ReDUCE Documentation

Model description

Serious bacterial infections are among the most common medical complications of injection opioid use. Hospitalization for these infections is common and represents opportunities for intervention. Other infections typical of drug use include HIV and Hepatitis C (HCV), which further affect mortality and costs associated with injection opioid use. Further complicating the picture, sexually transmitted infections (i.e., syphilis, gonorrhea, and chlamydia) are prevalent among people who inject drugs (PWID) given the association with high-risk sexual practices.

The **Reducing Infections Related to Drug Use Cost Effectiveness (ReDUCE) Model** is a microsimulation model that simulates the natural history of injection drug use in the U.S. for the purpose of forecasting injection-related bacterial infections, HIV, and Hepatitis C (HCV). The model also incorporates sexual behaviors for the purpose of forecasting STIs in this population and to account for additional risk factors for HIV and HCV. The model uses injection frequency, injection practices, and sexual behaviors as the basis to estimate outcomes of interest including incidence of infections and deaths. This simulation modeling framework can help demonstrate how interventions might yield long-term benefits and to measure the potential magnitude of those benefits for people who inject drugs.

Model structure and components

Model structure. In designing the model, we considered a number of different structures, in following with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practices for conceptualizing a model, including: 1) Markov Model, which is a health state-transition model in which “health states” represent key elements of a disease and are useful for decisions involving repeated events or changing conditions over long periods. These are memoryless, so they cannot incorporate time and history. The advantage of this model structure is that advanced calibration using Bayesian methods is possible. The principal elements of a Markov model are that states are mutually exclusive and collectively exhaustive, that movement among states is governed by transition probabilities, and that cycle lengths are fixed. A semi-Markov model can incorporate time and history. 2) Monte Carlo, which is an individual-based model that hypothetical individuals transition through one at a time. The initial health state is determined using the distribution of p^0 and simulate individual trajectory through health states using random numbers to determine actual transitions from transition probabilities. These incorporate memory (can track individual history) but can be difficult to debug and will introduce stochastic noise. 3) Agent-based model, which allows for inclusion of interdependent behaviors (such as within families) and produces simulations of autonomous individuals who operate according to defined preferences or rules of action. Given the disease processes and outcomes for this model, an agent-based model is not appropriate. Considering the benefits and limitations of these structures, the ReDUCE model is a **Monte Carlo microsimulation.**

Cycle Length. The cycle length is one week. Injection frequency is usually reported as injection frequency in the past month” and while frequency may change daily depending on drug availability, most frequency use is somewhat stable over a one-week period. Additionally, typical hospitalizations for endocarditis or skin and soft tissue infections are approximately one-week increments. Finally, most treatments for STIs can be measured on a weekly basis. If we ever want to change the cycle length, it requires minor code changes.

Modules. The model is designed as a number of modules through which simulated individuals pass. Briefly, a cohort module helps to “create” the population of interest. Next, individuals created during cohort generation enter the “sequelae of drug use (SDU)” module, which is where they encounter probabilities of fatal or nonfatal overdose, infective endocarditis, skin and soft tissue infections, HIV, and HCV. From the SDU module, individuals then enter the sequelae of sex (SOS) module, where they encounter probabilities of HIV, HCV, and STIs (ie. chlamydia, gonorrhea, and syphilis). From there, individuals enter back into the simulation or link to the “inpatient” module. In the “inpatient” module, individuals are hospitalized for their SDU. There are a variety of interventions (beyond standard hospital treatment) that individuals may encounter if those services are turned “on” by the user. Following the inpatient module, individuals have a probability of receiving outpatient care/services in the “outpatient” module. Probabilities of receiving outpatient care may vary based on whether a given service is available outpatient, the type of services an individual encountered in the hospital and/or the type of SDU they have (overdose vs infection), as well as whether or not they are in an outpatient intervention arm, such as comprehensive tele-harm reduction. They may unlink from outpatient care/services or never receive certain services. . The “behavioral transitions” module is when individuals have the probability of moving between injection frequency drug use states (high frequency, low frequency, or no current drug use), between sterile injection practice states (skin cleaning or no skin cleaning), and sharing/reusing needles, sex risk states (high risk, low risk, no current sex), and condom/sexual education states. After the “behavioral transitions” module, individuals move to the “mortality, cost, and quality of life” module. At this point, the model begins again in cycle n+1.

Modules

Module 1: Cohort initiation

When the model is initiated, a cohort of individuals is generated using 20 parameters:

1. ever injection drug use status (ever/never)
2. age (0-99). If we only want a certain age range, leave the unwanted ages as 0.
3. sex (M/F)
4. race (white/Black/other)
5. injection frequency (high/low/no current/never)
6. reusing/sharing equipment (yes/no/never).
7. sterile injection practice (cleaning/no cleaning/never)
8. HIV status (positive/negative)
9. HIV awareness (aware/unaware of diagnosis)
10. ART status, for known HIV positive (on ART/not on ART)
11. PrEP status, for known HIV negative (on PrEP/not on PrEP)
12. “Risky” sexual behavior (high risk/low risk/no current risk)
13. HCV status (positive/negative)
14. HCV awareness (aware/unaware of diagnosis)
15. Syphilis status (positive/negative)
16. Syphilis awareness (aware/unaware of diagnosis)
17. Gonorrhea status (positive/negative)
18. Gonorrhea awareness (aware/unaware of diagnosis)
19. Chlamydia status (positive/negative)
20. Chlamydia awareness (aware/unaware of diagnosis)

From these parameters, the cohort developed is a distribution of people who have ever or never injected drugs and those who are ever are stratified by injection frequency and injection practices. The model is structured such that first the user specifies the proportion of the population that has ever injected drugs. Following that, there are two methods by which the model can draw age, sex, and race. The first is by using age/sex/race tables and the second is by directly specifying age and sex distribution parameters in the configuration file. For the former, there is an “evers_age_racedistribution.csv” table and a “nevers_age_race_distribution.csv” table. Both of which are identically formatted but should have different input values for each group. In the latter method of drawing from age, sex, and race, the user inputs values directly into the deterministic parameter configuration file. These inputs include proportion male, proportion White, proportion Black, average male age, standard deviation male age, average female age, standard deviation female age, and minimum age. The model currently does not have separate input values for ever and never; therefore, this function should generally only be used for a cohort of all “ever injection drug use.” The age/sex/race tables will be used if mean age of either male or female is set to 0; otherwise, the inputs from the parameter configuration file will be used. Through either method, an age (in years), sex, and race stratified distribution of the population of ever drug users and of never drug users is developed. Since we have weekly cycles, the drawn age in years will be converted to age in weeks with the assumption that everyone is in the middle of their age_years.

Next, among those who are ever drug users, the probability of injection frequency is drawn from an age/sex/race stratified SQL table—high, low, and no current injection drug use. For this, all three probabilities of an age/sex/race group should equal to 1, and the model draws from this set of probabilities. For the probabilistic sensitivity analysis component of the model, since all probabilities are drawn from distributions, the user specifies two of the input distributions (low and high frequency) and the 3rd input (no current) is the difference. For example, if the user specifies every probability for an age/sex/race group to be 0, then the model assumes that “no current use” has a probability of 1. The model does not allow for the added probability to be greater than 1.

All persons who are ever drug users, are assigned an initial status of being a skin cleaner and a needle sharer which does not depend on age, sex, or race. While these are the initial attributes, all individuals have the possibility of “picking up” additional attributes as they move through the model. All never drug users are assigned “never” injection frequency, skin cleaning and needle sharing status.

Everybody is next assigned a sex risk state, defined as low, high, or no current sex. Specific definitions of low and high are left to the user. Sex risk is also drawn from an age, sex, race distribution, where the user specifies the proportion of each age/sex/race combo that is low and high risk (which must sum to 1 or less), and no current sex is calculated by the model using those proportions. **For this analysis, we assume everybody has low sex risk for the duration of the simulation.**

For people with *ever* injection drug use, the probability of starting with hepatitis C is calculated based off user input for the *proportion of HCV in the population*. Note that this probability is *not* conditional on any attribute other than ever injection drug use. All persons, regardless of HCV infection status, have a probability of knowing their HCV status (as either positive or negative) conditional on their age, sex, and race.

Among people who are HCV *positive* and aware of their HCV status, the probability of starting on treatment for HCV (DAA) is drawn, based only off the user input proportion of DAA among the population.

In the model, there are two possible states of HCV: HCV stages F1-F3, and HCV stage F4 (ie. “late stage” HCV). By default, anyone who has been drawn as having HCV is labeled as being in the early stage (F1-F3) for the purpose of determining awareness and treatment. For those who are drawn as *not* being on DAA, there is a probability that the individuals start with late-stage HCV. This probability is drawn (which is not conditional

on anything; it is a simple user provided probability), and any individual as having drawn late-stage HCV is then updated to have late-stage HCV.

Next, people who are either ever or never injection drug users have a probability of starting as HIV infected or HIV uninfected that is based on their age/sex/race/injection frequency (note: in this case a never injector is assigned to have no current injection frequency). If injection frequency, for example, is not obtainable data, then the conditional probability will only be calculated for the age/sex/race, and all injection frequency categories can be set to be the same probability to account for this. All persons, regardless of HIV infection status, have a probability of knowing their HIV infection status (i.e., HIV awareness). The probability of knowing one's status is conditional on their age, sex, race, and HIV status (positive or negative).

Next, among people who are HIV *infected* and *know their status* (ie. HIV aware), there is a probability that they are on ART, which is stratified by age, sex, and race. Among people who are HIV *uninfected* and *know their status* as uninfected, there is a probability that they are on PrEP, which is stratified by age, sex, and race.

In the model, there are two possible states of HIV: HIV with CD4 count >200 and CD4 count <200. By default, anyone who has been drawn as having HIV is labeled as having CD4 count >200 for the purpose of determining awareness and treatment. For those who are drawn as *not* being on ART, there is a probability that the individuals start with HIV with CD4 count <200. This probability is drawn (which is not conditional on anything, it is a simple user provided probability), and any individual as having drawn CD4 count <200 is then updated to have CD4 count <200. **In this analysis, we assume any individuals starting with HIV have CD4 count >200.**

Individuals can start the simulation with any of three STIs: chlamydia, gonorrhea, and syphilis. Among individuals with low or high sex risk, the probability of each STI is drawn based off user input for the prevalence of that STI in the population. These probabilities are only conditional on having low or high sex risk. The probability of being aware of having STI(s) is drawn conditional on age, sex, and race. We assume that if someone is aware of their infection status for any STI in the model, then they are aware of their infection status for *all* STIs in the model, since STI tests often test for all chlamydia, gonorrhea, and syphilis. **We do not model STIs in this analysis.**

Assumptions built into the model for the initial cohort:

1. no one starts on treatment for opioid use disorder (MOUD, addiction counseling, etc)
2. no one starts out with a history of overdose
3. no one starts with a history of infection
4. no one starts in the hospital or linked to outpatient care
5. Being on ART means that you are taking the meds as prescribed
6. Being on PrEP means that you are taking the meds regularly as prescribed
7. Being on DAA means that you are taking the meds as prescribed
8. Risky sexual behaviors will be dependent on how they are defined cohort to cohort
9. No one starts on other STI (chlamydia, gonorrhea, syphilis) treatment

Module 2a. Sequelae of Drug Use.

Once the cohort is initialized and each individual has been assigned an initial drug use status, age, sex, injection frequency and practices (injection profile), HIV status/awareness/treatment/prevention, HCV status/awareness/treatment, and STI status/awareness, individuals enter the sequelae of drug use (SDU) module. Broadly, the SDU in this model includes infective endocarditis (IE), skin and soft tissue infections

(SSTIs), incident HIV, incident HCV, and overdose (OD). When an individual first enters, the model checks their ever/never status. If they are “never,” then they exit the module and return to the simulation. Therefore, only “ever” drug users can progress through this module. The model then checks their injection frequency. If they are “no current,” then they return to the simulation. Therefore, only “low frequency” and “high frequency” injectors will progress through this module. Additionally, if the individual is currently in inpatient care, they will return to the simulation. If a person is currently on antibiotics, they will progress through the SDU module, but they cannot acquire a new infection (SSTI or IE). If a person is HIV infected, regardless of awareness or ART, they cannot acquire HIV again but should progress through the module, as they can acquire other SDU. If a person is HIV uninfected but on PrEP, then they cannot acquire HIV, but can still acquire other SDU. If a person is HCV infected, which includes the time that they are on treatment, then they cannot acquire HCV during the cycle, but can acquire other SDU.

At this point, remaining individuals are subject to probabilities for acquiring an SDU based on their current SDUs (or lack thereof), their injection profile, and whether they are on PrEP. On the first cycle of this model, no one has a history of IE/SSTI/OD but should have the possibility of acquiring one or multiple throughout their life. Individuals do have a possibility of having HIV or HCV at the first cycle. History of SDU is tracked as it has implications for future SDU. One assumption of the model is that in each cycle, an individual can have more than one SDU but only acquires one bacterial infection at a time. Individuals can, however, acquire OD, HIV, and/or HCV concurrently. Additionally, individuals may have concurrent SDU (meaning that they may acquire IE in cycle 1 and then SSTI in cycle 2, if they have not been hospitalized for their existing SDU. Another assumption of the model is that SDUs can only be acquired while not “inpatient” or on antibiotics.

Individuals who are eligible for an SDU, then progress through a number of probabilities of acquiring an SDU. Probabilities of acquiring OD, IE, SSTI, HIV, and HCV are stratified by injection frequency (high and low), and the infectious SDU are also stratified by injection practices (skin cleaning, needle sharing). None of the SDU probabilities are stratified by age, sex, or race.

Since overdose is generally more common than infectious SDUs, the model is structured such that an individual first encounters a combined probability of overdose (fatal + nonfatal), stratified by injection frequency. If an individual has a current bacterial infection, their overdose rate is multiplied by the current infection multiplier. A proportion of overdoses are fatal, and a proportion are nonfatal. If a person draws an overdose, the model checks whether they are within their OEND effective cycles and dependent on that, fatal overdose is drawn. One aspect of the model is that at this point, if a person draws a fatal overdose, then they are flagged as “dead, fatal overdose.” They can continue to proceed through the rest of the modules but cannot acquire any further attributes (e.g., they cannot get another infection, be hospitalized, start MOUDs, change their behaviors). These individuals should, however, accrue the full costs of the cycle (based on background costs, costs of fatal overdose, and costs of any other SDUs that are untreated) and utilities (based on age, sex, and other current health states at the end of the cycle).

For those that have a nonfatal overdose or do not have an overdose, they then face a combined probability of infectious SDU (IE + SSTI), stratified by injection frequency, skin cleaning and needle sharing attributes. A proportion of that probability is IE, and the other is SSTI. The model is structured to account for a history of SDU (treated in hospital, resolved because it was a nonfatal OD) and for existing SDUs. An existing SDU is anything that an individual has during the current cycle. From a clinical perspective, this represents an “untreated” infection (e.g., someone has not gone to the hospital for their endocarditis, or someone is currently on outpatient antibiotics but not cured) or a current nonfatal overdose. Once treatment is complete or the SDU resolves (as is the case with nonfatal overdose which resolves in 1 cycle), then the person is flagged with a history of the corresponding SDU.

Next, the model checks if an individual is not HIV positive and is not on PrEP. If these conditions are met, the individual then faces a probability of HIV infection, stratified by injection frequency, needle sharing, and skin cleaning behavior. If a user chooses to stratify only by injection frequency, for example, they can set the probabilities for each skin cleaning/needle sharing combo to be equal for that injection frequency category. If an individual is on PrEP, it is assumed that their probability of acquiring HIV is 0. If the individual does become HIV infected, their HIV status is set to positive with CD4 count >200. All incident HIV cases start in the CD4 count >200 stage. Later in the simulation, if this person does not get treatment for HIV, they have a chance of progressing to the CD4 count <200 stage – process is detailed in the HIV Progression section at the end of this document.

Finally, the model checks if the individual is HCV negative, then the individual faces a probability of HCV infection, stratified by injection frequency, needle sharing, and skin cleaning behavior. If an individual becomes HCV infected *for the first time*, they start in the early stage (F1-F3) of the disease. If an individual previously had HCV, they start in the stage that they ended in during their previous infection. For example, if someone started with early-stage HCV, then progressed to late-stage HCV prior to receiving treatment and has since received treatment and been cleared of HCV infection, if they draw HCV again, they start with late-stage HCV and cannot progress further. Further details on HCV progression are detailed in the HCV Progression section at the end of this document.

An existing *bacterial* SDU or OD causes a change in the likelihood of another *bacterial* SDU or OD. In the model, there is a single multiplier for one or more existing SDUs that is applied to both the probability of OD and the probability of bacterial SDU. This multiplier exists until the individual is treated for the SDU. For those who have a nonfatal overdose, the existing SDU multiplier will be applied to the probability of infection in the same cycle only since an existing nonfatal OD (that does not link to inpatient), only lasts one cycle.

Additionally, a history of OD/bacterial SDUs changes the probability of future OD/bacterial SDUs. Multipliers are only applied to the SDU for which there is a history (e.g., OD history changes the probability of recurrent OD; any infection history changes the probability of future infection [any infection, not just the one that occurred]). For OD, there are 4 multipliers (e.g., 1 past nonfatal OD, 2-3 past nonfatal OD, 4-7 past nonfatal OD, and 8+ past nonfatal ODs). For history of treated infections, there is only one multiplier (1+ past treated infections).

For instance, in cycle 1, an individual gets IE but does not go to the hospital/receive treatment and does not die in cycle 1. By cycle 2, having IE makes that individual have a greater probability of OD or SSTI. For this model, individuals will not be able to acquire the same SDU in that next cycle. From the previous example, the individual with IE will only be able to acquire OD, SSTI, HIV, and/or HCV, not IE in cycle 2. While that infection remains untreated, there is an effect on getting another bacterial infection/OD. Once that infection is treated, there is a separate effect of this infection on future bacterial infections.

This module has two multipliers: 1) one that can change the probability of an additional SDU if current SDU is untreated, and 2) one that can change the probability of a recurrent SDU (in the future) if the current SDU is fully treated and they survive it. These multipliers *do not* apply to HIV or HCV. At this point, all individuals exit module 2a and progress to module 2b.

Attributes that an individual can acquire in this module and should be tracked:

- Current IE
- Current SSTI
- Current OD, non-fatal
- Current OD, fatal

- Incident HIV
- Incident HCV
- History of treated IE
- History of treated SSTI
- History of treated OD

Module 2b. Sequelae of sexual behavior.

Once individuals leave the SDU module, they progress to the sequelae of sex (SOS) module. At cohort initiation, each individual has been assigned a sexual behavior status (high risk, low risk, no current risk), HIV status, HCV status, and STI status. Broadly, the SOS in this model include HIV, HCV, syphilis, gonorrhea, and chlamydia. When they first enter, the model checks their sexual behavior status. If they are “no current,” then they exit the module and return to the simulation. Therefore, only “low risk” and “high risk” individuals will progress through this module. Additionally, if the individual is currently in inpatient care, they will return to the simulation.

If a person is currently on a treatment for a specific infection (ART, DAA, or antibiotic for specific STI—penicillin for syphilis, ceftriaxone for gonorrhea, azithromycin for chlamydia), they will progress through the SOS module, but they cannot acquire the infection for which they are being treated. At this point, remaining individuals are subject to probabilities for acquiring an SOS based on their sexual behavior.

Unlike the SDU module, each SOS is independent of the history of SOS. For example, having had gonorrhea does not make one more likely to get an SOS in the future. Incident SOS will be tracked. One assumption of the model is that in each cycle, an individual can have more than one SOS at a time and may concurrently acquire any of the infections in this module. Their acquisition, however, will be independent. Another assumption of the model is that SOS can only be acquired while not “inpatient” or on treatment for that specific infection.

All individuals will pass through both the SDU and SOS modules. As noted above, a person with no current drug use will return to the simulation from the SDU module and move through the SOS module next. If they also have no current sexual behavior, then they do not acquire an SOS and they will proceed to the next module (inpatient) a non-IDU/non-sexually active person with no SDU or SOS acquired this cycle. Individuals who are in a current drug use state will move to the SOS module whether they have an SDU or not.

Attributes that an individual can acquire in this module and should be tracked:
- Incident HIV
- Incident HCV
- Incident chlamydia
- Incident gonorrhea
- Incident syphilis

HIV, HCV, and STIs *do not* lead to hospitalization in this model.

Module 3. Inpatient Hospitalization Module.

Each individual with 1+ SDU (excluding HIV or HCV) has a probability per cycle of presenting to an inpatient setting for their care. A multiplier on the probability of presenting to inpatient is applied for those in comprehensive care (more specifically, the probability of presenting is converted to a rate, then multiplier applied, then converted back to a probability). When individuals enter the inpatient module, the model checks their current SDU status. If they do not have a current untreated SDU (IE, SSTI, OD) or died of fatal overdose in the previous module, or they are on outpatient antibiotics for IE or SSTI, then they return to the simulation. Therefore, only those individuals with active IE, SSTI, and/or OD can progress through this module. We assume that individuals cannot be hospitalized because of HIV or HCV but can be tested and/or treated for HIV and HCV while inpatient.

The path through the inpatient module is conditional on the SDU(s) that an individual has: nonfatal OD, IE, SSTI, or combination. The hospitalization duration for overdose is 1 cycle; the hospitalization duration for SSTI and IE are drawn stochastically from a normal distribution with a user defined mean and standard deviation; the model allows for a maximum hospitalization to be set so that at the end of the max amount of time a person will leave the hospital. Each hospitalization is associated with a cost that is accrued in later module.

The key feature of this module is that individuals may encounter a variety of in hospital services. These services are either turned on or off by the user depending on the analysis. If they are on, then individuals will have a probability of being offered and of accepting those services during their hospitalization. Some services only apply to individuals with infections (e.g., ID consultation, outpatient parenteral antibiotic treatment [OPAT]). Other services apply to people with any of the SDUs—infections or overdose—such as MOUDs, skin cleaning, HIV, HCV, or STI testing, and treatment/prevention for HIV, HCV, or STI. Bacterial infections (SSTI and IE) and overdose are sequelae of drug use (and by virtue, of their OUD), thus individuals may receive services and/or treatment for any other OUD-related conditions. Each service has an effect either within this module or elsewhere in the simulation.

Each service is also associated with a cost that is applied in a separate module at the end of the simulation. Individuals should be “marked” as using/receiving an inpatient service such that the cost can be tabulated in the separate module. Additionally, some of the services have an independent effect on quality of life. Similar to cost, this is applied in a separate module at the end of the simulation. Hospitalization is associated with a decreased QoL so there is a hospitalization QoL weight that can be applied in a separate module at the end of the simulation.

Hospital-based service	**SDU/SOS for which service applies (eligibility)**	**Effect in the model**	**Independent cost**	**Independent QoL**
Addiction consult service	OD, SSTI, IE, combination	Change (increase) probability of linkage to outpatient addiction care*	Yes, this recurs on a weekly basis while inpatient	No
Initiation/continuation of MOUD (e.g., buprenorphine)	OD, SSTI, IE, combination	change probability of linkage to outpatient MOUD. Change probability of transitioning between injection frequency states. See treatment effect description below.	See treatment effect. Yes, recurs on a weekly basis while inpatient	Yes

Overdose education, naloxone distribution (OEND)*	OD, SSTI, IE, combination	Decrease proportion of fatal overdose for X subsequent cycles	Yes, one time per hospitalization episode	No
Skin cleaning education*	OD, SSTI, IE, combination	Decrease probability of unclean injection for X subsequent cycles after end of hospitalization	Yes, one time per hospitalization episode	No
Clean needle distribution*	OD, SSTI, IE, combination	Decrease probability of reuse needles for X subsequent cycles after end of hospitalization	Yes, one time per hospitalization episode	No
ID consult	SSTI and/or IE	Decrease in-hospital mortality from IE or SSTI during active infection; Allows to access (if available, with offer/accept) OPAT	Yes, this recurs on a weekly basis while inpatient	No
OPAT**	SSTI and/or IE	Decrease hospital length of stay	Yes, one time per hospitalization episode	No
HIV testing	Any without previous diagnosis of HIV positive and knowledge thereof, and eligible for a test based on weeks since last test	Eligible to initiate ART if positive or PrEP if negative	Yes, one time per hospitalization episode	No
ART initiation/continuation	HIV infected and known	Decreases mortality risk from HIV, changes probability of outpatient unlinkage from ART	Yes, one time per hospitalization episode	Yes
PrEP initiation/continuation	HIV uninfected and known	Decreases risk of HIV, changes probability of outpatient unlinkage from PrEP	Yes, one time per hospitalization episode	Yes
HCV testing	Any, without current known diagnosis of HCV, and eligible for a test based on weeks since last test	Eligible to initiate DAA	Yes, one time per hospitalization episode	No
DAA initiation/continuation	HCV infected and known	Decreases mortality risk from HCV, changes probability of outpatient unlinkage from DAA	Yes, one time per hospitalization episode	Yes
STI testing	Any, without current known diagnosis of any STI, and eligible for a test	Eligible to initiate antibiotics for any/all STIs	Yes, one time per hospitalization episode	No

	based on weeks since last test			
Syphilis treatment	Syphilis infected and known	Changes syphilis cost from untreated to on treatment, increases QoL	Yes, one time per hospitalization episode	Yes
GC treatment	GC infected and known	Changes gonorrhea cost from untreated to on treatment, increases QoL	Yes, one time per hospitalization episode	Yes
Chlamydia treatment	Chlamydia infected and known	Changes chlamydia cost from untreated to on treatment, increases QoL	Yes, one time per hospitalization episode	Yes

*These interventions are applied only in the last cycle of hospitalization and they will have post-treatment effective cycles drawn from a normal distribution.
**OPAT: If person has an infection and have received ID consult service and there are more than 1 cycles

MOUD continuation: instead of clearing all outpatient flags upon entering inpatient, code will first check if a person is currently in outpatient MOUD and inpatient MOUD service is available. If so, person will get automatically linked to inpatient MOUD without further draw and keeps his/her outpatient MOUD flag ON, so upon exiting inpatient he/she will go back to MOUD outpatient (without draw). However, since person is considered as inpatient, cost and mortality of inpatient are applied (no outpatient MOUD cost). The inpatient cycles are not counted toward accumulated outpatient MOUD cycles in output but they are considered by behavior transition module when deciding MOUD effect on injection frequency transition.

ART continuation: instead of clearing all outpatient flags upon entering inpatient, code checks if a person is currently on ART. Since standard of care is to continue ART in the hospital, patients who are on ART will remain on it without further draw and keeps their outpatient ART flag ON. This means that upon exiting inpatient he/she will go back to ART outpatient without a draw. However, since a person is considered as inpatient, cost and mortality of inpatient are applied (no outpatient ART cost) while they are hospitalized.

PrEP continuation: instead of clearing all outpatient flags upon entering inpatient, code checks if a person is currently on PrEP. Since standard of care is to continue PrEP in the hospital, patients who are on it will remain on it without further draw and keeps their outpatient PrEP flag ON. This means that upon exiting inpatient he/she will go back to outpatient care without a draw. However, since a person is considered as inpatient, cost and mortality of inpatient are applied (no outpatient PrEP cost) while they are hospitalized.

DAA continuation: instead of clearing all outpatient flags upon entering inpatient, code checks if a person is currently on DAA. Since standard of care is to continue DAA in the hospital, patients who are on it will remain on it without further draw and keeps their outpatient DAA flag ON. This means that upon exiting inpatient he/she will go back to outpatient DAA care without a draw. However, since a person is considered as inpatient, cost and mortality of inpatient are applied (no outpatient DAA cost) while they are hospitalized.

HIV/HCV/STI test: To represent real-life testing strategies, the model allows for user input for the number of cycles/weeks that must pass since a previous test to be eligible for the next test. These cycles are tracked separately for each of the three tests: HIV, HCV, and STI. An individual can also only receive a test if they are “unknown” for that infection. An individual remains known after receiving a test until they participate in behavior that has the potential to change their status (whether or not it actually does), ie. any injection or sex.

ART/PrEP/DAA initiation: if a person receives an HIV test or HCV while inpatient, then their status is assumed to be "known." Standard of care is to initiate ART at the time of diagnosis. This does not happen in reality for a variety of reasons. If a person tests positive for HIV while inpatient, they will receive a probability of initiating ART. This is not a one-time offer and should be applied on a weekly basis while inpatient. The same is the case for PrEP and HCV. If a person tests negative for HIV but is currently at risk for HIV (they carry a current drug use flag or a current high risk sex flag), then they have a probability of initiating PrEP on a weekly basis while inpatient. If a person tests positive for HCV, then they have a probability of initiating DAA on a weekly basis while inpatient.

Syphilis/gonorrhea/chlamydia treatment: Both gonorrhea and chlamydia treatments can occur (in real life) during one cycle. Syphilis is a bit more complicated and can require up to 3 weeks of treatment. For this model, we assume that syphilis treatment is also a single cycle occurrence as the majority of injections can be treated on a single cycle. If a person receives a test and is diagnosed with any of these STIs while inpatient, then they will receive treatment for said STI. While this should be coded as a probability of receiving the appropriate treatment, the default input is 1.0. If a person has been diagnosed with these STIs prior to inpatient and their status is known but has not received treatment for it, then they will receive treatment while inpatient. If a person is diagnosed with but is unaware of their status, then they must receive testing again inpatient in order to receive treatment.

In order to "leave against medical advice", ID consult and OPAT have to be on, and OPAT linkage probability has to be less than 1. In order to allow people to "leave against medical advice" with OPAT turned off, the above needs to be true, ID consult should be set to 1 (mortality benefit set to 1), OPAT linkage should be set to 0, and OPAT and ID consult costs should be set to 0.

Each individual has a probability of in-hospital mortality that is discussed in detail in the mortality module section. It is mentioned here to note that it is an attribute that an individual can acquire.

During hospitalization, individuals "carry" a flag/marker that designates them as hospitalized. While hospitalized, individuals cannot get a new SDU so they will not enter SDU module. They have an "in hospital" mortality that is conditional on the SDU for which they are hospitalized. For the duration of their hospitalization, their injection frequency is considered to be "no current" regardless of their actual status and they are not exposed to behavior transitions. The exception to this rule is as follows: In the last hospitalization cycle, individuals are exposed to behavior transitions based on their pre-hospitalization status. If they have received any intervention that would affect their behaviors (MOUD, skin cleaning education or clean needle distribution), the intervention effect will be applied to their actual or pre-hospitalization behaviors and post-treatment effective cycles will be drawn. These behavioral changes are assigned in the last inpatient cycle so that they take effect the first cycle out of inpatient. However, cost-life-mortality module still consider them as "no current".

When the inpatient hospitalization time has lapsed, then individuals move to the outpatient module. In the outpatient module, they have a probability of then linking to different types of care.

Module 4. Outpatient Care Module.

Much like the inpatient module, the outpatient module will have a variety of services that can be turned on or off. In the C-THR model of care, for example, all of the aforementioned services will be available. Within this module then, people have the probability of receiving "care" without falling out of care completely. Or they can fall out of care completely and unlink from the program. Staying with this same trial, the control group will enter

and have no onsite services turned on in the outpatient module and will have to receive services via referral (for the most part), which is considered the standard of care.

All individuals enter the outpatient module, and their probabilities of receiving services depend on whether they are in comprehensive care, their SDU/SOS state(s), treatments they're receiving, and other events that happened earlier in the cycle. Individuals can receive services (ie. link to an outpatient care service) via background linkage, meaning that those who are not hospitalized or currently receiving a service can "decide" to seek care in this module. An individual can also be linked to outpatient services based on services they received inpatient – some services they are guaranteed to link to in the same cycle (eg. MOUD), others they have generally increased probability of linking to.

At cohort initiation, all individuals have a probability of being in comprehensive care (the intervention). This will dictate their initial probability of linking to services (and subsequent probabilities as long as they stay in the comprehensive care group). So in a trial where everyone is in comprehensive care, this probability will be "1". In real life, this is likely to be a number between 0 and 1. In the case of testing a trial such as C-THR, all individuals will be assigned a "1" at cohort initiation.

For individuals entering from the simulation (background). Each individual encounters the outpatient module. Individuals with a "death" flag from a previous module (fatal overdose) enter the outpatient module and immediately return to the simulation. Individuals who are currently hospitalized immediately return to the simulation. All other "ever" drug user individuals and/or individuals with sex risk have a probability of progressing through the module and linking to outpatient care services, regardless of history of SDU, SOS, sexual risk status, or drug use status.

For individuals entering from the inpatient module (inpatient linkage). When the inpatient hospitalization time has lapsed, then individuals link to outpatient services with an inpatient multiplier applied, depending on which inpatient services they received. This follows from the assumption that if someone received a service in the hospital, they have a modified probability of receiving the service once they leave.
The outpatient module will be structured much like the inpatient module in which a variety of services can either be turned on or off. When individuals enter the outpatient module, the model checks their current inpatient status. If they have a current IE/SSTI/OD for which they are hospitalized, or died of fatal overdose in the previous module, then they return to the simulation. Therefore, only those individuals who are not hospitalized and not dead can progress through this module.

The path through the outpatient module is conditional on which SDUs or SOSs a person has, whether they are known or unknown, and if a service is available in comprehensive care or not. Each service that is encountered is associated with a cost that is accrued in a later module. The key feature of this module is that individuals may encounter a variety of outpatient services that may be offered in comprehensive care (as part of a package) or only available via referral. These services are either turned on or off by the user depending on the analysis. If they are on, then individuals will have a probability of being offered and of accepting those services during their outpatient encounter. Some services only apply to individuals with infections (e.g., outpatient parenteral antibiotic treatment [OPAT]). Other services apply to people with any of the SDUs—IE, SSTI, HIV, HCV, or overdose—such as MOUDs. Other services can apply to anyone with "ever" drug use or any sex risk, such as needle exchange, condom distribution, HIV, STI, or HCV testing.

First, the model checks if an individual is in the comprehensive care group. If they are, then the probability of receiving a service is set to the comprehensive care probability, which is determined by the user in a configuration file. An individual in comprehensive care is not required to receive a service if it is available in comprehensive care, but rather, they have a different probability of encountering that service than outside of

comprehensive care. If an individual does not receive a service within comprehensive care, they still have a probability of encountering that service *outside* of comprehensive care, if that service is turned on. The probability of receiving that service is then set to the non-comprehensive care (or background, for short) probability.

Individuals not in the comprehensive care group only ever encounter the non-comprehensive care (ie. background) probability of receiving that service.

Each service has an effect either within this module or elsewhere in the simulation. Each service is associated with a cost that is applied in a separate module at the end of the simulation. Individuals should be "marked" as using/receiving a service such that the cost can be tabulated in the separate module. Additionally, some of the services have an independent effect on quality of life. Similar to cost, this is applied in a separate module at the end of the simulation.

Outpatient antibiotics. Outpatient antibiotics should be the difference between the pre-specified total duration and the duration they received in the hospital. Once the duration of antibiotics is completed, individuals with infections will be considered "cured/treated," they should unlink from outpatient antibiotics and this service will not be available to them on subsequent cycles unless they get a new infection, enter hospital and get another OPAT. This service should have a duration associated with it. There should be a probability that individuals unlink spontaneously from outpatient antibiotics (i.e., do not finish their full duration of antibiotics). For any cycle in which an individual is maintained on antibiotics, they cannot acquire a new infection. They can, however, acquire a new infection starting in the cycle following the completion of the antibiotics.

MOUD: In the previous version of the model, instead of having individual outpatient services, there was a broad "addiction care" service. Now, this has been replaced by individual services, which are listed in the table below. This model still has outpatient MOUD but is no longer dependent on someone linking to "addiction care" first – it is assumed that if someone links to MOUD, that they had first linked to addiction care, which is incorporated into a conditional probability. Probabilities of linking to MOUD as follows:

1. Linking from inpatient addiction care: if someone receives inpatient addiction care services, then they receive this probability of linking to outpatient MOUD
2. Linking from inpatient MOUD: if someone receives MOUD in the hospital, then they get this probability of receiving outpatient MOUD
3. Linking from inpatient (no intervention) or background: if someone either does not receive any addiction care or MOUD in the hospital, or does not go to the hospital, they receive this probability of getting MOUD. This allows for individuals to "choose" to pursue treatment without requiring hospitalization

To reduce input numbers required from the user, a multiplier for MOUD is calculated using the background probabilities (which are converted to rates). This is used to modify the probability of linking to MOUD from inpatient with addiction care or MOUD, such that those in comprehensive care may have different probabilities of linking to MOUD from the hospital compared to those not in comprehensive care.

HIV/HCV/STI test: To represent real-life testing strategies, the model allows for user input for the number of cycles/weeks that must pass since a previous test to be eligible for the next test. These cycles are tracked separately for each of the three tests: HIV, HCV, and STI. An individual can also only receive a test if they are "unknown" for that infection. An individual remains known after receiving a test until they participate in behavior that has the potential to change their status (whether or not it actually does), ie. any injection or sex.

The remaining outpatient services are more straightforward – if a service is turned "on", a probability is drawn (which depends on if the person is in comprehensive care or not, as described above), and then the person is flagged as having gotten that service or not. The table below details the services in the model.

Outpatient service	**Eligibility**	**Effect in the model, while linked**	**Independent cost**	**Independent QoL**
Outpatient antibiotics (IV or oral)	Active SSTI, active IE, OPAT available inpatient, OPAT accepted and linked	Prevent new infection while on antibiotics. No infection related cost, utility and mortality	Yes	No
Outpatient MOUD	Any ever IDU in the simulation not actively hospitalized	change (decrease) needle sharing, change (increase) probability of moving to lower frequency state and change (decrease) probability of moving out of no/low frequency state. See treatment effect document.	Yes	Yes
Skin cleaning intervention	Any current IDU in the simulation not actively hospitalized	Change (decrease) probability of unclean injection for number of cycles drawn from user input distribution	Yes	No
Clean needle distribution	Any current IDU in the simulation not actively hospitalized	Change (decrease) needle sharing for number of cycles drawn from user input distribution	Yes	No
HIV testing	Any without previous diagnosis of HIV and knowledge thereof	Eligible to initiate ART or PrEP if negative, HIV aware flag turned on	Yes, if received	No
ART initiation/continuation	HIV infected and known	Decreases mortality risk from HIV, ART flag turned on	Yes	Yes
PrEP initiation/continuation	HIV uninfected and known	Decreases risk of HIV, PrEP flag turned on	Yes	Yes
HCV testing	Any without current known diagnosis of HCV	Eligible to initiate DAA if tested positive, HCV aware flag turned on	Yes	No
DAA initiation/continuation	HCV infected and known	Decreases mortality risk from HCV, DAA flag turned on, DAA cycles (until treated) calculated	Yes	Yes
STI testing	Any, without current known diagnosis of syphilis	Eligible to initiate STI treatment for any STIs that tested positive, STI aware flag turned on	Yes	No
Syphilis treatment	Syphilis infected and known	Changes flag from untreated to treated, syphilis antibiotics flag turned on	Yes	Yes

GC treatment	GC infected and known	Changes flag from untreated to treated	Yes	Yes
Chlamydia treatment	Chlamydia infected and known	Changes flad from untreated to treated	Yes	Yes
Safer sex counseling and/or condom distribution	No restrictions	Changes probability of movement from high-risk sexual behavior to low risk or no current risk	Yes	No

Module 5: Behavioral Transitions Module.

Following the inpatient and outpatient modules, individuals will move to the behavioral transitions module. Individuals may also enter this module "from the simulation." This latter represents the ability of someone to change their behaviors organically (without prescribed interventions). This is the module in which they can move between high frequency, low frequency, and no current injection drug use states, move from never and ever IDU, move between skin cleaning and not skin cleaning states, move between sharing needles and not sharing needles states, move between high risk, low risk, and no current risk sexual behavior, and move between using or not using condoms. There will be a prior probability of movement between states (status quo) and various "flags" acquired throughout the model progression that will impact certain probabilities. These have been outlined in various other module descriptions but will also be outlined below.

Treatment Effects: The primary driver of morbidity and mortality in the module is the injection frequency. High frequency individuals are at higher risk than low frequency injectors of sequelae of drug use (SDUs), which include overdose, skin/soft tissue infections, endocarditis, HIV, and Hepatitis C in this model. All persons who are "ever" injectors have the possibility of moving to a higher or lower injection frequency state (depending on their current state) or staying in their current state per cycle. For instance, a high frequency injector may remain as a high frequency injector or may move to low frequency or no current use states. There are a few ways that the injection frequency can be modified in the model. In brief, however, only hospitalization and MOUDs can change injection frequency in the model.

Mechanisms by which transitions between injection frequency states are changed:

1. **Hospitalization.** If an individual becomes hospitalized for an SDU, then cost, life, and mortality modules will consider their injection state as "no current use" and behavior module returns them to simulation (without any changes) during their hospitalization cycles. The only exception is the last hospitalization cycles in which behavior module considers them as their pre-hospitalization behavior states and updates their behaviors based on inpatient services received (if none, then no intervention values are used).
2. **Outpatient MOUD initiation.** Individuals have the possibility of initiating MOUDs in the model by linking to outpatient MOUD care (linkage to outpatient care comes either via "background linkage" or linkage following hospitalization). When an individual initiates MOUDs in the outpatient setting, there is an immediate treatment effect which lasts for 4 cycles (4 weeks). During those 4 cycles, there is a high probability of moving to no active use state and a low probability of moving to or back to a higher drug use state (relapsing). After the treatment initiation effect but while still on MOUDs, they encounter a probability of remaining in the no current drug use state or moving to a lower drug use state that is different than the "no MOUD" status (since the longer a person remains on treatment, the more likely they are not to relapse) and "immediate treatment effect".

3. **Inpatient MOUD initiation.** In some scenarios, individuals have the opportunity to initiate MOUDs during their hospitalization for SDU (i.e., when certain inpatient services are available). When an individual initiates MOUDs in the inpatient module and then links to outpatient care, the individual automatically links to MOUDs in outpatient (ie if a person links from inpatient with MOUD to outpatient, they cannot link to outpatient without MOUD as this doesn't make sense). If an individual unlinks from inpatient care and does not link to outpatient care, they discontinue MOUD.
4. **Behavioral transitions with MOUD**. When an individual links to MOUD, whether inpatient or outpatient, there is a treatment effect which changes the probability of moving to different drug use states (higher probability of staying off drugs or moving to a lower drug use state, lower probability of moving to a higher drug use state). Eventually, the model should be able to differentiate between the 4 week "initiation effect", and the post-4 week "maintenance effect", which have different relapse rates. In the model, it is possible for people who are known HIV positive or on PrEP to have different rates of behavior transitions than those who are not. These behavior transitions are thus stratified into three tables with identical structure: background, HIV positive aware, and on PrEP. This is to account for potential differences in behavior that may result from one knowing they're HIV positive or from being on PrEP.

Mechanisms by which skin cleaning is modified:
Proper skin cleaning can be modified in the model via two mechanisms. However, both of these influence the transition probabilities. Again, these probabilities are stratified into three categories: known HIV positive, on PrEP, or neither.

1. **Outpatient skin cleaning intervention.** Risk reduction is a component of addiction care, this includes skin cleaning education. This increases the probability of moving to skin cleaning status. The effect is applied for a set duration of time after the outpatient intervention. Durations are drawn from a normal distribution and have a maximum value, the parameters of which are determined by the user..
2. **Inpatient skin cleaning intervention.** Simply put, if a skin cleaning intervention is available and an individual receives the intervention, then this increases their probability of being a "skin cleaner". This probability is applied in the last hospitalization cycle and until post-treatment effective cycles, which are drawn from a normal distribution are in effect.

Mechanisms by which cleaning needles/not reusing is modified:
Proper needle sharing can be modified in the model via two mechanisms. However, both of these influence the transition probabilities. Again, these probabilities are stratified into three categories: known HIV positive, on PrEP, or neither.

1. **Outpatient needle distribution.** Risk reduction is a component of addiction care, this can include needle distribution. This increases the probability of moving to non needle sharing status. The effect is applied for a set duration of time after the person receives the outpatient intervention. Durations are drawn from a normal distribution and have a maximum value, these parameters are determined by the user.
2. **Inpatient clean needle distribution.** Simply put, if a needle distribution is available and an individual receives the intervention, then this increases their probability of being a "non-sharer". This probability is applied in the last hospitalization cycle and until post-treatment effective cycles(which are drawn from a normal distribution) are in effect.

Mechanisms by sex behavior risk is modified:

Similar to injection frequency, sex risk can be modified either by the following. Again, these probabilities are stratified by known HIV positive, on PrEP, or neither:

a. Being inpatient: when in the hospital, the individual is assumed to have “no current” sex risk, and once they exit inpatient, they return to their pre-inpatient sex risk state.
b. Background transitions: these represent changes in people’s behavior without any intervention
c. Transitions with intervention: the intervention can be either sex education or condom distribution – the definition should be decided before entering any probabilities. The intervention allows for different transition probabilities between those receiving the intervention and those that are not. If there is no intervention in the model scenario, the intervention and non-intervention probabilities can be set to be equal.

Module 6: Mortality Module.

The mortality module is more than mortality. It includes costs and quality of life adjustments as well.

Mortality

There are two places in the model that an individual can die: fatal overdoses in the SDU module and in the mortality module. To review, in the SDU module, an individual draws a combined probability of all types of overdose which is stratified by injection frequency (high and low frequency). From that combined probability, an individual can draw either a fatal or non-fatal overdose. If an individual draws a fatal overdose, then go through the remainder of the cycle with a “fatal OD” flag up which does not allow them to get any further interventions, collect additional costs, change their behavior status, etc., however, they will accumulate the background cost and utility of that cycle. As such, the background mortality in the mortality module should exclude overdose mortality.

The background mortality risk will be an age, sex, and race adjusted mortality probability (excluding fatal overdose). This will be derived from the NVSS database, with overdose removed from this data. Any person aged 100 years will automatically be set to “dead”. There are a number of occurrences in the model that can impact the weekly risk of mortality, thereby modifying this background mortality per individual on a weekly basis.

First, individuals who are hospitalized for an SDU (non-fatal overdose, SSTI, or endocarditis) have an increased risk of death. If the inpatient individual further gets an ID consult, their infection inpatient mortality rate is augmented by an ID consult mortality multiplier (ID consult will not affect overdose mortality).

Second, individuals who have an untreated skin and soft tissue infection or untreated infective endocarditis will have an increased risk of death. These risks are input as probabilities (and converted to rates by the model) which are then ***added*** to the background mortality at the end of each cycle. Additionally, individuals who have untreated HIV or untreated HCV can also have an increased risk of death. If these conditions are treated, a treated HIV/HCV probability may be used instead. Both HIV and HCV can have two stages in the model, and probability of death is further stratified by disease stage. For HIV, the stages are defined as the individual having a CD4 count of >200 or <200. Those with a CD4 count of <200 have a higher risk of death than those with CD4 count >200. For HCV, the stages are defined as early-stage (stage F1-F3) and late-stage (stage F4). Those with late-stage HCV have a higher risk of death than those in the early stages.

Once a patient is cured of their infection (SSTI, IE, HCV), their SDU flags are removed and their mortality goes back to background mortality. The mortality risk only applies for each cycle that they have that risk. For example, a person gets endocarditis and does not present to inpatient care during a cycle. Then they have an

“existing endocarditis” flag that the end of the cycle should prompt the rate of death for untreated endocarditis to be added to the background mortality. On cycles 2-5 that same individual, however, is hospitalized and being treated for their endocarditis. For those cycles, the “untreated” SDU flag drops off but they get an “in-hospital for endocarditis” flag such that the in-hospital endocarditis mortality rate is added to their background mortality each cycle. On cycle 6, this person leaves the inpatient setting (completes treatment) so all flags are, therefore, off and at the end of that cycle they get only background mortality.

Individuals on outpatient antibiotics are not considered as being in inpatient or having an untreated infection, therefore, they do not have additional mortality due to infection. However, if someone has HIV or HCV, even if treated, they have additional mortality risk due to HIV and/or HCV.

For this version of the model, we do not include an additional mortality risk for being an active drug user since most of that risk will be folded into overdose and other SDUs. We assume that STIs (ie. chlamydia, gonorrhea, and syphilis) *do not* affect mortality in this model.

Cause of death as an output: In the model, individuals can die of background causes or as a direct result of their injection drug use. Direct causes of injection drug use include:

- Overdose (combination of fatal overdose/ hospitalized and nonfatal OD that dies in the hospital)
- endocarditis (combination of hospitalized and non-hospitalized)
- SSTI (combination of hospitalized and non-hospitalized)
- HIV (early and late stages)
- HCV (early and late stages)

Aside from fatal overdose, all of the other causes of death get added to the background mortality as outlined above. For instance, an individual’s weekly probability of death (conditional on not dying of a fatal overdose) may be p_d and they may have endocarditis which increases their risk of death by *x.* The individual’s weekly risk of death is, therefore, *the sum of the rates converted to a probability.* However, as an output, we need to be able to determine the attributable cause of death (this person may have died of endocarditis OR background causes). To do this, we use the sum of the rates as the denominator and the individual mortality risk (rates) as the numerator in drawing the cause of death. Important for consistency, the input parameters are probabilities and therefore all rates are calculated in the model. For instance, background mortality rate is x (prob = p_x), untreated endocarditis is y (prob = p_y), and untreated SSTI is z (prob = p_z). Total rate = x + y + z. This is converted to a probability of death, p_c. If death = yes, then to determine the cause, the model draws from the following probabilities: probability that death was from background = r_x/r_c; probability that death was from endocarditis = r_y/r_c; probability that death was from SSTI = r_z/r_c, and so on for HIV and HCV. To reiterate - cause of death should be calculated based on rate ratios. The same methodology would hold true if there were two concurrent SDUs. As outputs, we only want to output background deaths, endocarditis deaths, SSTI deaths, and overdose deaths, and do not need to stratify by inpatient vs outpatient.

We also make the following assumptions:

- Individuals who die at 100yo, are considered to have background cause.
- Background mortalities are the same for ever and never IDUs.