenance treatment capacity*	N-SSATS	«ITS19MMT»	«ITS31MMT»
Vivitrol® treatment capacity*	IQVIA	«ITS19Viv»	«ITS31Viv»
Naloxone kits distributed	IQVIA, various**	«ITS19NxKD»	«ITS31NxKD»
Heroin price index («StartYear» = 1)	UNODC, STRIDE	«ITS19HPrice»	«ITS31HPrice»
Fentanyl penetration	NFLIS	«ITS19Fent»	«ITS31Fent»
* Neither MMT nor Vivitrol capacity data are directly available; instead we calculate capacity based on treatment utilization data from the sources listed; see S3.c.iii) ** See S3.c.iii) and S3.d.iv.(1) for full details of data sources & calculations			

Different baseline assumptions for inputs will obviously have substantial effects on parts of the model directly driven by those inputs. For instance, switching between BAU and 'constant' assumptions about future opioid prescribing trends results in large differences in prescription opioid supply. However, major downstream outcomes are not very sensitive to the baseline case used. Switching from BAU to 'constant' assumptions changes total use disorder prevalence (measured in cumulative person-years from «EndYear»-«ProjEndTime») by «BCDeltaUD», and total cumulative overdose deaths by «BCDeltaOD».

To assess the impacts of baseline assumptions about individual exogenous inputs on these downstream outcomes, we test each input variable *j* in two ways: 1) setting all input assumptions except *j* to their BAU trajectories but holding *j* constant after «EndYear»; and 2) holding all input assumptions constant after «EndYear» but setting *j* to its BAU trajectory. We then calculate the percentage change in key outcomes (cumulative overdose deaths and person-years of use disorder from «EndYear»-«ProjEndTime») from the all-inputs BAU case and constant case respectively, as well as the mean absolute percentage change for each input *j* and across all inputs. With the exception of fentanyl penetration in the illicit drug supply, these outcomes are not very sensitive to changes in input assumptions (see **Table 12**).

Table 12. *Sensitivity of key projected outcomes to alternative base case assumptions.*

	Base Projected cumulative overdose deaths	Base Projected cumulative UD person years	Cnst Projected cumulative overdose deaths	Cnst Projected cumulative UD person years	Avg Projected cumulative overdose deaths	Avg Projected cumulative UD person years
Fent	-0.15844	0.007135	0.179698	-0.00792	-0.16907	0.007525
HPI	0.004326	0.001493	-0.00426	-0.00139	0.004296	0.001444
MME	0.014317	0.03772	-0.02339	-0.04817	0.018852	0.042944
BMDCap	0.008757	0.003454	-0.01427	-0.00333	0.011512	0.003394
MMTCap	0.039382	0.008508	-0.04313	-0.00817	0.041257	0.008337
VivCap	0.001904	0.00155	-0.00281	-0.00164	0.002358	0.001596
NxKD	0.054327	-0.00248	-0.04734	0.002181	0.050835	-0.00233
PtRx	0.037555	0.069997	-0.04743	-0.07466	0.042492	0.07233
ADF	-6.62E-05	7.21E-06	1.89E-05	-6.34E-06	-4.25E-05	6.78E-06
RxPP	-0.00281	-0.00439	0.004929	0.008667	-0.00387	-0.00653
MAC	0.032188	0.013674	0.036728	0.015614	0.034458	0.014644

S7) Model equations

#	Variable	Units	Equation
001	ADF effect coeff initiating heroin with Rx OUD	dmnl	EXP(ADF fraction of Rx street supply net*(-ADF effect strength initiating heroin with Rx OUD))
002	ADF effect strength initiating heroin with Rx OUD	dmnl	0.01
003	ADF fraction of prescribed Rx opioids	dmnl	Projection output data[ADF]+RAMP(IF THEN ELSE(Policy change ADF fraction of prescribed Rx opioids>=0,Policy change ADF fraction of prescribed Rx opioids*(1-Projection output data[ADF]),Policy change ADF fraction of prescribed Rx opioids*Projection output data[ADF])/(Policy rampup duration),Policy activation time,Policy activation time+(Policy rampup duration))
004	ADF fraction of prescribed Rx opioids base	dmnl	EXTERNAL_DATA(ADF fraction of prescribed Rx opioids base)
005	ADF fraction of Rx street supply base	dmnl	ADF fraction of prescribed Rx opioids^ADF substitutability factor
006	ADF fraction of Rx street supply net	dmnl	(1-Counterfeit penetration Rx supply)*ADF fraction of Rx street supply base
007	ADF relative price	dmnl	1
008	ADF substitutability factor	dmnl	1
009	Average MME per opioid Rx	MME/Rx	Projection output data[MME]*(1+RAMP(Policy change average MME per Rx/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
010	Average MME per opioid Rx reference	MME/Rx	INITIAL(Average MME per opioid Rx)
011	Average MME per opioid Rx relative	dmnl	Average MME per opioid Rx/Average MME per opioid Rx reference
012	Average prescription duration	person*Years/Rx	0.047
013	Average prescription duration net	person*Years/Rx	Average prescription duration*(1+RAMP(Policy change average prescription duration/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))

014	Average total duration with active prescription	person * Years / person	Prescriptions per person*Average prescription duration net
015	Avg MME per opioid Rx IQVIA	MME/Rx	Total Rx MME prescribed IQVIA/Total prescription opioid Rx IQVIA
016	Base survival probability fentanyl OD	dmnl	INITIAL(Base survival probability H OD*Fentanyl effect on base survival max relative to H)
017	Base survival probability H OD	dmnl	INITIAL(Base survival probability H OD relative to Rx*Base survival probability Rx OD)
018	Base survival probability H OD relative to Rx	dmnl	0.977718
019	Base survival probability net H OD	dmnl	Max(0,Base survival probability H OD+(Base survival probability fentanyl OD-Base survival probability H OD)*Fentanyl penetration curve)
020	Base survival probability Rx OD	dmnl	0.969273
021	BaseErr	dmnl	BaseErr[Normal,Elm] = PEType[Normal]*IF THEN ELSE(DataVar[Elm]=NAREPLACEMENT,0,-((SimVar[Elm]-DataVar[Elm])*Weights[Normal,Elm])^2)
022	Bup capacity effective	person	Bup providers*Bup effective capacity per provider net
023	Bup demand fulfilment ratio prior	dmnl	IF THEN ELSE(Time=2018,0.587,NAREPLACEMENT)
024	Bup effective capacity decay constant	1/person	3.50E-05
025	Bup effective capacity decay constant net	1/person	Bup effective capacity decay constant*(1+RAMP(Policy change Bup effective capacity decay constant/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
026	Bup effective capacity per provider base	dmnl	30
027	Bup effective capacity per provider net	dmnl	zidz((zidz(Bup effective capacity per provider base*EXP(-Bup effective capacity decay constant net*Bup providers),-Bup effective capacity decay constant net)+zidz(Bup effective capacity per provider base,Bup effective capacity decay constant net)),Bup providers)
028	Bup patients per provider	dmnl	zidz(Total by MOUD[Bup],Bup providers)
029	Bup patients per provider DATA	dmnl	zidz(Tx point patients Bup DATA,Bup providers)
030	Bup providers	people	Projection output data[BMDCap]*(1+RAMP(Policy change Bup providers/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))

031	Bup providers DATA	people	EXTERNAL_DATA(2.0)
032	Counterfeit penetration Rx supply	dmnl	0
033	Counterfeit supply relative	dmnl	Counterfeit penetration Rx supply/(1-Counterfeit penetration Rx supply)*Rx supply relative net
034	Counterfeit supply weight	dmnl	0.1
035	Cumulative nonfatal overdoses	people	Total nonfatal overdoses0.0
036	Cumulative Nx utilization deaths averted	people	Nx utilization deaths averted H user+Nx utilization deaths averted Rx user0.0
037	Cumulative overdose deaths	person	Total overdose deaths0.0
038	Cumulative overdose deaths synth excess	people	Total overdose deaths synth excess0.0
039	Cumulative projections start time	Years	2019
040	Cumulative UD person years	person * Years	Total with UD0.0
041	DataPrior		DataPrior[Elm] = IF THEN ELSE(Time<=MaxDataTime,DataPriorBase[Elm],NAREPLACEMENT)
042	DataPriorBase		DataPriorBase[StElm] = NAREPLACEMENT
043	DataVar		DataVar[Elm] = IF THEN ELSE(Time<=MaxDataTime,DataVarBase[Elm],NAREPLACEMENT)
044	DataVarBase	people/year	DataVarBase[RMis] = Rx misuse no PY heroin NSDUH redef corrected
045	Developing HUD no Rx OUD	people/year	Nondisordered heroin use*Developing HUD rate no Rx OUD effective
046	Developing HUD rate no Rx OUD	dmnl/year	0.291806
047	Developing HUD rate no Rx OUD effective	1/year	Developing HUD rate no Rx OUD*Heroin price coeff developing HUD*Social influence coeff developing HUD
048	Developing HUD rate with Rx OUD	dmnl/year	0.688118
049	Developing HUD rate with Rx OUD effective	1/year	Developing HUD rate with Rx OUD*Social influence coeff developing HUD*Rx vs H price coeff developing HUD with Rx OUD
050	Developing HUD with Rx OUD	people/year	Rx OUD with PY heroin no MOUD*Developing HUD rate with Rx OUD effective
051	Developing Rx OUD	people/year	Rx misuse no PY heroin*Developing Rx OUD rate effective
052	Developing Rx OUD rate	dmnl/year	0.0101936
053	Developing Rx OUD rate effective	1/year	Developing Rx OUD rate*Rx availability coeff developing Rx OUD*Social influence coeff developing Rx OUD

054	Effect of MOUD Tx on NonOD death rate	dmnl	Effect of MOUD Tx on NonOD death rate[MMT] = 0.37
055	Effect of MOUD Tx on OD death rate	dmnl	Effect of MOUD Tx on OD death rate[MMT] = 0.295
056	Effect of MOUD Tx on Rx consumption	dmnl	Effect of MOUD Tx on Rx consumption[TxT] = 0.7,0.66,0
057	Effective SI users heroin initiation	people	HUD total+Nondisordered heroin use+Rx OUD with PY heroin total
058	Effective SI users HUD development	people	HUD total
059	Effective SI users Rx misuse initiation	people	Rx misuse no PY heroin+Rx OUD no PY heroin total+Rx OUD with PY heroin total+Nondisordered heroin use*Fraction of NDHU with Rx avg
060	Effective SI users Rx OUD development	people	Rx OUD no PY heroin total+Rx OUD with PY heroin total
061	eps	dmnl	0.0001
062	Fentanyl effect on base survival max relative to H	dmnl	0.7661
063	Fentanyl effect on OD rate H max	dmnl	5.27094
064	Fentanyl effect on OD rate H max net	1	Fentanyl effect on OD rate H max*(1+RAMP(Policy change fentanyl effect on OD rate/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
065	Fentanyl introduction time	year	2012.5
066	Fentanyl penetration curve	dmnl	Projection output data[Fent]*(1-Switch for no fentanyl)
067	Fentanyl penetration curve NFLIS	dmnl	EXTERNAL_DATA(Fentanyl penetration curve NFLIS)
068	Fraction HUD by MOUD	dmnl	Fraction HUD by MOUD[TxT] = zidz((HUD by MOUD[TxT]+HUD in remission in MOUD Tx[TxT]),Total by MOUD[TxT])
069	Fraction Nx kits to H users	dmnl	0.86
070	Fraction of all heroin users with HUD	dmnl	HUD total/Total heroin users
071	Fraction of all heroin users with HUD DATA	dmnl	HUD DATA/Total heroin users DATA
072	Fraction of all Rx users excl heroin with OUD	dmnl	Rx OUD no PY heroin total/Total Rx use excl heroin
073	Fraction of all Rx users excl heroin with OUD DATA	dmnl	IF THEN ELSE(Time<2019,Rx OUD no PY heroin NSDUH/Total Rx users excl heroin DATA,NAREPLACEMENT)

074	Fraction of heroin initiation no Rx	dmnl	Initiating heroin no Rx/Total heroin initiation
075	Fraction of heroin initiation no Rx DATA	dmnl	Initiating heroin no Rx DATA/Total heroin initiation DATA
076	Fraction of heroin initiation with Rx misuse	dmnl	Initiating heroin with Rx misuse/Total heroin initiation
077	Fraction of heroin initiation with Rx misuse DATA	dmnl	Initiating heroin with Rx misuse DATA/Total heroin initiation DATA
078	Fraction of heroin initiation with Rx OUD	dmnl	Initiating heroin with Rx OUD/Total heroin initiation
079	Fraction of heroin initiation with Rx OUD DATA	dmnl	Initiating heroin with Rx OUD DATA/Total heroin initiation DATA
080	Fraction of HUD who use rx NSDUH	dmnl	EXTERNAL_DATA(Fraction of HUD who use rx NSDUH)
081	Fraction of HUD with Rx OUD or misuse avg	dmnl	GET DATA MEAN(Fraction of HUD who use rx NSDUH,2002,2018)
082	Fraction of NDHU who use Rx NSDUH	dmnl	EXTERNAL_DATA(Fraction of NDHU who use Rx NSDUH)
083	Fraction of NDHU with Rx avg	dmnl	GET DATA MEAN(Fraction of NDHU who use Rx NSDUH,2002,2018)
084	Fraction Rx OUD by MOUD	dmnl	Fraction Rx OUD by MOUD[TxT] = zidz((Rx OUD by MOUD[TxT]+Rx OUD no PY heroin in remission in MOUD Tx[TxT]+Rx OUD with PY heroin in remission in MOUD Tx[TxT]),Total by MOUD[TxT])
085	Heroin price coeff developing HUD	dmnl	Heroin price index^(-Heroin price strength developing HUD)
086	Heroin price coeff initiating NDHU no Rx	dmnl	Heroin price index^(-Heroin price strength initiating NDHU no Rx)
087	Heroin price coeff net quit NDHU	dmnl	Heroin price index^Heroin price strength net quit NDHU
088	Heroin price index	dmnl	Projection output data[HPI]
089	Heroin price index DATA	dmnl	EXTERNAL_DATA(Heroin price index DATA)
090	Heroin price strength developing HUD	dmnl	0.01
091	Heroin price strength initiating NDHU no Rx	dmnl	0.01
092	Heroin price strength net quit NDHU	dmnl	2

093	HUD by MOUD	people	HUD by MOUD[TxT] = (((Tx engagement HUD[TxT]-Tx exit in remission HUD[TxT])-Tx exit with UD HUD[TxT])-NonOD death HUD in MOUD Tx[TxT])-Overdose death HUD in MOUD Tx[TxT]Initial HUD in MOUD Tx[TxT]
094	HUD DATA	people	HUD NSDUH RAND
095	HUD in remission	people	((((SUM(Tx exit in remission HUD[TxT]))-NonOD death HUD in remission)-Relapsing to HUD)+Remitting HUD no MOUD Tx)-Stabilizing remission HUDInitial HUD in remission
096	HUD in remission in MOUD Tx	person	HUD in remission in MOUD Tx[TxT] = HUD by MOUD[TxT]*Remission fraction in Tx[TxT]
097	HUD in remission total	people	HUD in remission+SUM(HUD in remission in MOUD Tx[TxT])
098	HUD in remission total prior	people	IF THEN ELSE(Time=2013,596174,NAREPLACEMENT)
099	HUD in stable remission	people	Stabilizing remission HUD-NonOD death HUD in stable remissionInitial HUD in stable remission
100	HUD in stable remission total prior	people	IF THEN ELSE(Time=2013,345649,NAREPLACEMENT)
101	HUD no MOUD	people	(((((Developing HUD no Rx OUD+Developing HUD with Rx OUD)-Remitting HUD no MOUD Tx)-NonOD death HUD)-Overdose death HUD)+Relapsing to HUD)+(SUM((Tx exit with UD HUD[TxT]-Tx engagement HUD[TxT])))Initial HUD
102	HUD NSDUH RAND	people	EXTERNAL_DATA(HUD NSDUH RAND)
103	HUD total	person	HUD no MOUD+SUM((1-Remission fraction in Tx[TxT])*HUD by MOUD[TxT])
104	Increased risk of nonOD death among medical opioid users	dmnl	1.72
105	Initial fraction lifetime Rx users with lifetime H use NESARC	dmnl	0.0512
106	Initial HUD	people	INITIAL(Initial HUD total-SUM((1-Remission fraction in Tx[TxT])*Initial HUD in MOUD Tx[TxT]))
107	Initial HUD in MOUD Tx	people	Initial HUD in MOUD Tx[Bup] = INITIAL(Initial stock base values[HUB]*Initial stock correction[HUB])
108	Initial HUD in remission	people	INITIAL(Initial stock base values[HUR]*Initial stock correction[HUR])
109	Initial HUD in remission NESARC	people	253594
110	Initial HUD in stable remission	people	INITIAL(Initial stock base values[HUS]*Initial stock correction[HUS])
111	Initial HUD in stable remission NESARC	people	147028
112	Initial HUD total	people	INITIAL(Initial stock base values[HUT]*Initial stock correction[HUT])

113	Initial MMT fraction with HUD	dmnl	0.92
114	Initial MMT fraction with Rx OUD with H	dmnl	0.0056
115	Initial NDHU	people	INITIAL(Initial stock base values[NDH]*Initial stock correction[NDH])
116	Initial Rx misuse no H	people	INITIAL(Initial stock base values[RXM]*Initial stock correction[RXM])
117	Initial Rx OUD in remission NESARC	people	1.17E+06
118	Initial Rx OUD in stable remission NESARC	people	679176
119	Initial Rx OUD no H	people	INITIAL(Initial Rx OUD no H total-SUM((1-Remission fraction in Tx[TxT])*Initial Rx OUD no H in Tx[TxT]))
120	Initial Rx OUD no H in remission	people	INITIAL(Initial stock base values[OUR]*Initial stock correction[OUR])
121	Initial Rx OUD no H in stable remission	people	INITIAL(Initial stock base values[OUS]*Initial stock correction[OUS])
122	Initial Rx OUD no H in Tx	people	Initial Rx OUD no H in Tx[Bup] = INITIAL(Initial stock base values[OUB]*Initial stock correction[OUB])
123	Initial Rx OUD no H total	people	INITIAL(Initial stock base values[OUT]*Initial stock correction[OUT])
124	Initial Rx OUD with H	people	INITIAL(Initial Rx OUD with H total-SUM((1-Remission fraction in Tx[TxT])*Initial Rx OUD with H in Tx[TxT]))
125	Initial Rx OUD with H in remission	people	INITIAL(Initial stock base values[OHR]*Initial stock correction[OHR])
126	Initial Rx OUD with H in stable remission	people	INITIAL(Initial stock base values[OHS]*Initial stock correction[OHS])
127	Initial Rx OUD with H in Tx	people	Initial Rx OUD with H in Tx[Bup] = INITIAL(Initial stock base values[OHB]*Initial stock correction[OHB])
128	Initial Rx OUD with H total	people	INITIAL(Initial stock base values[OHT]*Initial stock correction[OHT])
129	Initial stock base values	people	Initial stock base values[RXM] = INITIAL(Rx misuse no PY heroin NSDUH redef corrected)
130	Initial stock correction	dmnl	Initial stock correction[Initials] = 1.01799,1.02517,1.05762,1.2,1.09558,0.869523,1.0535,1,1.16412,0.8,0.937737,0.8,0.8,1,0.841935,1.03489,0.82041,0.8,0.8,1
131	Initial total in Tx by type	people	Initial total in Tx by type[TxT] = INITIAL(Initial HUD in MOUD Tx[TxT]+Initial Rx OUD no H in Tx[TxT]+Initial Rx OUD with H in Tx[TxT])
132	Initiating heroin no Rx	people/year	Initiating heroin no Rx net*Heroin price coeff initiating NDHU no Rx*Perceived risk coeff initiating NDHU no Rx*Social influence coeff initiating NDHU no Rx

133	Initiating heroin no Rx base	people/year	57889.6
134	Initiating heroin no Rx DATA	people/year	Initiating heroin no Rx NSDUH RDAS RAND
135	Initiating heroin no Rx net	people/year	Initiating heroin no Rx base*(1+RAMP(Policy change initiating NDHU no Rx/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
136	Initiating heroin no Rx NSDUH RDAS RAND	people/year	EXTERNAL_DATA(Initiating heroin no Rx NSDUH RDAS RAND)
137	Initiating heroin with Rx misuse	person/Years	Rx misuse no PY heroin*Initiation rate heroin with Rx misuse effective
138	Initiating heroin with Rx misuse DATA	people/year	Initiating heroin with Rx misuse NSDUH RDAS RAND
139	Initiating heroin with Rx misuse NSDUH RDAS RAND	people/year	EXTERNAL_DATA(Initiating heroin with Rx misuse NSDUH RDAS RAND)
140	Initiating heroin with Rx OUD	people/year	Rx OUD no PY heroin no MOUD*Initiation rate heroin with Rx OUD effective
141	Initiating heroin with Rx OUD DATA	person/Years	Initiating heroin with Rx OUD NSDUH RDAS RAND
142	Initiating heroin with Rx OUD NSDUH RDAS RAND	people/year	EXTERNAL_DATA(Initiating heroin with Rx OUD NSDUH RDAS RAND)
143	Initiating Rx misuse diverted	people/year	Initiating Rx misuse diverted net*Perceived risk coeff initiating Rx misuse diverted*Rx availability coeff initiating Rx misuse*Social influence coeff initiating Rx misuse
144	Initiating Rx misuse diverted base	people/year	2.00E+06
145	Initiating Rx misuse diverted net	people/year	Initiating Rx misuse diverted base*(1+RAMP(Policy change initiating Rx misuse diverted/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
146	Initiating Rx misuse diverted RDAS SAMHSA	person/Years	EXTERNAL_DATA(Initiating Rx misuse diverted RDAS SAMHSA)
147	Initiating Rx misuse own Rx	people/year	Patients with current opioid Rx*Initiation rate Rx misuse own Rx effective
148	Initiating Rx misuse own Rx RDAS SAMHSA	people/year	EXTERNAL_DATA(Initiating Rx misuse own Rx RDAS SAMHSA)
149	Initiating Rx misuse own Rx RDAS SAMHSA redef correction	person/Years	Total Rx misuse initiation SAMHSA redef corrected-Initiating Rx misuse diverted RDAS SAMHSA
150	Initiation rate heroin with Rx misuse	dmnl/year	0.00466093

151	Initiation rate heroin with Rx misuse effective	1/year	Initiation rate heroin with Rx misuse net*Rx vs H price coeff initiating NDHU with Rx*Perceived risk coeff initiating NDHU with Rx*Social influence coeff initiating NDHU with Rx
152	Initiation rate heroin with Rx misuse net	1/Years	Initiation rate heroin with Rx misuse*(1+RAMP(Policy change initiation rate heroin with Rx misuse/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
153	Initiation rate heroin with Rx OUD	dmnl/year	INITIAL(Initiation rate heroin with Rx misuse*Initiation rate heroin with Rx OUD relative to Rx misuse)
154	Initiation rate heroin with Rx OUD effective	1/year	Initiation rate heroin with Rx OUD*Rx vs H price coeff initiating heroin with Rx OUD*Perceived risk coeff initiating heroin with Rx OUD*Social influence coeff initiating heroin with Rx OUD*ADF effect coeff initiating heroin with Rx OUD
155	Initiation rate heroin with Rx OUD relative to Rx misuse	dmnl	4.91209
156	Initiation rate Rx misuse own Rx	dmnl/year	0.0378775
157	Initiation rate Rx misuse own Rx effective	1/year	Initiation rate Rx misuse own Rx net*Perceived risk coeff initiating Rx misuse own Rx
158	Initiation rate Rx misuse own Rx net	1/year	Initiation rate Rx misuse own Rx*(1+RAMP(Policy change initiation rate Rx misuse own Rx/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
159	IsYear		IsYear[Year] = EXTERNAL_DATA(2.0)
160	Logistic growth curve		Logistic growth curve[Proj] = IF THEN ELSE(Projection curve end value[Proj]>Projection last data value[Proj],MIN(Projection curve end value[Proj],((Projection curve end value[Proj]-Projection last data value[Proj])/0.5)/(1+EXP((-5/(Projection curve end time[Proj]-Projection last data time[Proj]))*(Time-Projection last data time[Proj])))+(Projection curve end value[Proj]-(Projection curve end value[Proj]-Projection last data value[Proj])/0.5)),Max(Projection curve end value[Proj],((Projection curve end value[Proj]-Projection last data value[Proj])/0.5)/(1+EXP((-5/(Projection curve end time[Proj]-Projection last data time[Proj]))*(Time-Projection last data time[Proj])))+(Projection curve end value[Proj]-(Projection curve end value[Proj]-Projection last data value[Proj])/0.5)))
161	MaxDataTime	year	2019

162	MMT capacity estimated	person	Projection output data[MMTCap]*(1+RAMP(Policy change MMT capacity/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
163	MMT capacity estimated DATA	people	Tx point patients OTP MMT NSSATS/MMT OTP capacity utilization NSSATS
164	MMT OTP capacity utilization NSSATS	dmnl	0.866
165	Net quit rate heroin with Rx misuse	dmnl/year	0.01
166	Net quit rate heroin with Rx OUD	dmnl/year	0.01
167	Net quit rate NDHU	dmnl/year	0.238937
168	Net quit rate Rx misuse	dmnl/year	0.196521
169	Net quitting heroin with Rx misuse	people/year	Nondisordered heroin use*Net quit rate heroin with Rx misuse*Perceived risk coeff net quit NDHU with Rx
170	Net quitting heroin with Rx OUD	people/year	Rx OUD with PY heroin no MOUD*Net quit rate heroin with Rx OUD*Perceived risk coeff net quit heroin with Rx OUD
171	Net quitting NDHU	people/year	Nondisordered heroin use*Net quit rate NDHU*Perceived risk coeff net quit NDHU*Heroin price coeff net quit NDHU
172	Net quitting Rx misuse	people/year	Rx misuse no PY heroin*Net quit rate Rx misuse*Perceived risk coeff net quit Rx misuse*Rx availability coeff net quit Rx misuse
173	NoiseStartTime	year	2031
174	Nondisordered heroin use	people	(((((Initiating heroin no Rx+Initiating heroin with Rx misuse)-Developing HUD no Rx OUD)-Net quitting heroin with Rx misuse)-Net quitting NDHU)-NonOD death NDHU)-Overdose death NDHUInitial NDHU
175	Nondisordered heroin use DATA	people	Nondisordered heroin use NSDUH RAND
176	Nondisordered heroin use NSDUH RAND	people	EXTERNAL_DATA(Nondisordered heroin use NSDUH RAND)
177	Nonfatal OD ratio heroin	dmnl	Total nonfatal overdoses heroin/Total overdose deaths heroin
178	Nonfatal OD ratio heroin prior	dmnl	IF THEN ELSE(Time<Fentanyl introduction time,30,NAREPLACEMENT)
179	Nonfatal OD ratio HUD	dmnl	Overdose rate net HUD/Overdose death rate HUD-1
180	Nonfatal OD ratio NDHU	dmnl	Overdose rate net NDHU/Overdose death rate NDHU-1
181	Nonfatal OD ratio Rx	dmnl	Total nonfatal overdoses Rx/Total overdose deaths Rx
182	Nonfatal OD ratio Rx misuse	dmnl	Overdose rate base Rx misuse/Overdose death rate Rx misuse-1
183	Nonfatal OD ratio Rx OUD no H	dmnl	Overdose rate total Rx OUD no H/Overdose death rate Rx OUD no H-1
184	Nonfatal OD ratio Rx OUD with H	dmnl	Overdose rate base Rx OUD/Overdose death rate Rx OUD with H-1

185	Nonfatal OD ratio Rx prior	dmnl	IF THEN ELSE(Time<Fentanyl introduction time,35,NAREPLACEMENT)
186	Nonfatal OD ratio total	dmnl	XIDZ(Total nonfatal overdoses,Total overdose deaths,1)
187	Nonfatal ODs HUD	people/year	Total overdose deaths HUD*Nonfatal OD ratio HUD
188	Nonfatal ODs NDHU	people/year	Overdose death NDHU*Nonfatal OD ratio NDHU
189	Nonfatal ODs Rx misuse	people/year	Overdose death Rx misuse*Nonfatal OD ratio Rx misuse
190	Nonfatal ODs Rx OUD no H	people/year	Total overdose deaths Rx OUD no H*Nonfatal OD ratio Rx OUD no H
191	Nonfatal ODs Rx OUD with H	people/year	Total overdose deaths Rx OUD with H*Nonfatal OD ratio Rx OUD with H
192	NonOD death HUD	people/year	HUD no MOUD*NonOD death rate HUD or OUD
193	NonOD death HUD in MOUD Tx	person/Years	NonOD death HUD in MOUD Tx[TxT] = HUD by MOUD[TxT]*NonOD death rate HUD or OUD in Tx[TxT]
194	NonOD death HUD in remission	person/Years	HUD in remission*NonOD death rate nonuser
195	NonOD death HUD in stable remission	person/Years	HUD in stable remission*NonOD death rate nonuser
196	NonOD death in Tx total	people/year	NonOD death in Tx total[TxT] = NonOD death HUD in MOUD Tx[TxT]+NonOD death Rx OUD no H in Tx[TxT]+NonOD death Rx OUD with H in Tx[TxT]
197	NonOD death misuse	people/year	Rx misuse no PY heroin*NonOD death rate misuse
198	NonOD death NDHU	people/year	Nondisordered heroin use*NonOD death rate NDHU
199	NonOD death rate HUD or OUD	dmnl/year	0.0143
200	NonOD death rate HUD or OUD in Tx	1/year	NonOD death rate HUD or OUD in Tx[TxT] = (1-Remission fraction in Tx[TxT])*NonOD death rate HUD or OUD*Effect of MOUD Tx on NonOD death rate[TxT]+Remission fraction in Tx[TxT]*NonOD death rate nonuser
201	NonOD death rate misuse	dmnl/year	(NonOD death rate nonuser+(Increased risk of nonOD death among medical opioid users*NonOD death rate nonuser))/2
202	NonOD death rate NDHU	dmnl/year	(NonOD death rate HUD or OUD+NonOD death rate misuse)/2
203	NonOD death rate nonuser	1/year	0.00842
204	NonOD death Rx OUD no H	people/year	Rx OUD no PY heroin no MOUD*NonOD death rate HUD or OUD
205	NonOD death Rx OUD no H in remission	person/Years	Rx OUD no heroin in remission*NonOD death rate nonuser
206	NonOD death Rx OUD no H in stable remission	person/Years	Rx OUD no heroin in stable remission*NonOD death rate nonuser
207	NonOD death Rx OUD no H in Tx	person/Years	NonOD death Rx OUD no H in Tx[TxT] = Rx OUD no heroin by MOUD[TxT]*NonOD death rate HUD or OUD in Tx[TxT]
208	NonOD death Rx OUD with H	people/year	Rx OUD with PY heroin no MOUD*NonOD death rate HUD or OUD

209	NonOD death Rx OUD with H in remission	person/Years	Rx OUD with heroin in remission*NonOD death rate nonuser
210	NonOD death Rx OUD with H in stable remission	person/Years	Rx OUD with heroin in stable remission*NonOD death rate nonuser
211	NonOD death Rx OUD with H in Tx	person/Years	NonOD death Rx OUD with H in Tx[TxT] = Rx OUD with heroin by MOUD[TxT]*NonOD death rate HUD or OUD in Tx[TxT]
212	NormErr		NormErr[TSElm] = IF THEN ELSE(DataVar[TSElm]=NAREPLACEMENT,NAREPLACEMENT,zidz((DataVar[TSElm]-SimVar[TSElm]),SimVar[TSElm]))
213	NSDUH misuse redefinition effect	dmnl	1-RAMP(NSDUH misuse redefinition fixed effect/(1+NSDUH misuse redefinition fixed effect)/OneYear,NSDUH misuse redefinition time,(NSDUH misuse redefinition time+OneYear))
214	NSDUH misuse redefinition fixed effect	dmnl	0.421873
215	NSDUH misuse redefinition time	year	2014
216	Nx kit distribution efficiency	person/kit	0.00167
217	Nx kit distribution efficiency net	person/kit	Nx kit distribution efficiency*(1+RAMP(Policy change Nx kit distribution efficiency/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
218	Nx kit utilization fraction H user	dmnl	Nx utilization events H user*Nx kits per utilization event/Nx kits distributed H user
219	Nx kit utilization fraction Rx user	dmnl	Nx utilization events Rx user*Nx kits per utilization event/Nx kits distributed Rx user
220	Nx kits distributed H user	kits	Nx kits distributed net*Fraction Nx kits to H users
221	Nx kits distributed HR IQVIA	kits	EXTERNAL_DATA(Nx kits distributed HR IQVIA)
222	Nx kits distributed net	kits	Projection output data[NxKD]*(1+RAMP(Policy change Nx kits distributed/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
223	Nx kits distributed Rx user	kits	Nx kits distributed net*(1-Fraction Nx kits to H users)
224	Nx kits per 100k population H user	kits/person	Nx kits distributed H user/Population*100000
225	Nx kits per 100k population Rx user	kits/person	Nx kits distributed Rx user/Population*100000
226	Nx kits per utilization event	kits/(person/year)	1

227	Nx utilization deaths averted H user	people/year	Nx utilization events H user*(1-Base survival probability net H OD)*(1-Probability of calling emergency services net)
228	Nx utilization deaths averted Rx user	people/year	Nx utilization events Rx user*(Total overdoses Rx synth baseline fraction*(1-Base survival probability fentanyl OD)+(1-Total overdoses Rx synth baseline fraction)*(1-Base survival probability Rx OD))*(1-Probability of calling emergency services net)
229	Nx utilization events H user	people/year	Total overdoses heroin*Probability OD witnessed net*Probability Nx bystander heroin
230	Nx utilization events H user fraction	dmnl	zidz(Nx utilization events H user,Nx utilization events total)
231	Nx utilization events H user fraction prior	dmnl	IF THEN ELSE(Time=2013,0.86,NAREPLACEMENT)
232	Nx utilization events Rx user	people/year	Total overdoses Rx*Probability OD witnessed net*Probability Nx bystander Rx
233	Nx utilization events total	person/Years	Nx utilization events H user+Nx utilization events Rx user
234	OD death fraction base HUD	dmnl	Overdose death rate base HUD/Overdose death rate HUD
235	OD death fraction base NDHU	dmnl	Overdose death rate base NDHU/Overdose death rate NDHU
236	OD death fraction base Rx OUD no H	dmnl	Overdose death rate base Rx OUD/Overdose death rate Rx OUD no H
237	OD death fraction synth baseline Rx OUD no H	dmnl	Overdose death rate synth baseline/Overdose death rate Rx OUD no H
238	OD death fraction synth HUD	dmnl	Overdose death rate synth HUD/Overdose death rate HUD
239	OD death fraction synth NDHU	dmnl	Overdose death rate synth NDHU/Overdose death rate NDHU
240	OD death rate HUD in MOUD Tx	1/Years	OD death rate HUD in MOUD Tx[TxT] = (1-Remission fraction in Tx[TxT])*Overdose death rate HUD*Effect of MOUD Tx on OD death rate[TxT]
241	OD death rate Rx OUD no H in Tx	1/Years	OD death rate Rx OUD no H in Tx[TxT] = (1-Remission fraction in Tx[TxT])*Overdose death rate Rx OUD no H*Effect of MOUD Tx on OD death rate[TxT]
242	OD death rate Rx OUD with H in Tx	1/Years	OD death rate Rx OUD with H in Tx[TxT] = (1-Remission fraction in Tx[TxT])*Overdose death rate Rx OUD with H*Effect of MOUD Tx on OD death rate[TxT]
243	OD deaths synth baseline estimated	people/year	IF THEN ELSE(Time<Fentanyl introduction time,Total overdose deaths synth no H NVSS,NAREPLACEMENT)
244	OD deaths synth excess estimated	people/year	Max(0,Total overdose deaths synth heroin NVSS+IF THEN ELSE(Time<Fentanyl introduction time,NAREPLACEMENT,IF THEN ELSE(Time>Total overdose data last time,NAREPLACEMENT,Total overdose deaths synth no H NVSS-Total overdose deaths synth base)))

245	OneYear	year	1
246	Overdose death HUD	people/year	HUD no MOUD*Overdose death rate HUD
247	Overdose death HUD in MOUD Tx	person/Years	Overdose death HUD in MOUD Tx[TxT] = HUD by MOUD[TxT]*OD death rate HUD in MOUD Tx[TxT]
248	Overdose death in Tx total	person/Years	Overdose death in Tx total[TxT] = Overdose death HUD in MOUD Tx[TxT]+Overdose death Rx OUD no H in Tx[TxT]+Overdose death Rx OUD with H in Tx[TxT]
249	Overdose death MU	people/year	Patients with current opioid Rx*Overdose death rate base MU
250	Overdose death NDHU	people/year	Nondisordered heroin use*Overdose death rate NDHU
251	Overdose death rate base HUD	1/Years	Overdose rate base HUD*(1-Base survival probability H OD)*Probability OD death not averted heroin user*(1-Fentanyl penetration curve)
252	Overdose death rate base HUD no synth counterfactual	1/year	Overdose rate base HUD*(1-Base survival probability H OD)*Probability OD death not averted heroin user
253	Overdose death rate base MU	dmnl/year	0.00017
254	Overdose death rate base NDHU	1/Years	Overdose rate base NDHU*(1-Base survival probability H OD)*Probability OD death not averted heroin user*(1-Fentanyl penetration curve)
255	Overdose death rate base Rx OUD	1/year	Overdose rate base Rx OUD*(1-Base survival probability Rx OD)*Probability OD death not averted Rx user
256	Overdose death rate HUD	dmnl/year	Overdose rate net HUD*(1-Base survival probability net H OD)*Probability OD death not averted heroin user
257	Overdose death rate HUD no Nx counterfactual	1/year	Overdose rate net HUD*(1-Base survival probability net H OD)*(1-Probability OD witnessed net*Probability of calling emergency services net)
258	Overdose death rate NDHU	1/year	Overdose rate net NDHU*(1-Base survival probability net H OD)*Probability OD death not averted heroin user
259	Overdose death rate Rx misuse	dmnl/year	Overdose rate base Rx misuse*(1-Base survival probability Rx OD)*Probability OD death not averted Rx user
260	Overdose death rate Rx OUD no H	1/year	Overdose death rate base Rx OUD+Overdose death rate synth baseline
261	Overdose death rate Rx OUD with H	1/year	Overdose death rate base Rx OUD
262	Overdose death rate synth baseline	1/year	Overdose rate synth baseline*(1-Base survival probability fentanyl OD)*Probability OD death not averted Rx user
263	Overdose death rate synth HUD	1/Years	Max(0,Overdose death rate HUD-Overdose death rate base HUD)
264	Overdose death rate synth NDHU	1/Years	Max(0,Overdose death rate NDHU-Overdose death rate base NDHU)
265	Overdose death Rx misuse	people/year	Rx misuse no PY heroin*Overdose death rate Rx misuse

266	Overdose death Rx OUD no H	people/year	Rx OUD no PY heroin no MOUD*Overdose death rate Rx OUD no H
267	Overdose death Rx OUD no H in Tx	person/Years	Overdose death Rx OUD no H in Tx[TxT] = Rx OUD no heroin by MOUD[TxT]*OD death rate Rx OUD no H in Tx[TxT]
268	Overdose death Rx OUD with H	people/year	Rx OUD with PY heroin no MOUD*Overdose death rate Rx OUD with H
269	Overdose death Rx OUD with H in Tx	person/Years	Overdose death Rx OUD with H in Tx[TxT] = Rx OUD with heroin by MOUD[TxT]*OD death rate Rx OUD with H in Tx[TxT]
270	Overdose rate base HUD	dmnl/year	0.0878854
271	Overdose rate base NDHU	dmnl/year	INITIAL(Overdose rate base HUD*Overdose rate NDHU relative to HUD)
272	Overdose rate base Rx misuse	dmnl/year	0.0108244
273	Overdose rate base Rx OUD	dmnl/year	0.172829
274	Overdose rate NDHU relative to HUD	dmnl	0.25
275	Overdose rate net HUD	1/year	Overdose rate base HUD*(1+Fentanyl penetration curve*(Fentanyl effect on OD rate H max net-1))
276	Overdose rate net NDHU	dmnl/year	Overdose rate base NDHU*(1+Fentanyl penetration curve*(Fentanyl effect on OD rate H max net-1))
277	Overdose rate synth baseline	1/year	0.00786312
278	Overdose rate total Rx OUD no H	1/Years	Overdose rate base Rx OUD+Overdose rate synth baseline
279	OxyContin withdrawal lag	year	0.25
280	OxyContin withdrawal magnitude	dmnl	0.45
281	OxyContin withdrawal supply impact	dmnl/year	PULSE(OxyContin withdrawal time,OxyContin withdrawal lag)*OxyContin withdrawal magnitude/OxyContin withdrawal lag
282	OxyContin withdrawal time	year	2010.75
283	Patients receiving opioid prescription	people/year	Projection output data[PtRx]*(1+RAMP(Policy change patients with opioid prescription/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
284	Patients receiving opioid prescription IQVIA SH	people/year	EXTERNAL_DATA(Patients receiving opioid prescription IQVIA SH)
285	Patients receiving opioid prescription reference	people/year	INITIAL(Patients receiving opioid prescription)
286	Patients receiving opioid prescription relative	dmnl	Patients receiving opioid prescription/Patients receiving opioid prescription reference
287	Patients with current opioid Rx	people	Patients receiving opioid prescription*Average total duration with active prescription

288	Perceived risk coeff initiating heroin with Rx OUD	1	Perceived risk heroin use relative^-Perceived risk strength initiating heroin with Rx use
289	Perceived risk coeff initiating NDHU no Rx	1	Perceived risk heroin use relative^-Perceived risk strength initiating NDHU no Rx
290	Perceived risk coeff initiating NDHU with Rx	1	Perceived risk heroin use relative^-Perceived risk strength initiating heroin with Rx use
291	Perceived risk coeff initiating Rx misuse diverted	1	Perceived risk Rx use relative^-Perceived risk strength initiating Rx misuse diverted
292	Perceived risk coeff initiating Rx misuse own Rx	dmnl	Perceived risk Rx use relative^-Perceived risk strength initiating Rx misuse own Rx
293	Perceived risk coeff net quit heroin with Rx OUD	1	Perceived risk heroin use relative^Perceived risk strength net quit heroin with Rx OUD
294	Perceived risk coeff net quit NDHU	1	Perceived risk heroin use relative^Perceived risk strength net quit NDHU
295	Perceived risk coeff net quit NDHU with Rx	1	Perceived risk heroin use relative^Perceived risk strength net quit NDHU with Rx
296	Perceived risk coeff net quit Rx misuse	1	Perceived risk Rx use relative^Perceived risk strength net quit Rx misuse
297	Perceived risk decrease time	year	20
298	Perceived risk heroin use current	people/year	SMOOTHI(Perceived risk heroin use indicated,IF THEN ELSE(Perceived risk heroin use current<Perceived risk heroin use indicated,Perceived risk increase time,Perceived risk decrease time),Perceived risk heroin use reference)
299	Perceived risk heroin use indicated	people/year	Total overdose deaths heroin+Total nonfatal overdoses heroin*Perceived risk weight NFOD
300	Perceived risk heroin use reference	people/year	INITIAL(Perceived risk heroin use indicated)
301	Perceived risk heroin use relative	1	ACTIVE INITIAL(Perceived risk heroin use current/Perceived risk heroin use reference,1)
302	Perceived risk increase time	year	2
303	Perceived risk Rx use current	people/year	SMOOTHI(Perceived risk Rx use indicated,IF THEN ELSE(Perceived risk Rx use current<Perceived risk Rx use indicated,Perceived risk increase time,Perceived risk decrease time),Perceived risk Rx use reference)
304	Perceived risk Rx use indicated	people/year	Total overdose deaths Rx+Perceived risk weight NFOD*Total nonfatal overdoses Rx
305	Perceived risk Rx use reference	people/year	INITIAL(Perceived risk Rx use indicated)

306	Perceived risk Rx use relative	dmnl	ACTIVE INITIAL(XIDZ(Perceived risk Rx use current,Perceived risk Rx use reference,1),1)
307	Perceived risk strength initiating heroin with Rx use	dmnl	0.467195
308	Perceived risk strength initiating NDHU no Rx	dmnl	0.201234
309	Perceived risk strength initiating Rx misuse diverted	dmnl	0.839887
310	Perceived risk strength initiating Rx misuse own Rx	dmnl	0.799283
311	Perceived risk strength net quit heroin with Rx OUD	dmnl	0.01
312	Perceived risk strength net quit NDHU	dmnl	0.01
313	Perceived risk strength net quit NDHU with Rx	dmnl	0.01
314	Perceived risk strength net quit Rx misuse	dmnl	1.18906
315	Perceived risk weight NFOD	dmnl	0.1
316	PEType	dmnl	PEType[PET] = 0,0,1,0,0
317	Policy activation time	year	2021
318	Policy change ADF fraction of prescribed Rx opioids	dmnl	0
319	Policy change average MME per Rx	dmnl	0
320	Policy change average prescription duration	dmnl	0
321	Policy change Bup effective capacity decay constant	dmnl	0
322	Policy change Bup providers	dmnl	0
323	Policy change fentanyl effect on OD rate	dmnl	0
324	Policy change initiating NDHU no Rx	dmnl	0

325	Policy change initiating Rx misuse diverted	dmnl	0
326	Policy change initiation rate heroin with Rx misuse	dmnl	0
327	Policy change initiation rate Rx misuse own Rx	dmnl	0
328	Policy change MMT capacity	dmnl	0
329	Policy change Nx kit distribution efficiency	dmnl	0
330	Policy change Nx kits distributed	dmnl	0
331	Policy change patients with opioid prescription	dmnl	0
332	Policy change prescriptions per person	dmnl	0
333	Policy change probability OD witnessed	dmnl	0
334	Policy change probability of calling emergency services	dmnl	0
335	Policy change relapse rate	dmnl	0
336	Policy change Rx street supply shocks	1/year	0
337	Policy change Rx supply relative	dmnl	0
338	Policy change Tx average duration	dmnl	0
339	Policy change Tx intake delay	dmnl	Policy change Tx intake delay[TxT] = 0
340	Policy change Tx seeking affordability loss fraction	dmnl	0
341	Policy change Tx seeking nonaffordability loss fraction	dmnl	0
342	Policy change Tx seeking rate Rx OUD no H total	dmnl	0
343	Policy change Viv capacity	dmnl	0
344	Policy rampup duration	year	3
345	Population	people	EXTERNAL_DATA(Population)

346	Prescriptions per person	Rx/person	Projection output data[RxPP]*(1+RAMP(Policy change prescriptions per person/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
347	Prescriptions per person reference	Rx/person	INITIAL(Prescriptions per person)
348	Prescriptions per person relative	dmnl	Prescriptions per person/Prescriptions per person reference
349	Prescriptions per person SH	Rx/person	Total prescription opioid Rx IQVIA/Patients receiving opioid prescription IQVIA SH
350	PriorErr		PriorErr[Elm] = IF THEN ELSE(DataPrior[Elm]=NAREPLACEMENT:OR:SimPrior[Elm]=NAREPLACEMENT,0,-((SimPrior[Elm]-DataPrior[Elm])*Weights[Normal,Elm])^2/2)
351	Probability Nx bystander heroin	dmnl	1-EXP(-Nx kit distribution efficiency net*Nx kits per 100k population H user)
352	Probability Nx bystander heroin prior	dmnl	IF THEN ELSE(Time=2019,0.2,NAREPLACEMENT)
353	Probability Nx bystander Rx	dmnl	1-EXP(-Nx kit distribution efficiency net*Nx kits per 100k population Rx user)
354	Probability OD death not averted heroin user	dmnl	1-Probability OD witnessed net*(1-(1-Probability Nx bystander heroin)*(1-Probability of calling emergency services net))
355	Probability OD death not averted Rx user	dmnl	1-Probability OD witnessed net*(1-(1-Probability Nx bystander Rx)*(1-Probability of calling emergency services net))
356	Probability OD witnessed	dmnl	0.764
357	Probability OD witnessed net	dmnl	Probability OD witnessed+RAMP(IF THEN ELSE(Policy change probability OD witnessed>=0,Policy change probability OD witnessed*(1-Probability OD witnessed),Policy change probability OD witnessed*Probability OD witnessed)/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration)
358	Probability of calling emergency services	dmnl	0.424
359	Probability of calling emergency services net	dmnl	Probability of calling emergency services+RAMP(IF THEN ELSE(Policy change probability of calling emergency services>=0,Policy change probability of calling emergency services*(1-Probability of calling emergency services),Policy change probability of calling emergency services*Probability of calling emergency services)/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration)
360	Projected cumulative overdose deaths	people	Projected total overdose deaths0.0

361	Projected cumulative UD person years	person * Years	Projected total with UD0.0
362	Projected total overdose deaths	people/year	IF THEN ELSE(Time<Cumulative projections start time,0,Total overdose deaths)
363	Projected total with UD	people	IF THEN ELSE(Time<Cumulative projections start time,0,Total with UD)
364	Projection curve end time	year	Projection curve end time[Fent] = INITIAL(Projection curve end time fentanyl penetration)
365	Projection curve end time ADF fraction of prescribed Rx opioids	year	2030
366	Projection curve end time avg MME per Rx	year	2030
367	Projection curve end time Bup providers	year	2030
368	Projection curve end time fentanyl penetration	year	2030
369	Projection curve end time heroin price index	year	2030
370	Projection curve end time MMT capacity	year	2030
371	Projection curve end time Nx kits distributed	year	2030
372	Projection curve end time patients with opioid prescription	year	2030
373	Projection curve end time prescriptions per person	year	2030
374	Projection curve end time Viv capacity	year	2030
375	Projection curve end value		Projection curve end value[Fent] = INITIAL(Projection curve end value fentanyl penetration)
376	Projection curve end value ADF fraction of prescribed Rx opioids	dmnl	0.0425
377	Projection curve end value avg MME per Rx	MME/Rx	580
378	Projection curve end value Bup providers	people	159043

379	Projection curve end value fentanyl penetration	dmnl	0.6566
380	Projection curve end value heroin price index	dmnl	0.57
381	Projection curve end value MMT capacity	people	784682
382	Projection curve end value Nx kits distributed	dmnl	3.38E+06
383	Projection curve end value patients with opioid prescription	people	5.00E+07
384	Projection curve end value prescriptions per person	Rx/person	2
385	Projection curve end value Viv capacity	people	45669
386	Projection input data	dmnl	Projection input data[Fent] = Fentanyl penetration curve NFLIS
387	Projection last data time	year	Projection last data time[Proj] = INITIAL(GET DATA LAST TIME(Projection input data[Proj]))
388	Projection last data value		Projection last data value[Proj] = INITIAL(GET DATA AT TIME(Projection input data[Proj],Projection last data time[Proj]))
389	Projection output data		Projection output data[Proj] = IF THEN ELSE(Time<=Projection last data time[Proj],Projection input data[Proj],Switch for constant projections[Proj]*Projection input data[Proj]+(1-Switch for constant projections[Proj])*Logistic growth curve[Proj])
390	Relapse rate HUD	dmnl/year	0.11284
391	Relapse rate HUD net	1/year	Relapse rate HUD*(1+RAMP(Policy change relapse rate/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
392	Relapse rate Rx OUD relative to HUD	dmnl	0.5
393	Relapsing from remission total	people/year	Relapsing to Rx OUD no H+Relapsing to Rx OUD with H+Relapsing to HUD
394	Relapsing to HUD	person/Years	HUD in remission*Relapse rate HUD net
395	Relapsing to HUD total	people/year	Relapsing to HUD+SUM(Tx exit with UD HUD[TxT])
396	Relapsing to Rx OUD no H	people/year	Rx OUD no heroin in remission*Relapse rate HUD net*Relapse rate Rx OUD relative to HUD
397	Relapsing to Rx OUD no H total	people/year	Relapsing to Rx OUD no H+SUM(Tx exit with UD Rx OUD no H[TxT])

398	Relapsing to Rx OUD with H	person/Years	Rx OUD with heroin in remission*Relapse rate HUD net*Relapse rate Rx OUD relative to HUD
399	Relapsing to Rx OUD with H total	people/year	Relapsing to Rx OUD with H+SUM(Tx exit with UD Rx OUD with H[TxT])
400	Remission fraction in Tx	dmnl	Remission fraction in Tx[Bup] = Remission fraction in Tx Bup
401	Remission fraction in Tx Bup	dmnl	Tx success fraction[Bup]
402	Remission fraction in Tx MMT	dmnl	Tx success fraction[MMT]
403	Remission fraction in Tx Viv	dmnl	Tx success fraction[Viv]
404	Remission rate HUD no MOUD Tx	dmnl/year	0.135
405	Remission rate Rx OUD no H no MOUD Tx	dmnl/year	INITIAL(Remission rate HUD no MOUD Tx*Remission rate Rx OUD relative to HUD)
406	Remission rate Rx OUD relative to HUD	dmnl	1
407	Remission rate Rx OUD with H no MOUD Tx	dmnl/year	INITIAL(Remission rate HUD no MOUD Tx*Remission rate Rx OUD relative to HUD)
408	Remission relative to disorder	1	Total in Remission/Total with UD
409	Remitting HUD no MOUD Tx	people/year	HUD no MOUD*Remission rate HUD no MOUD Tx
410	Remitting Rx OUD no H no MOUD Tx	people/year	Rx OUD no PY heroin no MOUD*Remission rate Rx OUD no H no MOUD Tx
411	Remitting Rx OUD with H no MOUD Tx	people/year	Rx OUD with PY heroin no MOUD*Remission rate Rx OUD with H no MOUD Tx
412	RepErr		RepErr[TSElm] = IF THEN ELSE(Switch for historical noise=1,SUM(RepErrRaw[TSElm,Year]*IsYear[Year]),IF THEN ELSE(NormErr[TSElm]=NAREPLACEMENT,SUM(RepErrRaw[TSElm,Year]*IsYear[Year]),NormErr[TSElm]))
413	RepErrRaw	dmnl	RepErrRaw[TSElm,Year] = 0
414	RepVar		RepVar[TSElm] = SimVar[TSElm]*(1+RAMP(1,NoiseStartTime,NoiseStartTime+1)*RepErr[TSElm])
415	Rx availability coeff developing Rx OUD	dmnl	Rx availability for misuse relative^Rx availability strength developing Rx OUD
416	Rx availability coeff initiating Rx misuse	dmnl	Rx availability for misuse relative^Rx availability strength initiating Rx misuse
417	Rx availability coeff net quit Rx misuse	dmnl	Rx availability for misuse relative^-Rx availability strength net quit Rx misuse

418	Rx availability for misuse relative	dmnl	(Rx supply relative net+Counterfeit supply relative*Counterfeit supply weight)/Rx demand for misuse relative
419	Rx availability for UD relative	dmnl	Rx availability for misuse relative*Max((1-Rx street supply disruption),0.01)
420	Rx availability strength developing Rx OUD	dmnl	1.43936
421	Rx availability strength initiating Rx misuse	dmnl	0.407239
422	Rx availability strength net quit Rx misuse	dmnl	1.23346
423	Rx demand for misuse	MME/year	(Rx misuse no PY heroin*Rx demand Rx misuse)+(Nondisordered heroin use*Fraction of NDHU with Rx avg*Rx demand NDHU)+(Rx OUD no PY heroin no MOUD*Rx demand Rx OUD no H)+(Rx OUD with PY heroin no MOUD*Rx demand Rx OUD with H)+(HUD no MOUD*Fraction of HUD with Rx OUD or misuse avg*Rx demand HUD with Rx OUD or misuse)+SUM((Rx OUD no heroin by MOUD[TxT]*Rx demand Rx OUD no H*Effect of MOUD Tx on Rx consumption[TxT])+(Rx OUD with heroin by MOUD[TxT]*Rx demand Rx OUD with H*Effect of MOUD Tx on Rx consumption[TxT])+(HUD by MOUD[TxT]*Fraction of HUD with Rx OUD or misuse avg*Rx demand HUD with Rx OUD or misuse*Effect of MOUD Tx on Rx consumption[TxT]))
424	Rx demand for misuse reference	MME/Years	INITIAL(Rx demand for misuse)
425	Rx demand for misuse relative	dmnl	Rx demand for misuse/Rx demand for misuse reference
426	Rx demand HUD with Rx OUD or misuse	MME/person/year	13000
427	Rx demand NDHU	MME/person/year	4400
428	Rx demand Rx misuse	MME/person/year	2000
429	Rx demand Rx OUD no H	MME/person/year	12000
430	Rx demand Rx OUD with H	MME/person/year	17000
431	Rx misuse no PY heroin	people	((((((Initiating Rx misuse diverted+Initiating Rx misuse own Rx)-Developing Rx OUD)-Initiating heroin with Rx misuse)-Net quitting Rx misuse)+Net quitting heroin with Rx misuse)-NonOD death misuse)-Overdose death Rx misuseInitial Rx misuse no H

432	Rx misuse no PY heroin NSDUH	people	EXTERNAL_DATA(Rx misuse no PY heroin NSDUH)
433	Rx misuse no PY heroin NSDUH redef corrected	person	IF THEN ELSE(Time<2019,NSDUH misuse redefinition effect*Rx misuse no PY heroin NSDUH,NAREPLACEMENT)
434	Rx OUD all total	person	Rx OUD no PY heroin total+Rx OUD with PY heroin total
435	Rx OUD all total DATA	people	X IF MISSING(Rx OUD no PY heroin NSDUH+Rx OUD with PY heroin DATA,NAREPLACEMENT)
436	Rx OUD by MOUD	person	Rx OUD by MOUD[TxT] = Rx OUD no heroin by MOUD[TxT]+Rx OUD with heroin by MOUD[TxT]
437	Rx OUD in remission total	people	Rx OUD no heroin in remission+Rx OUD with heroin in remission+SUM(Rx OUD no PY heroin in remission in MOUD Tx[TxT]+Rx OUD with PY heroin in remission in MOUD Tx[TxT])
438	Rx OUD in remission total prior	people	IF THEN ELSE(Time=2013,1.52192e+06,NAREPLACEMENT)
439	Rx OUD in stable remission total prior	people	IF THEN ELSE(Time=2013,882376,NAREPLACEMENT)
440	Rx OUD no heroin by MOUD	people	Rx OUD no heroin by MOUD[TxT] = (((Tx engagement Rx OUD no H[TxT]-Tx exit in remission Rx OUD no H[TxT])-Tx exit with UD Rx OUD no H[TxT])-NonOD death Rx OUD no H in Tx[TxT])-Overdose death Rx OUD no H in Tx[TxT]Initial Rx OUD no H in Tx[TxT]
441	Rx OUD no heroin in remission	people	((((SUM(Tx exit in remission Rx OUD no H[TxT]))-NonOD death Rx OUD no H in remission)-Relapsing to Rx OUD no H)+Remitting Rx OUD no H no MOUD Tx)-Stabilizing remission Rx OUD no HInitial Rx OUD no H in remission
442	Rx OUD no heroin in stable remission	people	Stabilizing remission Rx OUD no H-NonOD death Rx OUD no H in stable remissionInitial Rx OUD no H in stable remission
443	Rx OUD no PY heroin in remission in MOUD Tx	person	Rx OUD no PY heroin in remission in MOUD Tx[TxT] = Remission fraction in Tx[TxT]*Rx OUD no heroin by MOUD[TxT]
444	Rx OUD no PY heroin no MOUD	people	((((((Developing Rx OUD+Net quitting heroin with Rx OUD)-Initiating heroin with Rx OUD)-Remitting Rx OUD no H no MOUD Tx)-NonOD death Rx OUD no H)-Overdose death Rx OUD no H)+Relapsing to Rx OUD no H)+(SUM((Tx exit with UD Rx OUD no H[TxT]-Tx engagement Rx OUD no H[TxT])))Initial Rx OUD no H
445	Rx OUD no PY heroin NSDUH	people	EXTERNAL_DATA(Rx OUD no PY heroin NSDUH)
446	Rx OUD no PY heroin total	person	Rx OUD no PY heroin no MOUD+SUM((1-Remission fraction in Tx[TxT])*Rx OUD no heroin by MOUD[TxT])
447	Rx OUD with heroin by MOUD	people	Rx OUD with heroin by MOUD[TxT] = (((Tx engagement Rx OUD with H[TxT]-Tx exit in remission Rx OUD with H[TxT])-Tx exit with UD Rx OUD with H[TxT])-NonOD

			death Rx OUD with H in Tx[TxT])-Overdose death Rx OUD with H in Tx[TxT]Initial Rx OUD with H in Tx[TxT]
448	Rx OUD with heroin in remission	people	((((SUM(Tx exit in remission Rx OUD with H[TxT]))-NonOD death Rx OUD with H in remission)-Relapsing to Rx OUD with H)+Remitting Rx OUD with H no MOUD Tx)-Stabilizing remission Rx OUD with HInitial Rx OUD with H in remission
449	Rx OUD with heroin in stable remission	people	NonOD death Rx OUD with H in remission-NonOD death Rx OUD with H in stable remissionInitial Rx OUD with H in stable remission
450	Rx OUD with PY heroin DATA	people	Rx OUD with PY heroin NSDUH RAND
451	Rx OUD with PY heroin in remission in MOUD Tx	person	Rx OUD with PY heroin in remission in MOUD Tx[TxT] = Rx OUD with heroin by MOUD[TxT]*Remission fraction in Tx[TxT]
452	Rx OUD with PY heroin no MOUD	people	((((((Initiating heroin with Rx OUD-Developing HUD with Rx OUD)-Net quitting heroin with Rx OUD)-Remitting Rx OUD with H no MOUD Tx)-NonOD death Rx OUD with H)-Overdose death Rx OUD with H)+Relapsing to Rx OUD with H)+(SUM((Tx exit with UD Rx OUD with H[TxT]-Tx engagement Rx OUD with H[TxT])))Initial Rx OUD with H
453	Rx OUD with PY heroin NSDUH RAND	people	EXTERNAL_DATA(Rx OUD with PY heroin NSDUH RAND)
454	Rx OUD with PY heroin total	person	Rx OUD with PY heroin no MOUD+SUM((1-Remission fraction in Tx[TxT])*Rx OUD with heroin by MOUD[TxT])
455	Rx price endogenous	$/MME	(1/Rx availability for UD relative)*((1-ADF fraction of Rx street supply net)+ADF fraction of Rx street supply net*ADF relative price)
456	Rx price index endogenous	dmnl	Rx price endogenous/Rx price initial
457	Rx price initial	$/MME	1
458	Rx price StreetRx	$/MME	EXTERNAL_DATA(Rx price StreetRx)
459	Rx street supply disruption	dmnl	Rx street supply shocks-Rx street supply readjustment0.0
460	Rx street supply impact policy	1/year	PULSE(Policy activation time,Policy rampup duration)*Policy change Rx street supply shocks
461	Rx street supply readjustment	dmnl/year	Rx street supply disruption/Time to readjust Rx street supply
462	Rx street supply shocks	dmnl/year	OxyContin withdrawal supply impact+Rx street supply impact policy
463	Rx supply relative	dmnl	Average MME per opioid Rx relative^(3*Sensitivity of Rx supply to MME per Rx/(Sensitivity of Rx supply to MME per Rx+Sensitivity of Rx supply to patients receiving prescription+Sensitivity of Rx supply to Rx per person))*Patients receiving opioid prescription relative^(3*Sensitivity of Rx supply to patients receiving prescription/(Sensitivity of Rx supply to MME per Rx+Sensitivity of Rx supply to

			patients receiving prescription+Sensitivity of Rx supply to Rx per person))*Prescriptions per person relative^(3*Sensitivity of Rx supply to Rx per person/(Sensitivity of Rx supply to MME per Rx+Sensitivity of Rx supply to patients receiving prescription+Sensitivity of Rx supply to Rx per person))
464	Rx supply relative net	dmnl	Rx supply relative*(1+RAMP(Policy change Rx supply relative/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
465	Rx vs H price coeff developing HUD with Rx OUD	1	Rx vs heroin price index^Rx vs H price strength developing HUD with Rx OUD
466	Rx vs H price coeff initiating heroin with Rx OUD	dmnl	Rx vs heroin price index^Rx vs H price strength initiating heroin with Rx OUD
467	Rx vs H price coeff initiating NDHU with Rx	dmnl	Rx vs heroin price index misuse^Rx vs H price strength initiating NDHU with Rx
468	Rx vs H price strength developing HUD with Rx OUD	dmnl	0.650241
469	Rx vs H price strength initiating heroin with Rx OUD	dmnl	0.0528525
470	Rx vs H price strength initiating NDHU with Rx	dmnl	0.109457
471	Rx vs heroin price index	dmnl	XIDZ(Rx price index endogenous,Heroin price index,1)
472	Rx vs heroin price index misuse	dmnl	XIDZ(1/Rx availability for misuse relative,Heroin price index,1)
473	Sensitivity of Rx price to Rx demand	dmnl	-1
474	Sensitivity of Rx price to Rx supply	dmnl	1
475	Sensitivity of Rx price to street supply disruption	dmnl	1
476	Sensitivity of Rx supply to MME per Rx	dmnl	1
477	Sensitivity of Rx supply to patients receiving prescription	dmnl	1
478	Sensitivity of Rx supply to Rx per person	dmnl	1
479	SI on developing HUD current	dmnl	Effective SI users HUD development/Population
480	SI on developing HUD reference	dmnl	INITIAL(SI on developing HUD current)
481	SI on developing HUD relative	1	SI on developing HUD current/SI on developing HUD reference

482	SI on developing Rx OUD current	dmnl	Effective SI users Rx OUD development/Population
483	SI on developing Rx OUD reference	dmnl	INITIAL(SI on developing Rx OUD current)
484	SI on developing Rx OUD relative	dmnl	XIDZ(SI on developing Rx OUD current,SI on developing Rx OUD reference,1)
485	SI on initiating heroin current	dmnl	Effective SI users heroin initiation/Population
486	SI on initiating heroin reference	dmnl	INITIAL(SI on initiating heroin current)
487	SI on initiating heroin relative	dmnl	SI on initiating heroin current/SI on initiating heroin reference
488	SI on initiating Rx misuse current	dmnl	Effective SI users Rx misuse initiation/Population
489	SI on initiating Rx misuse reference	dmnl	INITIAL(SI on initiating Rx misuse current)
490	SI on initiating Rx misuse relative	dmnl	SI on initiating Rx misuse current/SI on initiating Rx misuse reference
491	SimPrior		SimPrior[StElm] = NAREPLACEMENT
492	SimVar	people/year	SimVar[RMis] = Rx misuse no PY heroin
493	Social influence coeff developing HUD	dmnl	SI on developing HUD relative^Social influence strength developing HUD
494	Social influence coeff developing Rx OUD	dmnl	SI on developing Rx OUD relative^Social influence strength developing Rx OUD
495	Social influence coeff initiating heroin with Rx OUD	dmnl	SI on initiating heroin relative^Social influence strength initiating heroin with Rx OUD
496	Social influence coeff initiating NDHU no Rx	dmnl	SI on initiating heroin relative^Social influence strength initiating NDHU no Rx
497	Social influence coeff initiating NDHU with Rx	dmnl	SI on initiating heroin relative^Social influence strength initiating NDHU with Rx
498	Social influence coeff initiating Rx misuse	dmnl	SI on initiating Rx misuse relative^Social influence strength initiating Rx misuse
499	Social influence strength developing HUD	dmnl	0.01
500	Social influence strength developing Rx OUD	dmnl	0.173237
501	Social influence strength initiating heroin with Rx OUD	dmnl	2
502	Social influence strength initiating NDHU no Rx	dmnl	0.334526

503	Social influence strength initiating NDHU with Rx	dmnl	2
504	Social influence strength initiating Rx misuse	dmnl	0.680626
505	Stabilizing remission HUD	person/Years	HUD in remission/Time to stabilize remission
506	Stabilizing remission Rx OUD no H	people/year	Rx OUD no heroin in remission/Time to stabilize remission
507	Stabilizing remission Rx OUD with H	person/Years	Rx OUD with heroin in remission/Time to stabilize remission
508	StDev	dmnl	StDev[Elm] = 1
509	Switch for constant projections	dmnl	Switch for constant projections[Proj] = 0
510	Switch for historical noise	dmnl	0
511	Switch for no fentanyl	dmnl	0
512	SynVar		SynVar[Elm] = IF THEN ELSE(DataVar[Elm]=NAREPLACEMENT,NAREPLACEMENT,RepVar[Elm])
513	Time to readjust Rx street supply	Years	1.4
514	Time to stabilize remission	Years	4
515	Total annual Tx receipt by MOUD	person/Years	Total annual Tx receipt by MOUD[TxT] = Total by MOUD[TxT]/Tx average duration net[TxT]
516	Total by MOUD	person	Total by MOUD[TxT] = HUD by MOUD[TxT]+Rx OUD no heroin by MOUD[TxT]+Rx OUD with heroin by MOUD[TxT]+HUD in remission in MOUD Tx[TxT]+Rx OUD no PY heroin in remission in MOUD Tx[TxT]+Rx OUD with PY heroin in remission in MOUD Tx[TxT]
517	Total heroin initiation	people/year	Initiating heroin no Rx+Initiating heroin with Rx misuse+Initiating heroin with Rx OUD
518	Total heroin initiation DATA	person/Years	Total heroin initiation SAMHSA RAND
519	Total heroin initiation SAMHSA RAND	people/year	EXTERNAL_DATA(Total heroin initiation SAMHSA RAND)
520	Total heroin users	people	Nondisordered heroin use+Rx OUD with PY heroin total+HUD total
521	Total heroin users DATA	people	X IF MISSING(HUD DATA+Rx OUD with PY heroin DATA+Nondisordered heroin use DATA,NAREPLACEMENT)
522	Total HUD in remission	person	Total HUD in remission not in tx+SUM(HUD in remission in MOUD Tx[TxT])
523	Total HUD in remission not in tx	person	HUD in remission+HUD in stable remission
524	Total in Remission	person	Total HUD in remission+Total in Rx OUD Remission

525	Total in Remission by MOUD	people	Total in Remission by MOUD[TxT] = HUD in remission in MOUD Tx[TxT]+Rx OUD no PY heroin in remission in MOUD Tx[TxT]+Rx OUD with PY heroin in remission in MOUD Tx[TxT]
526	Total in Remission in Treatment	people	SUM(Total in Remission by MOUD[TxT])
527	Total in Rx OUD Remission	person	SUM(Rx OUD no PY heroin in remission in MOUD Tx[TxT])+SUM(Rx OUD with PY heroin in remission in MOUD Tx[TxT])+Total Rx OUD in Remission not in Tx
528	Total nondisordered heroin users	person	Nondisordered heroin use+Rx OUD with PY heroin total
529	Total nondisordered heroin users DATA	people	X IF MISSING(Nondisordered heroin use DATA+Rx OUD with PY heroin DATA,NAREPLACEMENT)
530	Total nonfatal overdoses	people/year	Nonfatal ODs Rx OUD no H+Nonfatal ODs HUD+Nonfatal ODs NDHU+Nonfatal ODs Rx OUD with H+Nonfatal ODs Rx misuse
531	Total nonfatal overdoses heroin	people/year	Nonfatal ODs HUD+Nonfatal ODs NDHU
532	Total nonfatal overdoses Rx	people/year	Nonfatal ODs Rx OUD no H+Nonfatal ODs Rx misuse+Nonfatal ODs Rx OUD with H
533	Total overdose data last time	year	INITIAL(GET DATA LAST TIME(Total overdose deaths synth no H NVSS))
534	Total overdose deaths	person/Years	Overdose death Rx misuse+Overdose death NDHU+Overdose death MU+Total overdose deaths Rx OUD no H+Total overdose deaths Rx OUD with H+Total overdose deaths HUD
535	Total overdose deaths base heroin	people/year	Overdose death NDHU*OD death fraction base NDHU+Total overdose deaths HUD*OD death fraction base HUD
536	Total overdose deaths base heroin NVSS	people/year	EXTERNAL_DATA(Total overdose deaths base heroin NVSS)
537	Total overdose deaths base Rx	people/year	Overdose death MU+Overdose death Rx misuse+Total overdose deaths Rx OUD no H*OD death fraction base Rx OUD no H+Total overdose deaths Rx OUD with H
538	Total overdose deaths base Rx NVSS	people/year	EXTERNAL_DATA(Total overdose deaths base Rx NVSS)
539	Total overdose deaths heroin	person/Years	Overdose death NDHU+Total overdose deaths HUD
540	Total overdose deaths heroin and excess estimated	person/Years	IF THEN ELSE(Time>2018,NAREPLACEMENT,Total overdose deaths base heroin NVSS+OD deaths synth excess estimated)
541	Total overdose deaths HUD	people/year	Overdose death HUD+SUM(Overdose death HUD in MOUD Tx[TxT])
542	Total overdose deaths NVSS	people/year	X IF MISSING(Total overdose deaths base Rx NVSS+Total overdose deaths base heroin NVSS+Total overdose deaths synth no H NVSS+Total overdose deaths synth heroin NVSS,NAREPLACEMENT)
543	Total overdose deaths Rx	person/Years	Overdose death MU+Overdose death Rx misuse+Total overdose deaths Rx OUD no H+Total overdose deaths Rx OUD with H

544	Total overdose deaths Rx OUD no H	people/year	Overdose death Rx OUD no H+SUM(Overdose death Rx OUD no H in Tx[TxT])
545	Total overdose deaths Rx OUD with H	people/year	Overdose death Rx OUD with H+SUM(Overdose death Rx OUD with H in Tx[TxT])
546	Total overdose deaths synth	people/year	Total overdose deaths synth base+Total overdose deaths synth excess
547	Total overdose deaths synth base	people/year	Total overdose deaths Rx OUD no H*OD death fraction synth baseline Rx OUD no H
548	Total overdose deaths synth excess	people/year	Overdose death NDHU*OD death fraction synth NDHU+Total overdose deaths HUD*OD death fraction synth HUD
549	Total overdose deaths synth heroin NVSS	people/year	EXTERNAL_DATA(Total overdose deaths synth heroin NVSS)
550	Total overdose deaths synth no H NVSS	people/year	EXTERNAL_DATA(Total overdose deaths synth no H NVSS)
551	Total overdoses heroin	person/Years	Total nonfatal overdoses heroin+Total overdose deaths heroin
552	Total overdoses Rx	person/Years	Total nonfatal overdoses Rx+Total overdose deaths Rx
553	Total overdoses Rx synth baseline fraction	dmnl	Total overdoses synth baseline/Total overdoses Rx
554	Total overdoses synth baseline	people/year	Overdose rate synth baseline*Rx OUD no PY heroin no MOUD
555	Total prescription opioid Rx	Rx/year	Patients receiving opioid prescription*Prescriptions per person
556	Total prescription opioid Rx IQVIA	Rx/year	EXTERNAL_DATA(Total prescription opioid Rx IQVIA)
557	Total Rx misuse initiation	people/year	Initiating Rx misuse diverted+Initiating Rx misuse own Rx
558	Total Rx misuse initiation SAMHSA	people/year	EXTERNAL_DATA(Total Rx misuse initiation SAMHSA)
559	Total Rx misuse initiation SAMHSA redef corrected	person/Years	IF THEN ELSE(Time<2019,Total Rx misuse initiation SAMHSA*NSDUH misuse redefinition effect,NAREPLACEMENT)
560	Total Rx MME prescribed	MME/year	Patients receiving opioid prescription*Prescriptions per person*Average MME per opioid Rx
561	Total Rx MME prescribed IQVIA	MME/year	EXTERNAL_DATA(Total Rx MME prescribed IQVIA)
562	Total Rx OUD in Remission not in Tx	people	Rx OUD no heroin in remission+Rx OUD with heroin in remission+Rx OUD no heroin in stable remission+Rx OUD with heroin in stable remission
563	Total Rx use excl heroin	person	Rx misuse no PY heroin+Rx OUD no PY heroin total
564	Total Rx users	person	Rx misuse no PY heroin+Rx OUD all total+HUD total*Fraction of HUD who use rx NSDUH+Fraction of NDHU who use Rx NSDUH*Nondisordered heroin use
565	Total Rx Users corrected DATA	person	IF THEN ELSE(Time<2019,Rx misuse no PY heroin NSDUH redef corrected+Rx OUD all total DATA+(HUD DATA*Fraction of HUD who use rx NSDUH)+(Total

			nondisordered heroin users DATA*Fraction of NDHU who use Rx NSDUH),NAREPLACEMENT)
566	Total Rx users excl heroin DATA	people	Rx misuse no PY heroin NSDUH redef corrected+Rx OUD no PY heroin NSDUH
567	Total Tx engagement rate HUD	1/year	SUM(Tx engagement rate actual HUD[TxT])
568	Total Tx engagement rate Rx OUD no H	1/year	SUM(Tx engagement rate actual Rx OUD no H[TxT])
569	Total Tx engagement rate Rx OUD with H	1/year	SUM(Tx engagement rate actual Rx OUD with H[TxT])
570	Total with UD	people	HUD total+Rx OUD all total
571	Total with UD DATA	people	HUD DATA+Rx OUD all total DATA
572	Treatment gap HUD	dmnl	(1-zidz(SUM(Tx engagement HUD[TxT]),HUD no MOUD*SUM(Tx seeking rate HUD[TxT])))
573	Treatment gap Rx OUD	dmnl	(1-zidz(SUM(Tx engagement Rx OUD no H[TxT]+Tx engagement Rx OUD with H[TxT]),SUM(Rx OUD no PY heroin no MOUD*Tx seeking rate Rx OUD no H[TxT]+Rx OUD with PY heroin no MOUD*Tx seeking rate Rx OUD with H[TxT])))
574	Tx annual patients Bup IQVIA TPT	person/Years	EXTERNAL_DATA(Tx annual patients Bup IQVIA TPT)
575	Tx average duration	Years	Tx average duration[Bup] = INITIAL(Tx average duration Bup)
576	Tx average duration Bup	year	0.61
577	Tx average duration MMT	year	1
578	Tx average duration net	year	Tx average duration net[TxT] = Tx average duration[TxT]*(1+RAMP(Policy change Tx average duration/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
579	Tx average duration Viv	year	0.22
580	Tx capacity effective	people	Tx capacity effective[Bup] = Bup capacity effective*Tx effective capacity fraction[Bup]
581	Tx capacity effective utilization	dmnl	Tx capacity effective utilization[TxT] = zidz(Total by MOUD[TxT],Tx capacity effective[TxT])
582	Tx capacity relative to demand	dmnl	Tx capacity relative to demand[TxT] = zidz(Tx intake capacity[TxT],Tx demand Rx OUD no H[TxT]+Tx demand Rx OUD with H[TxT]+Tx demand HUD[TxT])
583	Tx demand fulfilment ratio	dmnl	Tx demand fulfilment ratio[TxT] = MIN(Tx capacity relative to demand[TxT],1)
584	Tx demand HUD	people/year	Tx demand HUD[TxT] = HUD no MOUD*Tx seeking rate HUD[TxT]*(1-Tx seeking barrier loss fraction)
585	Tx demand Rx OUD no H	person/Years	Tx demand Rx OUD no H[TxT] = Rx OUD no PY heroin no MOUD*Tx seeking rate Rx OUD no H[TxT]*(1-Tx seeking barrier loss fraction)

586	Tx demand Rx OUD with H	people/year	Tx demand Rx OUD with H[TxT] = Rx OUD with PY heroin no MOUD*Tx seeking rate Rx OUD with H[TxT]*(1-Tx seeking barrier loss fraction)
587	Tx demand total by type	people/year	Tx demand total by type[TxT] = Tx demand HUD[TxT]+Tx demand Rx OUD no H[TxT]+Tx demand Rx OUD with H[TxT]
588	Tx effective capacity fraction	dmnl	Tx effective capacity fraction[Bup] = 1
589	Tx engagement HUD	people/year	Tx engagement HUD[TxT] = Tx demand HUD[TxT]*Tx demand fulfilment ratio[TxT]
590	Tx engagement rate actual HUD	1/year	Tx engagement rate actual HUD[TxT] = Tx engagement HUD[TxT]/HUD total
591	Tx engagement rate actual Rx OUD no H	1/year	Tx engagement rate actual Rx OUD no H[TxT] = Tx engagement Rx OUD no H[TxT]/Rx OUD no PY heroin total
592	Tx engagement rate actual Rx OUD with H	1/year	Tx engagement rate actual Rx OUD with H[TxT] = Tx engagement Rx OUD with H[TxT]/Rx OUD with PY heroin total
593	Tx engagement Rx OUD no H	people/year	Tx engagement Rx OUD no H[TxT] = Tx demand Rx OUD no H[TxT]*Tx demand fulfilment ratio[TxT]
594	Tx engagement Rx OUD with H	people/year	Tx engagement Rx OUD with H[TxT] = Tx demand Rx OUD with H[TxT]*Tx demand fulfilment ratio[TxT]
595	Tx engagement total	person/Years	Tx engagement total[TxT] = Tx engagement HUD[TxT]+Tx engagement Rx OUD no H[TxT]+Tx engagement Rx OUD with H[TxT]
596	Tx exit in remission HUD	person/Years	Tx exit in remission HUD[TxT] = HUD by MOUD[TxT]*Tx exit in remission rate HUD[TxT]
597	Tx exit in remission rate HUD	dmnl/year	Tx exit in remission rate HUD[TxT] = 1/Tx average duration net[TxT]*Tx success fraction[TxT]
598	Tx exit in remission rate Rx OUD no H	dmnl/year	Tx exit in remission rate Rx OUD no H[TxT] = 1/Tx average duration net[TxT]*Tx success fraction[TxT]
599	Tx exit in remission rate Rx OUD with H	dmnl/year	Tx exit in remission rate Rx OUD with H[TxT] = 1/Tx average duration net[TxT]*Tx success fraction[TxT]
600	Tx exit in remission Rx OUD no H	person/Years	Tx exit in remission Rx OUD no H[TxT] = Rx OUD no heroin by MOUD[TxT]*Tx exit in remission rate Rx OUD no H[TxT]
601	Tx exit in remission Rx OUD with H	person/Years	Tx exit in remission Rx OUD with H[TxT] = Rx OUD with heroin by MOUD[TxT]*Tx exit in remission rate Rx OUD with H[TxT]
602	Tx exit in remission total	people/year	Tx exit in remission total[TxT] = Tx exit in remission HUD[TxT]+Tx exit in remission Rx OUD no H[TxT]+Tx exit in remission Rx OUD with H[TxT]
603	Tx exit total	people/year	Tx exit total[TxT] = Tx exit in remission total[TxT]+Tx exit with UD total[TxT]+NonOD death in Tx total[TxT]+Overdose death in Tx total[TxT]
604	Tx exit with UD HUD	person/Years	Tx exit with UD HUD[TxT] = HUD by MOUD[TxT]*Tx exit with UD rate HUD[TxT]

605	Tx exit with UD rate HUD	dmnl/year	Tx exit with UD rate HUD[TxT] = 1/Tx average duration net[TxT]*(1-Tx success fraction[TxT])
606	Tx exit with UD rate Rx OUD no H	dmnl/year	Tx exit with UD rate Rx OUD no H[TxT] = 1/Tx average duration net[TxT]*(1-Tx success fraction[TxT])
607	Tx exit with UD rate Rx OUD with H	dmnl/year	Tx exit with UD rate Rx OUD with H[TxT] = 1/Tx average duration net[TxT]*(1-Tx success fraction[TxT])
608	Tx exit with UD Rx OUD no H	person/Years	Tx exit with UD Rx OUD no H[TxT] = Rx OUD no heroin by MOUD[TxT]*Tx exit with UD rate Rx OUD no H[TxT]
609	Tx exit with UD Rx OUD with H	person/Years	Tx exit with UD Rx OUD with H[TxT] = Rx OUD with heroin by MOUD[TxT]*Tx exit with UD rate Rx OUD with H[TxT]
610	Tx exit with UD total	people/year	Tx exit with UD total[TxT] = Tx exit with UD HUD[TxT]+Tx exit with UD Rx OUD no H[TxT]+Tx exit with UD Rx OUD with H[TxT]
611	Tx intake capacity	people/year	Tx intake capacity[TxT] = Max(0,DELAY1(Tx exit total[TxT],Tx intake delay net[TxT])+(Tx capacity effective[TxT]-Total by MOUD[TxT])/Tx intake delay net[TxT])
612	Tx intake delay	year	0.083
613	Tx intake delay net	Years	Tx intake delay net[TxT] = Tx intake delay*(1+RAMP(Policy change Tx intake delay[TxT]/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
614	Tx point patients Bup DATA	people	Tx annual patients Bup IQVIA TPT*Tx average duration Bup
615	Tx point patients OTP MMT NSSATS	people	EXTERNAL_DATA(Tx point patients OTP MMT NSSATS)
616	Tx point patients Viv IQVIA	person	EXTERNAL_DATA(Tx point patients Viv IQVIA)
617	Tx seeking affordability loss fraction	dmnl	0.126
618	Tx seeking affordability loss fraction net	dmnl	Tx seeking affordability loss fraction+RAMP(IF THEN ELSE(Policy change Tx seeking affordability loss fraction>=0,Policy change Tx seeking affordability loss fraction*(1-Tx seeking affordability loss fraction),Policy change Tx seeking affordability loss fraction*Tx seeking affordability loss fraction)/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration)
619	Tx seeking barrier loss fraction	dmnl	MIN(1,Tx seeking affordability loss fraction net+Tx seeking nonaffordability loss fraction net)
620	Tx seeking fraction Bup HUD	dmnl	0.55
621	Tx seeking fraction Bup Rx OUD	dmnl	0.625
622	Tx seeking fraction by med HUD	dmnl	Tx seeking fraction by med HUD[Bup] = Tx seeking fraction Bup HUD

623	Tx seeking fraction by med Rx OUD	dmnl	Tx seeking fraction by med Rx OUD[Bup] = Tx seeking fraction Bup Rx OUD
624	Tx seeking fraction MMT HUD	dmnl	INITIAL((1-Tx seeking fraction Bup HUD)*Tx seeking fraction MMT HUD relative)
625	Tx seeking fraction MMT HUD relative	dmnl	0.8
626	Tx seeking fraction MMT Rx OUD	dmnl	INITIAL((1-Tx seeking fraction Bup Rx OUD)*Tx seeking fraction MMT Rx OUD relative)
627	Tx seeking fraction MMT Rx OUD relative	dmnl	0.15
628	Tx seeking nonaffordability loss fraction	dmnl	0.162
629	Tx seeking nonaffordability loss fraction net	dmnl	Tx seeking nonaffordability loss fraction+RAMP(IF THEN ELSE(Policy change Tx seeking nonaffordability loss fraction>=0,Policy change Tx seeking nonaffordability loss fraction*(1-Tx seeking nonaffordability loss fraction),Policy change Tx seeking nonaffordability loss fraction*Tx seeking nonaffordability loss fraction)/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration)
630	Tx seeking rate HUD	1/year	Tx seeking rate HUD[TxT] = Tx seeking rate Rx OUD no H total net*Tx seeking rate HUD relative to Rx OUD no H*Tx seeking fraction by med HUD[TxT]
631	Tx seeking rate HUD relative to Rx OUD no H	dmnl	4.85
632	Tx seeking rate Rx OUD no H	1/year	Tx seeking rate Rx OUD no H[TxT] = Tx seeking rate Rx OUD no H total net*Tx seeking fraction by med Rx OUD[TxT]
633	Tx seeking rate Rx OUD no H total	1/year	0.5
634	Tx seeking rate Rx OUD no H total net	1/year	Tx seeking rate Rx OUD no H total*(1+RAMP(Policy change Tx seeking rate Rx OUD no H total/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
635	Tx seeking rate Rx OUD with H	1/year	Tx seeking rate Rx OUD with H[TxT] = Tx seeking rate Rx OUD no H[TxT]
636	Tx success fraction	dmnl	Tx success fraction[TxT] = IF THEN ELSE(Tx average duration net[TxT]<=Tx success fraction inflection,zidz(Tx success fraction kappa^2,1+Tx success fraction kappa^2)*EXP((Tx success fraction lambda/Tx success fraction kappa)*(Tx average duration net[TxT]-Tx success fraction inflection)),1-zidz(1,1+Tx success fraction kappa^2)*EXP(-Tx success fraction lambda*Tx success fraction kappa*(Tx average duration net[TxT]-Tx success fraction inflection)))*Tx success fraction max

637	Tx success fraction inflection	Years	2.5
638	Tx success fraction kappa	dmnl	2.5
639	Tx success fraction lambda	1/year	2
640	Tx success fraction max	dmnl	0.85
641	Viv capacity estimated	person	Projection output data[VivCap]*(1+RAMP(Policy change Viv capacity/Policy rampup duration,Policy activation time,Policy activation time+Policy rampup duration))
642	Viv capacity estimated DATA	person	Tx point patients Viv IQVIA/Viv capacity utilization NSSATS
643	Viv capacity utilization NSSATS	dmnl	0.88
644	WeightMod	dmnl	WeightMod[Elm] = 1
645	WeightModManual	dmnl	WeightModManual[Elm] = 1
646	Weights	dmnl	Weights[Normal,Elm] = INITIAL(1/StDev[Elm]*WeightModManual[Elm])

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