

Ongoing FDA Work Related to Opioid Overdose Prevention

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Recent and Ongoing Activities Related to Naloxone

- Co-prescribing of Naloxone with RX Opioids
 - Results of recent public FDA Advisory Committee
- Over-the-Counter (OTC) Naloxone
 - Research to support labeling for OTC naloxone products to support product development
- Role of expanded naloxone availability in USG response to opioid crisis
 - Systems model of opioid crisis

The Opioid Crisis: FDA's Priorities & Strategies

1. Decreasing Exposure & Prevent New Addiction



Appropriate Dose/Duration Labeling



Appropriate Packaging, Storage, and Disposal



Health Care Provider Education

2. Supporting the Treatment of Those With Opioid Use Disorder



Naloxone



Medication Assisted Treatment (MAT)

3. Fostering the Development of Novel Pain Treatment Therapies



Partnerships & Meetings



Abuse Deterrent Formulations (ADFs)



Pain Treatment Alternatives

4. Improving Enforcement & Assessing Benefit-Risk



Improving Enforcement



Assessing Benefit-Risk

I. Naloxone Co-Prescribing with Rx Opioids



- Naloxone prescriptions rising (336.1K dispensed in 2017) but still inadequate
- FDA received Citizen Petition from maker of one of the naloxone products requesting FDA require co-prescribing of patients prescribed opioids
- FDA Advisory Committee held December 17-18 to get input from advisors and public

Annual Cost of Requiring Co-Prescribing: FDA Model

All Opioid Analgesic Rx Scenario



48.5 million new doses per year (4,689% increase)



With Generics: \$52.63/dose → \$1,287.87/dose
Without Generics: \$478.41/dose → \$11,707.95/dose



\$579.2 billion/year (Without Generics)
\$63.9 billion/year (With Generics)

Naloxone Advisory Committee (cont)



- In general:
 - Harm reduction advocacy groups very strong in their view that co-prescribing was not ‘enough’
 - Committee members not supportive of value of required co-prescribing
 - Concerns expressed about cost to healthcare system and diversion of resources (both money and naloxone) away from underserved areas
 - Focus should be on educating prescribers/patients and supporting harm reduction efforts
- In addition, Committee members called on USG to take on broader actions to ‘force’ expanded availability of naloxone. Examples:
 - Forced OTC switch
 - Revoking patents currently delaying generic/OTC product marketing
 - Manufacturing naloxone and making it available from USG stockpile(s)
 - Extending expiration dating for naloxone products

- FDA meeting internally on AC recommendations
 - Plan response to Citizen Petition
 - Discuss ideas raised by Committee members
 - Review AC Docket comments (>220 comments received so far)
 - Engage external stakeholders
 - Propose next steps to leadership

II. Over-The-Counter Naloxone: Why OTC Naloxone?

- Existing expanded access programs (such as pharmacy standing order programs) are a significant tool, but more is needed – not everyone can/wants to obtain the product through a healthcare professional
- Surgeon General's 2018 Advisory

U.S. Surgeon General Advisory



“I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, **knowing how to use naloxone and keeping it within reach can save a life.**”

Development Programs for Nonprescription Drugs

- Often rely on safety and efficacy established for the prescription product
- New studies may be required if proposing a new indication or a new patient population for the OTC market
- Need to “translate” key elements of the prescription label into consumer-friendly terms
- Consumer studies needed to evaluate the “OTC-ness” of product

Drug Facts Label

Drug Facts	
Active ingredient (in each tablet)	Purpose
Chlorpheniramine maleate 2 mg.....	Antihistamine
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat	
Warnings	
Ask a doctor before use if you have	
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis	
■ trouble urinating due to an enlarged prostate gland	
Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives	
When using this product	
■ drowsiness may occur ■ avoid alcoholic drinks	
■ alcohol, sedatives, and tranquilizers may increase drowsiness	
■ be careful when driving a motor vehicle or operating machinery	
■ excitability may occur, especially in children	
If pregnant or breast-feeding, ask a health professional before use.	
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.	
Directions	
adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)
Other information ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture
Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Label Comprehension Study

- Understanding the key label messages

Self-Selection Study

- Choosing the right product for “me”

Actual Use Study

- Using according to labeled directions

Human Factors Study

- Interacting with the product

FDA Proposed an Innovative Approach to Support OTC Naloxone Products:

- To develop a model Drug Facts Label (DFL) that could be understood by all potential consumers who might use OTC naloxone
- To iteratively refine the DFL and evaluate consumer comprehension through a contract with established consumer research firms with expertise in conducting label comprehension studies and interviewing substance abuse populations
- To conduct an independent review of the resulting data

FDA Proposed an Innovative Approach (cont'd):

- If study was successful, Sponsors could adapt the model DFL to their naloxone product
- Sponsors would only need to add information specific to their particular device and assess through human factors
- Label comprehension was the key study to be conducted – self-selection and actual use are likely not needed

Status of Research



- FDA-supported study completed December 2018
- Review by FDA scientists complete January 2019
 - FDA concluded that the results of this study are acceptable to support use of the tested naloxone DFL in the OTC setting
 - FDA in the process of making these results and findings public for use by manufacturers seeking to develop OTC naloxone products
 - FRN in clearance
 - Planned public announcement of results and article being written

Drug Facts	
Active ingredient (in each XX) Naloxone hydrochloride X mg	Purpose Emergency treatment of opioid overdose
Uses	
<ul style="list-style-type: none"> To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin This medicine can save a life 	
Directions	
 <p>1) CHECK</p>	<p>Step 1: CHECK:</p> <ul style="list-style-type: none"> CHECK for a <u>suspected overdose</u>: the person will not wake up or is very sleepy or not breathing well <ul style="list-style-type: none"> yell "Wake up!" shake the person gently if the person is not awake, go to Step 2
 <p>2) GIVE</p>	<p>Step 2: GIVE 1st dose</p> <ul style="list-style-type: none"> GIVE the 1st dose of this medicine place the injector on the LEG above the knee and press down
 <p>3) CALL</p>	<p>Step 3: CALL</p> <ul style="list-style-type: none"> CALL 911 immediately after giving the 1st dose
 <p>4) WATCH/GIVE 2-3 minutes</p>	<p>Step 4: WATCH & GIVE</p> <ul style="list-style-type: none"> WAIT 2-3 minutes after the 1st dose to give the medicine time to work if the person <u>wakes up</u>: Go to Step 5 if the person does <u>not wake up</u>: <ul style="list-style-type: none"> CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up It is safe to keep giving doses
 <p>5) STAY</p>	<p>Step 5: STAY</p> <ul style="list-style-type: none"> STAY until ambulance arrives: even if the person wakes up GIVE another dose if the person becomes very sleepy again You may need to give all the doses in the pack
Warnings	
When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.	
Other information • store at room temperature • [advise insert tamper evident statement here]	
Inactive Ingredients	
Questions? (phone number, website)	

Prototype Drug Facts Box for OTC Naloxone

III. Systems Model of Opioids Crisis Including Role of Naloxone

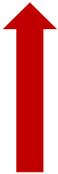
- Deliverable for the BHCC
- Successful model will help identify high-impact actions and anticipate consequences of policy changes
- Experts from across HHS providing input

OVERVIEW: WHY MODELING

Events



Patterns of behavior



Structure of the system

Every day, more than 115 people in the United States die after overdosing on opioids...

The total number of overdose death has been on the rise.

System architecture

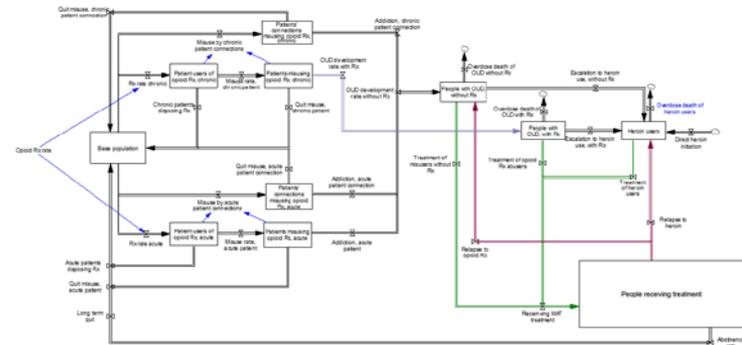
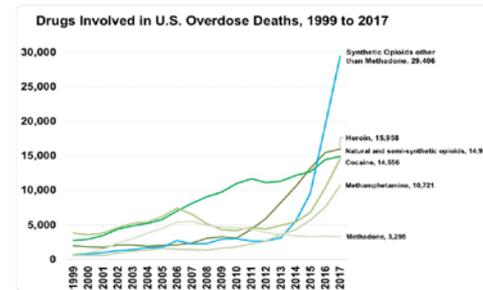
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- Stocks and flows
- Time delays

Information availability

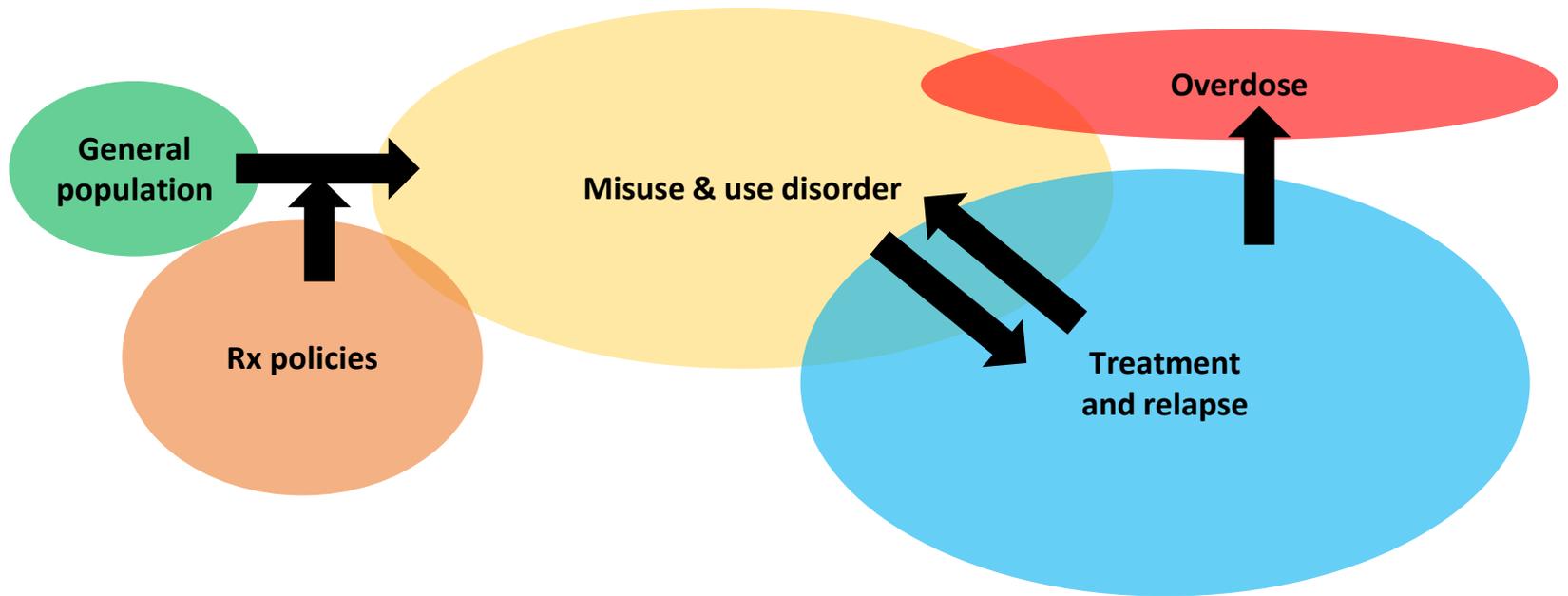
- Delays, biases, error, gaps
- Access & transparency

Mental models (of any stakeholder)

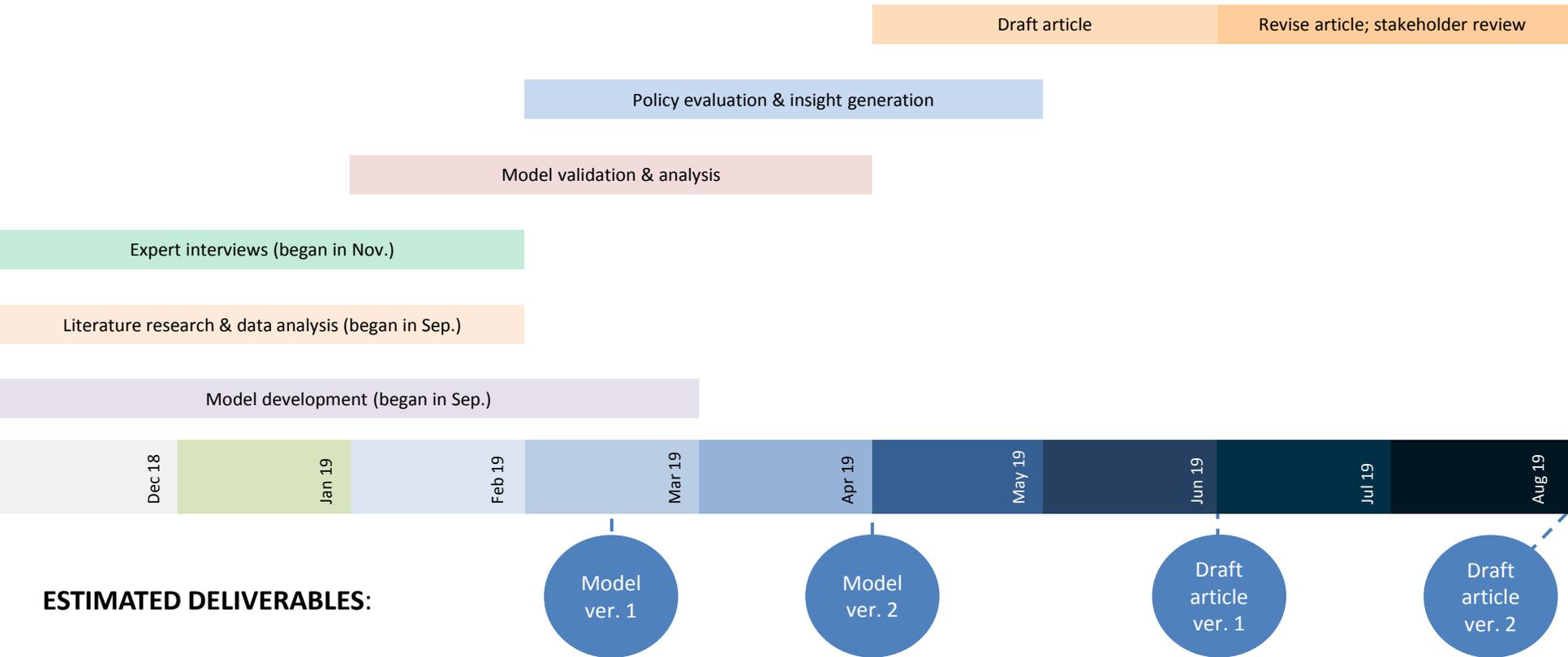
- Actor goals and incentives
- Time horizon, model boundary
- Misperceptions of feedback



Elements of Opioid Use/Misuse/Abuse Model (Simplified)



PROJECT TIMELINE



ESTIMATED DELIVERABLES:

Thank You



Backup Slides

FDA Estimates Differ from the Manufacturers Based on Several Key Assumptions

Key Assumption	FDA Model	Industry Model
Targeted Patient Population(s)	0.3-58.0 million	34.0 million
Compliance Rate	100% Prescribing; 70% Fill	8-10% Dispensed
Price Increase	Yes (up to 2,347%)	No
Prescription Fill Costs	Yes (\$3.94/dose)	No

FDA Estimate for Industry Population With 70% Adoption:

\$24.7 Billion/Year - \$224.0 Billion/Year

FDA Estimate for Industry Population With 8% Adoption:

\$0.5 Billion/Year - \$4.7 Billion/Year

(Industry: \$150 Million/Year)

Total **Annual Costs– Naloxone Co-prescribing** for All Opioid Analgesic Rx Estimated At **\$63.9 Billion - \$579.2 Billion**

New Doses (With Generics):

$$48.5 \text{ Million} \times (\$1,287.87 + \$3.94^{1,2}) = \$62.6 \text{ billion}$$

Existing Doses (With Generics):

$$1.0 \text{ Million} \times (\$1,287.87 - \$52.63) = \$ 1.3 \text{ billion}$$

Total (With Generics): = \$63.9 billion

¹Coalition for Community Pharmacy Action. The Cost of Dispensing Study. September 2015.

²Takes the payroll and prescription department costs per prescription and divides this number by 2 to convert it to a per-dose basis

Results: Patient Groups That Interact With the Health System

Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
All Opioid Analgesic Rx	58.0	63.9	579.2
High-Impact Chronic Pain	19.6	9.5	85.5
Rx Opioid Analgesics with CNS Depressants	3.5	0.6	5.3
Medication Assisted Treatment (MAT)	1.4	0.2	1.5
Opioid-Related ED Visit	0.8	0.1	0.7

Results: Patient Groups That Don't Interact With the Health System

Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
Misusing Opioids	11.4	3.8	34.0
Opioid Use Disorder	2.1	0.3	2.5
Recent Criminal Justice and Rx Opioid Misuse	0.9	0.1	0.8
Recent Criminal Justice and Heroin Use	0.4	<0.1	0.3
Recent Criminal Justice and Opioid Use Disorder	0.3	<0.1	0.2

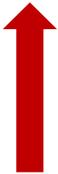
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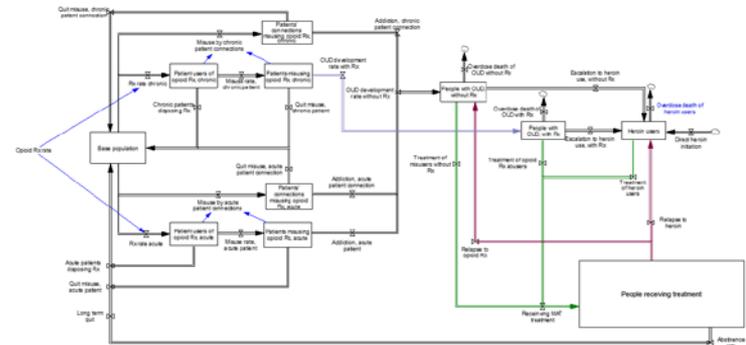
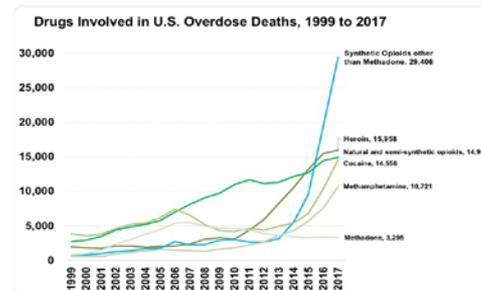
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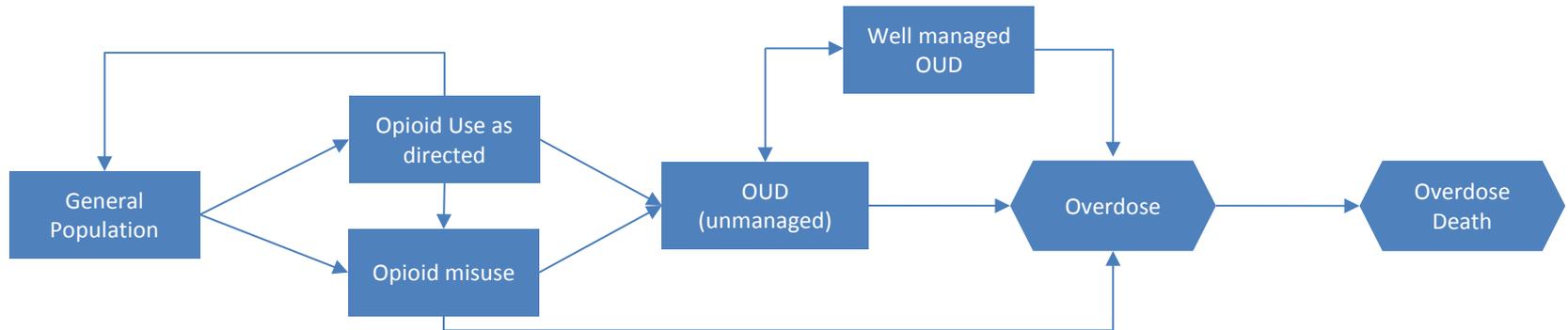
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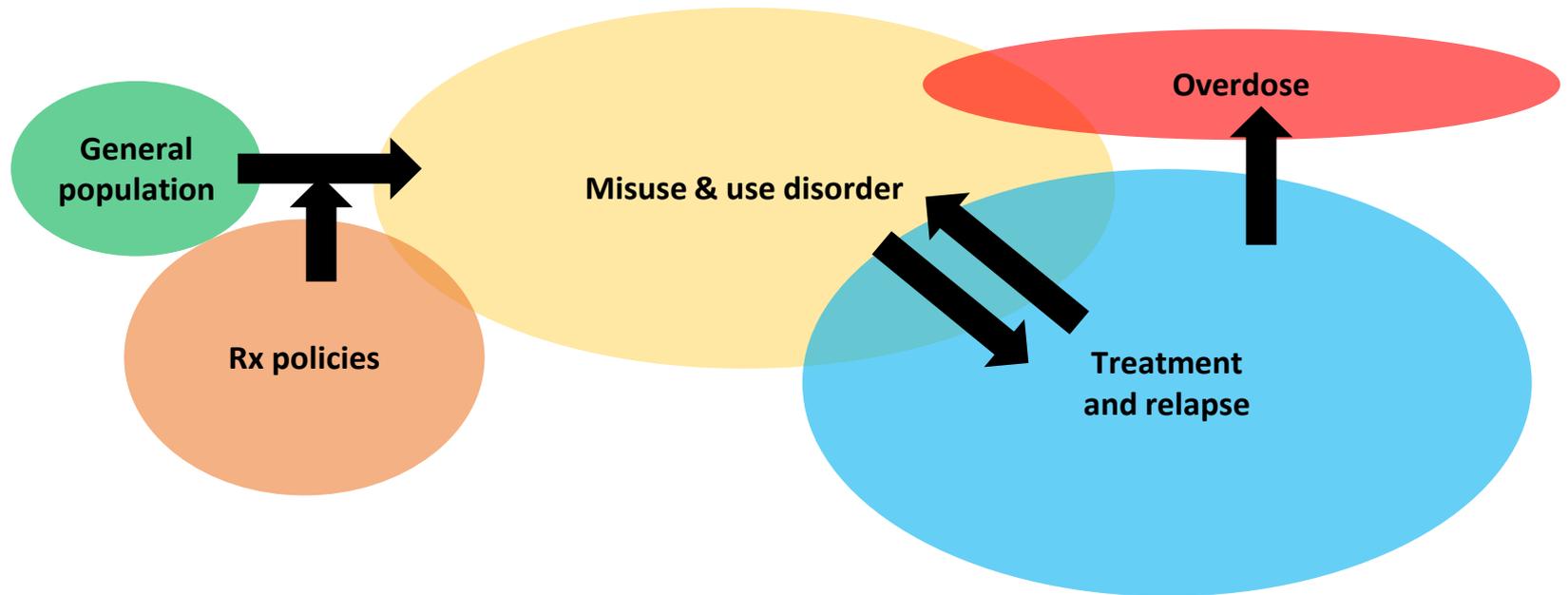
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MODEL BACKBONE



Illustrative pathway (simplified)



Illustrative pathway (detailed)

