Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value

Public Meeting – November 8, 2018

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Welcome and Introduction

- **Why are we here today?**
  - Innovation promising substantial benefits to patients and their families

- *Every day, more than 115 people in the United States die after overdosing on opioids. The misuse of and addiction to opioids is a serious national crisis that affects public health as well as social and economic welfare.*

  - National Institute on Drug Abuse, on the opioid overdose crisis (2018)

- *It is important that everybody has access to the entire array of treatments available: so that if one does not work, they will not think that this is all over. The more options they have, the better.*

  - Patient interviewed during ICER's scoping phase

Welcome and Introduction

- **Why are we here today?**
  - New mechanisms of action often raise questions about appropriate use, cost
  - Need for objective evaluation and public discussion of the evidence on effectiveness and value

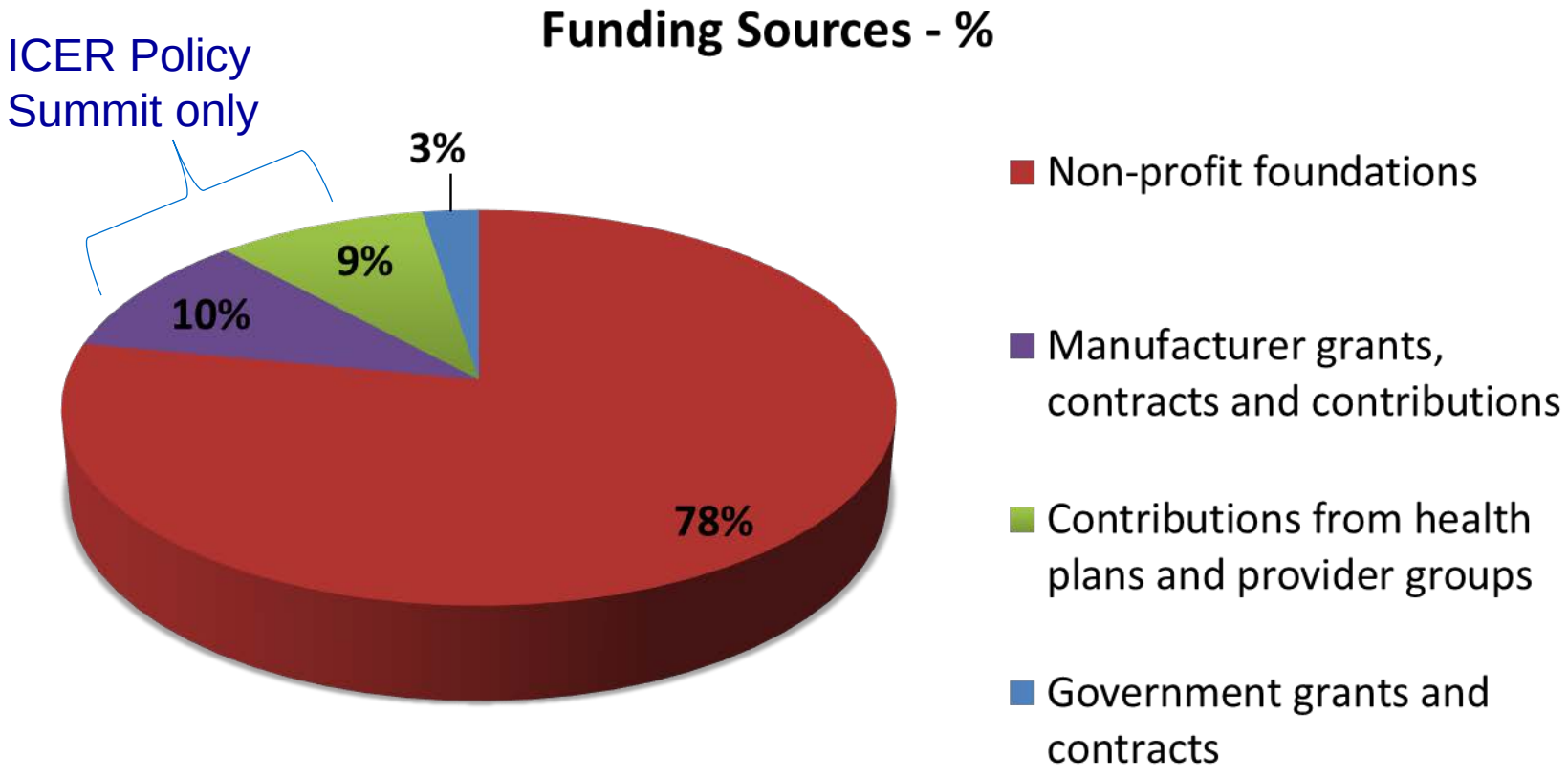
Welcome and Introduction

- New England Comparative Effectiveness Public Advisory Council (NE CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

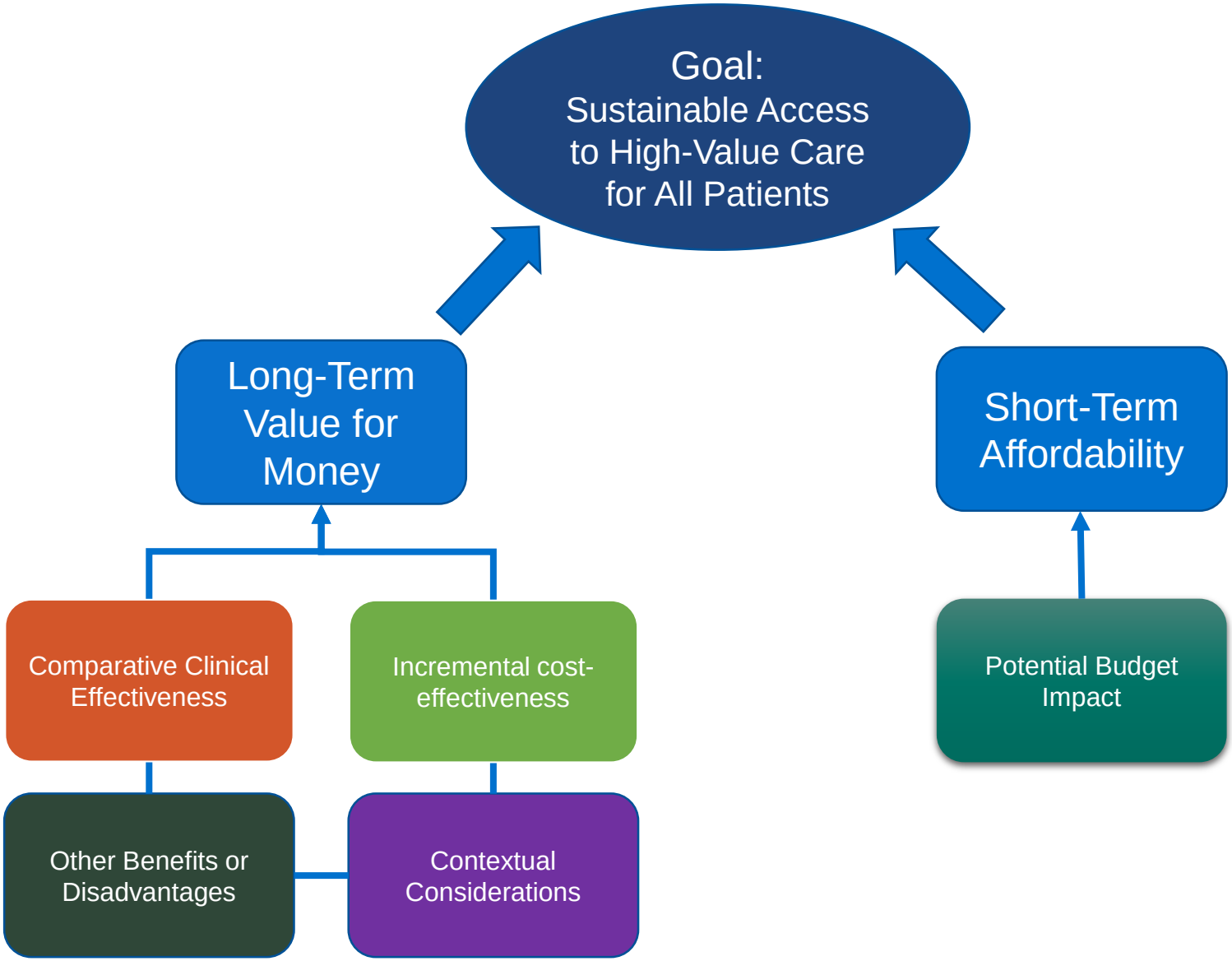
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on MATs for OUD developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis and cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Dr. Sarah Wakeman, MD
  - Dr. Ruth Potee, MD
- How is the evidence report structured to support NE CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

10:00am: Welcome and Opening Remarks

10:15 am: Presentation of the Evidence

Evidence Review: Reiner Banken, MD, MSc, ICER

Cost-Effectiveness: Varun Kumar, MBBS, MPH, MSc, ICER

11:15 am: Manufacturer Public Comment and Discussion

11:45 pm: Public Comments and Discussion

12:15 pm: Lunch

1:00 pm: New England CEPAC Deliberation and Votes

2:00 pm: Break

2:15 pm: Policy Roundtable

3:30 pm: Reflections

4:00 pm: Meeting Adjourned

Evidence Review

Reiner Banken, MD, MSc

Senior Fellow

Institute for Clinical and Economic Review

ICER

INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Key Review Team Members:

Reiner Banken, MD, MSc

Ifeoma Otuonye, MPH

Katherine Fazioli, BS

Dan Ollendorf, PhD

David Rind, MD, MSc

Disclosures:

We have no conflicts of interest relevant to this report.

Topic in Context

- In 2016, 2.1 million people suffered from OUD in the US and 116 Americans died per day from opioid-related drug overdoses
- Opioid epidemic is a nationwide public health emergency that has decreased overall life expectancy in the US
- OUD is a chronic condition with frequent relapses that requires long-term treatment

Effect on Lives Can Be Profound

- Devastating patients lives
- Fatal overdoses
- Devastating families
- Devastating communities

Terminology

- **OUD** is defined in DSM-5 by impaired control, social impairment, risky use, increased tolerance, and withdrawal. Replaces DSM-IV substance dependence and abuse
- **MAT** (Medication for addiction treatment) uses medications approved by the FDA in combination with individualized psychosocial support
- **Recovery** can be a state of no use, reduced use, or control of potential physical and emotional harm resulting from continued use
- **Relapse** involves loss of control, but different operational definitions in clinical trials, based on urine tests and use questionnaires

Management

- Variable paths to OUD and variable paths to recovery. Often psychiatric comorbidities
- MAT diminishes morbidity and mortality in OUD
- Important gap between the need for and the availability of treatment
- High prevalence of OUD in inmates with lack of access to MAT
- Long-term treatment, can be for a lifetime

FDA Approved Substances for MAT

- **Methadone**: Agonist, oral, long experience, used for withdrawal and maintenance, CSA schedule II limiting its use to SAMHSA and DEA regulated treatment programs
- **Buprenorphine**: Partial agonist, used for withdrawal and maintenance, CSA schedule III with SAMHSA prescribing waiver, transmucosal with naloxone as comparator for assessment
- **Naltrexone**: Antagonist, only for maintenance after prior withdrawal, does not diminish craving, not regulated through CSA, limited effectiveness of oral naltrexone due to limited treatment retention

Scope of the Review

Substance	Name	FDA Approval	FDA Recommended Dosing
Buprenorphine	Sublocade™ Indivior (s.c.)	Nov 30, 2017	Started after at least 7 days of 8 to 24 mg daily transmucosal bup. Monthly loading dose 300 mg times 2 then 100 mg monthly.
	Probuphine® Titan Pharmaceuticals, Inc. (Subdermal implant)	May 26, 2016	Started after 3 months of 8 mg or less daily transmucosal bup. Subdermal insertion for 6 months consecutively in each arm, then back to transmucosal bup.
	CAM2038 Braeburn (s.c.)	PDUFA date Dec 26, 2018 **?**	N/A
Naltrexone	Vivitrol® Alkermes (i.m.)	December 10, 2010 for OUD	Minimum of 7-10 days of opioid withdrawal. 380 mg injections every four weeks or once a month.

Population of Interest

- Patients aged 16 years and above with OUD in various treatment settings being considered for MAT

Outcomes of Interest

- Discontinuation
- Abstinence from use or diminishing illicit use of opioids
- Craving for opioids
- Mortality (prevention of overdose deaths, suicide)
- Diversion
- Health system utilization
- Infectious (HIV, hepatitis)
- Functional outcomes (cognitive, social/behavioral)
- Health-related quality of life
- Employment-related outcomes
- Accidental pediatric exposure

….

Insights from Discussions with Patients

- MAT is often difficult to access
- Stigma attached to OUD rooted in a belief that drug addiction is a moral failing rather than a medical condition
- Treatment is not one-size-fits-all
- Equal access to all types of medications
- Daily functioning and well-being are essential outcomes, not only abstinence from non-medical opioid use

Issues of Focus

Key Clinical Trials

	Trial	Study Design	Treatment Duration (Weeks)	Types of Outcomes
CAM2038	*Lofwall 2018*	*Phase III RCT Non-inferiority*	*24*	Urine samples used to assess abstinence
Sublocade	*Trial 13-0001*	*Phase III RCT*	*24*	Combination of urine samples and self-report used to assess abstinence
Probuphine	*Rosenthal 2016*	*Phase III Non-inferiority*	*24*	Urine samples and self-report used to assess abstinence
Vivitrol	*X-BOT*	*Phase IV*	*24*	Abstinence not reported Time to relapse event reported
	Tanum 2017	*Phase III RCT Non-inferiority*	*12*	Urine samples used to assess abstinence

Effectiveness of Extended-Release Compared to Buprenorphine/Naloxone

Intervention	Discontinuation	Opioid Negative Samples	Responders	Relapse
CAM2038	↔	Mixed	↔	No data
Probuphine	↔	↔	↑	No data
Vivitrol	↔	↔	No data	↑

Increase in Relapse with Vivitrol in intent to treat analysis.

No comparison of Sublocade to Buprenorphine/Naloxone.

Other Outcomes

- **Mortality**: No data
- **Health-Related Quality of Life**: Increase in quality of life in patients receiving Vivitrol compared with placebo
- **Healthcare Utilization**: Only for Vivitrol-no difference in trials; reduced inpatient admissions in observational study
- **Infectious diseases, Functional Outcomes, Employment-related Outcomes, Diversion and Accidental Pediatric Exposure**: No data, except one case in bup/nal arm in Probuphine

Harms

- Rates of serious adverse events were generally low
- Most common adverse events reported in the trials were injection/implant site pain, gastrointestinal issues, headaches, and insomnia

Potential Other Benefits and Contextual Considerations

- Decreasing diversion in correctional settings, less negative beliefs about opioid agonist therapy
- Perhaps no need for waivers in the future, if so increasing overall and regional access to MAT
- Prevention of accidental poisoning in children that currently occurs with transmucosal products
- Significant uncertainty about the magnitude or durability of the long-term benefits of extended-release formulations, given the 6-month duration of nearly all trials of these agents
- Action of Vivitrol cannot be reversed, so it becomes impossible to use opioids for emergency pain management

Controversies and Uncertainties

- **Lack of comparisons among interventions**: Differences in trial designs, population selection, and outcomes precluded formal comparisons among the four extended-release MATs.
- **Trial Population**: Patients with psychiatric comorbidities were generally excluded from the trials despite the high prevalence among patients with OUD.
- **Outcomes**: There's uncertainty whether outcomes measuring the rates of opioid-negative samples constitute a meaningful measure of success.

Public Comments Received

- Increasing access to MAT should be the policy question, comparing medications could decrease access.
- The issue of diversion has not received sufficient attention.
- Methadone should have been a comparator in addition to transmucosal buprenorphine.

Summary

- CAM2038 is non-inferior to buprenorphine and may add benefit to usual therapy.
- Evidence for Sublocade is limited to one 24-week Phase III trial compared to placebo.
- The study population for Probuphine may not be reflective of the more general population being considered for MAT.
- Vivitrol has the most mature evidence base of any of the treatments of focus for this review. Differences observed between Vivitrol and buprenorphine/naloxone are due at least in part to differences in treatment intent and goals.

ICER Evidence Ratings versus Transmucosal Buprenorphine/Naloxone

Drug	Evidence Rating
CAM2038	C+
Sublocade	I
Probuphine	P/I
Vivitrol	C

Cost Effectiveness

Varun Kumar, MPH, MSc

Health Economist

Institute for Clinical and Economic Review

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Key Review Team Members

Alexandra Ellis, PhD

Rick Chapman, PhD

Sumeyye Samur, PhD

Disclosures:

We have no conflicts of interest relevant to this report.

Methods in Brief

Objective

To estimate the cost-effectiveness of MATs in people diagnosed with and seeking treatment for opioid use disorder (OUD), using a decision analytic model

Methods Overview

- **Population:** Adults diagnosed with and seeking treatment for OUD
  - **Age**: 36 years; **Gender**: 30% Female; **Proportion using Rx opioid vs. injecting:** 50:50
- **Model:** Markov
- **Setting:** United States
- **Perspective:** Health care sector
- **Time Horizon:** Five years
- **Discount Rate:** 3% per year (costs and outcomes)
- **Cycle Length:** Four weeks

- **Outcomes:**
  - Life years
  - Quality-adjusted life years
  - Total costs (2018 dollars)
  - Incremental cost-effectiveness ratios (per quality-adjusted life year gained)

Modeled Interventions

Interventions

Subcutaneous Buprenorphine ER injection

- CAM2038
- Sublocade 300mg

Injectable Naltrexone ER

- Vivitrol 380mg

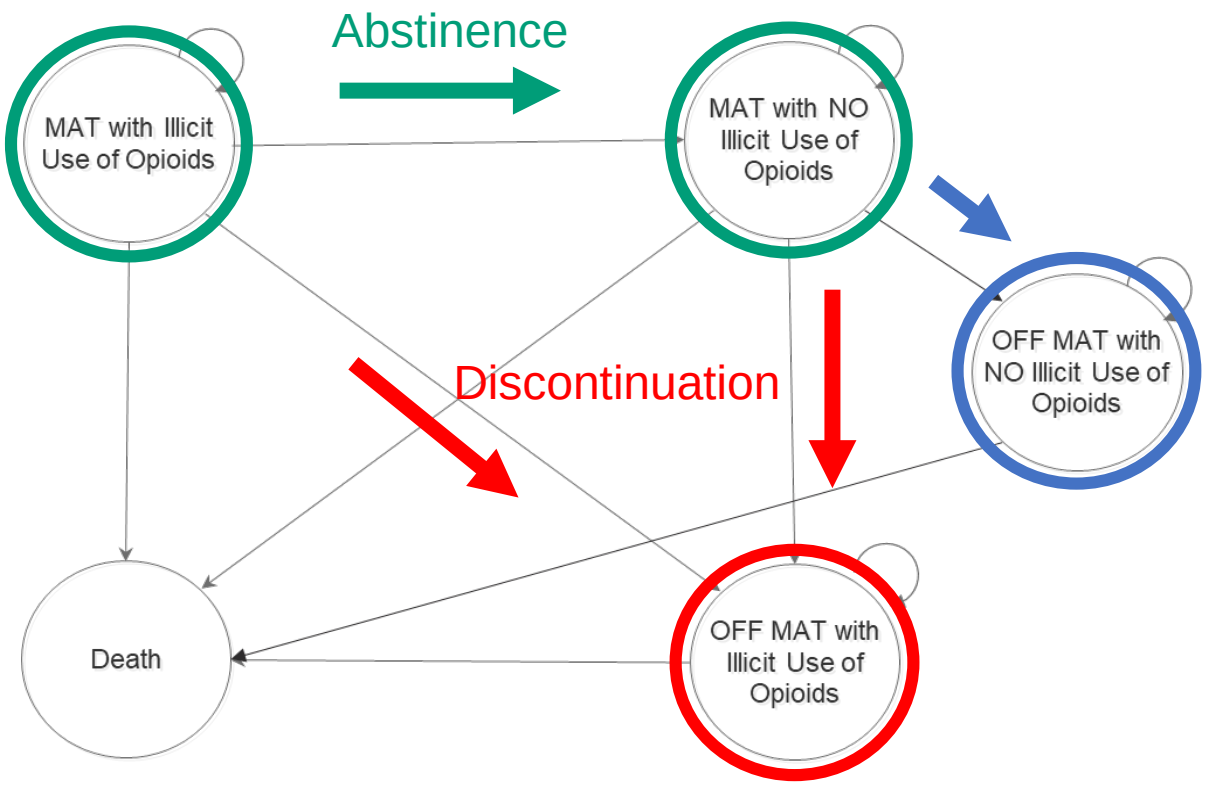
Subdermal Buprenorphine implant

- Probuphine

Comparator

SL Buprenorphine/Naloxone

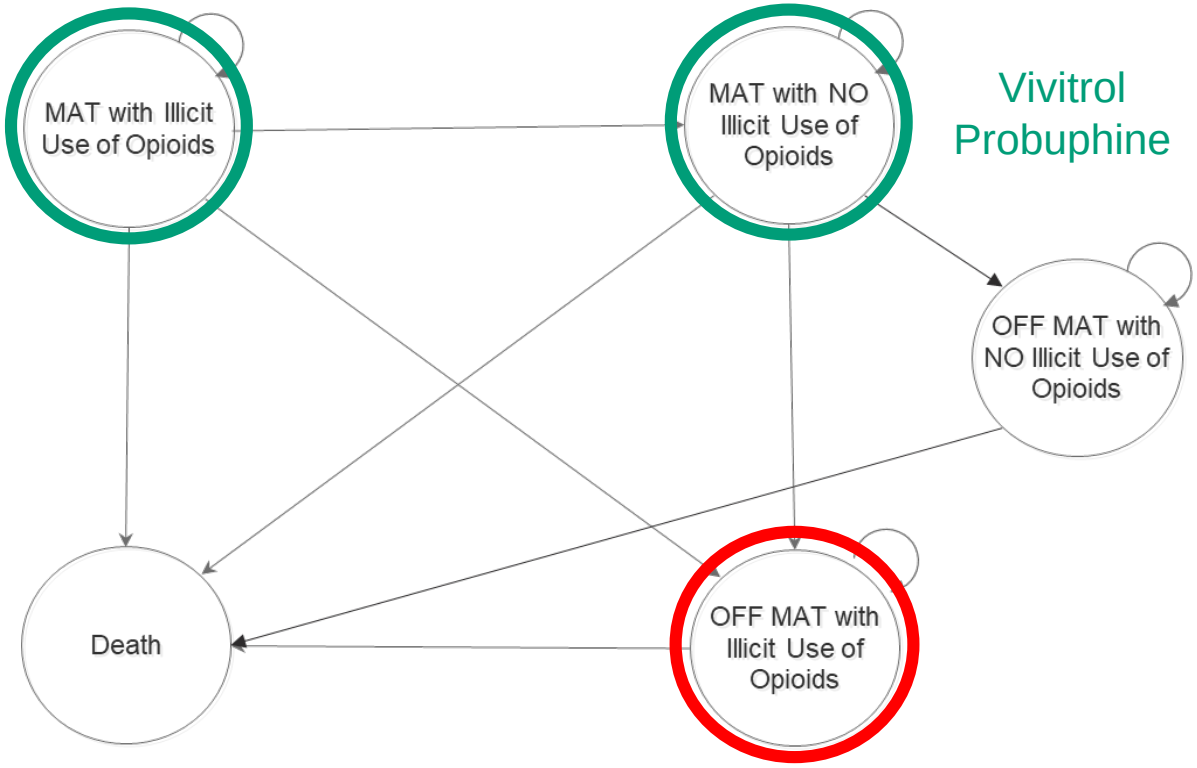
Model Schematic



Abstinence – Negative urine sample and self-report of NO illicit use
Relapse – Positive urine sample and/or self-report of illicit use

Pre-MAT Initiation Protocol

CAM2038
Sublocade



Vivitrol
Probuphine

Key Model Assumptions

- Upon relapse, patients were assumed to return to pre-MAT pattern of illicit use of opioids (prescription or injection).
- Opioid overdose-related mortality was attributed to only those patients currently illicitly using opioids when OFF MAT.
- Incidence of HIV and HCV infections was attributed only to people who inject drugs (PWID), with disutilities and costs attributed to these comorbidities.
- We assumed that 10% of all patients who remained in the “MAT with NO illicit Use of Opioids” health state for at least 12 months transitioned to an “OFF MAT with NO illicit use of opioids” health state.

Key Model Inputs - Efficacy

	Abstinence from Illicit Use of Opioids at 24 Weeks	
	Intervention	**Comparator (SL Buprenorphine/Naloxone)**
CAM2038[1]	34.2%	27.4%
Vivitrol*[2]	48%	44%
Probuphine[3]	80.5%	67.4%

*Among successfully detoxified patients

1. Lofwall et al. *JAMA internal medicine.* 2018;178(6):764-773.
2. Lee et al. *The Lancet.* 2018;391(10118):309-318.
3. Rosenthal et al. *JAMA.* 2016;316(3):282-290.

Key Model Inputs - Discontinuation

	Treatment Discontinuation at 24 Weeks	
	Intervention	**Comparator (SL Buprenorphine/Naloxone)**
CAM2038[1]	31%	27.4%
Vivitrol*[2]	52%	54%
Probuphine[3]	0%	32.6%

*Among successfully detoxified patients

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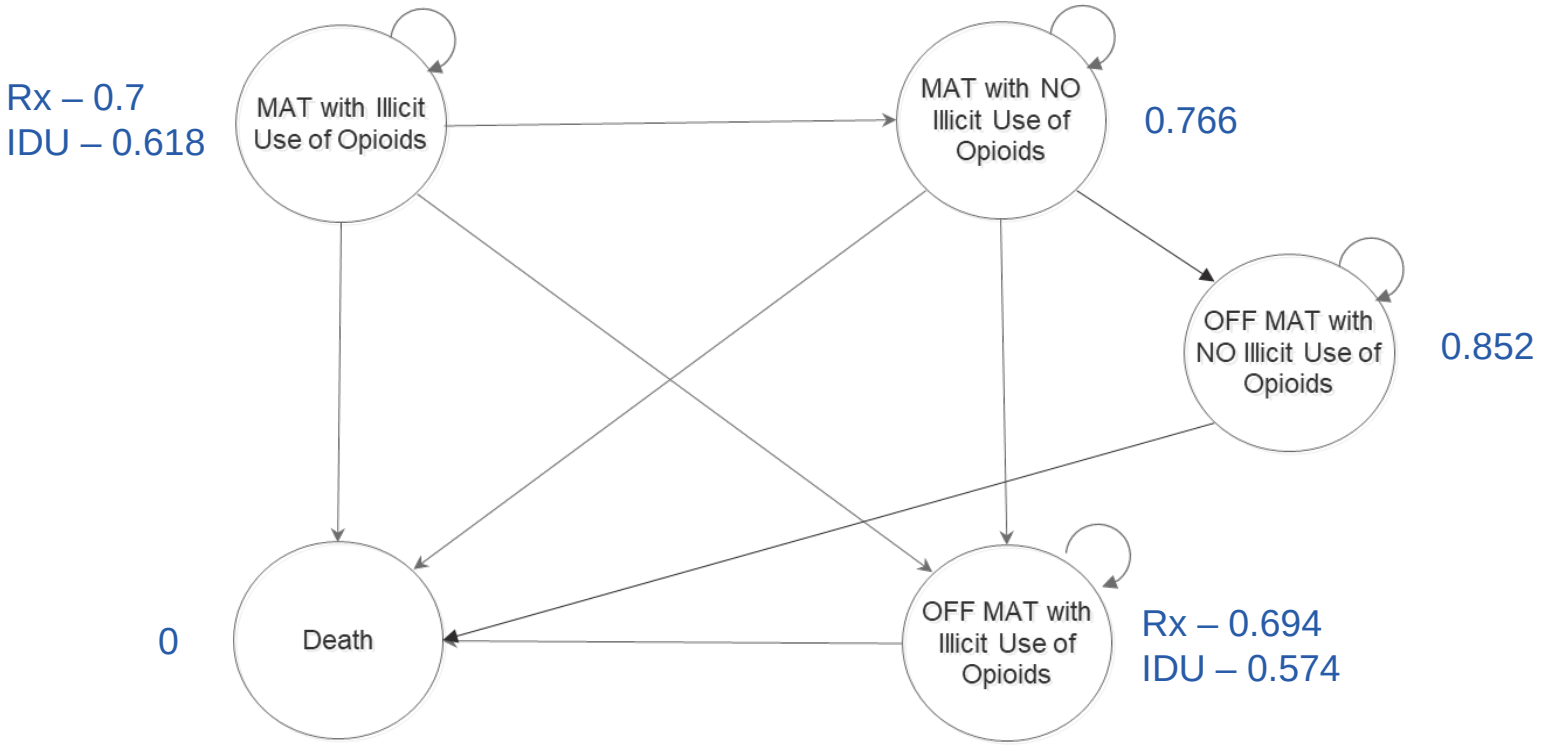
1. Lofwall et al. *JAMA internal medicine.* 2018;178(6):764-773.
2. Lee et al. *The Lancet.* 2018;391(10118):309-318.
3. Rosenthal et al. *JAMA.* 2016;316(3):282-290.

Health State Utilities



1. Wiitenberg et al. *Addiction. 2015;111(4):675-684.*
2. Connock et al. *Health technology assessment (Winchester, England). 2007;11(9):1-171, iii-iv.*
3. Sullivan et al. Med Decis Making. 2006;26(4):410-420.
3. Bernard et al. Annals of internal medicine. 2016:10.7326/M7315-2634.
4. Chhatwal et al. Ann Intern Med. 2015;162(6):397-406.

Drug Costs

Intervention	WAC per Dose	Net price per Dose	Net Price Discount from WAC	Annual Net Price
CAM2038 24/96 mg	-	-	-	-
Sublocade 300 mg	$1,580	$1,206.83	24%	$15,688.79
Vivitrol 380 mg	$1,309	$759.25*	42%	$9,870.25
Probuphine 296.8 mg	$4,950	$3640.32	26%	$3,640.32‡
Generic SL ER Buprenorphine/Naloxone 16 mg	$8.32	-	-	$3,037.46

*Manufacturer-provided net price

‡One time cost, assuming implant is used only once

Other Health Care Costs

	ON or OFF MAT with Illicit Use of Opioids	MAT with No Illicit Use of Opioids	OFF MAT with NO Illicit Use of Opioids
Inpatient Admissions[1]	$385.08	$332.94	-
Emergency Department Visits[1]	$81.01	$70.97	
Outpatient Visits[1]	$480.78	$727.98	-
All Health Care Costs[2]	-	-	$427.84

Drug and non-drug costs associated with HIV and HCV were included separately for patients who inject drugs (PWID)

ICER

1. Shah et al. Journal of Medical Economics. 2018;21(4):406-415.
2. Health Care Cost Institute. 2018.

Results

Base Case Results

	Total Costs	Total QALYs	Incremental Cost Effectiveness Ratio
CAM2038	-	3.26	-
Generic SL Buprenorphine/Naloxone	$70,100	3.20	

	Total Costs	Total QALYs	Incremental Cost Effectiveness Ratio
Vivitrol	$81,500	3.25	More Costly, Less Effective
Generic SL Buprenorphine/Naloxone	$71,200	3.28	

	Total Costs	Total QALYs	Incremental Cost Effectiveness Ratio
Probuphine	$77,900	3.38	$265,000 per QALY
Generic SL Buprenorphine/Naloxone	$75,100	3.37	

Probabilistic Sensitivity Analysis (1,000 Simulations)

Incremental Outcomes	Vivitrol	Probuphine
Higher Costs, More QALYs	1.2%	76.8%
Higher Costs, Fewer QALYs	98.8%	23.2%
Lower Costs, Fewer QALYs	0%	0%
Lower Costs, More QALYs	0%	0%

Scenario Analysis – Sublocade vs. SL Buprenorphine/Naloxone

Threshold Analysis ($150,000 per QALY)

- **For effectiveness**

$215,000 per QALY with 100% adherence and abstinence

- **For price**

~$400 per 300mg dose

FSS price - $1,206 per 300mg dose

Other Scenario Analyses

- Modified societal perspective — Probuphine – Dominant
  - Lost productivity
  - Criminal justice and incarceration
- Cohort comprising only PWID
- Excluding pre-MAT initiation protocols — Vivitrol – $1.1million/QALY
- Probuphine – Two consecutive implants

Directionally similar results to base case analysis

Limitations

- Model does not allow patients to cycle through different MATs, or retreatment with same MATs, once patients relapse
- Model does not consider diversion/switching to other opioids
- Model does not account for different levels of illicit use
  - Non-variable health care costs
  - Non-variable quality of life estimates
- No long-term data on efficacy, adherence or persistence

Comments Received

- Model should consider diversion since that greatly impacts outcomes and financial burden of OUD
- Model should consider various levels of illicit use
- Model should consider different patient populations for different MATs

Summary

- Interventions of interest show only marginal changes in QALYs relative to SL buprenorphine/naloxone
  - CAM2038 – Marginal increase in QALYs
  - Vivitrol – Marginal decrease in QALYs at higher cost
  - Probuphine – Slight increase in QALYs at higher cost
  - Sublocade – Well-above WTP threshold of $150,000 per QALY even under favorable assumptions
- Findings driven by intervention adherence rates, intervention costs, and incidence of HCV infection

Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Ted Buckley, PhD	Vice President, Government Affairs and Advocacy	Braeburn
Ponni Subbiah, MD, MPH	Chief Medical Officer	Indivior
Maria Sullivan, MD	Senior Medical Director	Alkermes

Public Comment and Discussion

Frederick Ryan

Chief of Police, Police Assisted Addiction Recovery Initiative, Arlington Police Department

Conflicts of interest:

- None declared.

Madeline Reinert

Policy and Programs Associate, Mental Health America

Conflicts of interest:

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies.

Mental Health American receives funding from Alkermes.

James Andersen, MD

Principal Investigator, Meridien Research

Conflicts of interest:

- Manufacturer support of research in the clinical area of this meeting in which you are participating.

Dr. Andersen served as principal investigator on RB 6000 (Sublocade) at Meridien Research.

Lunch

Meeting will resume at 1:00 pm

Voting Questions

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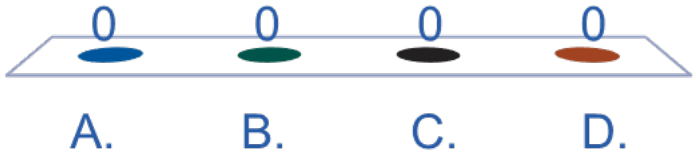
0. In 1990, two thieves posing as cops stole 12 paintings from which Boston-area museum?

A. Museum of Fine Arts

B. Institute of Contemporary Art

C. Peabody Essex Museum

D. Isabella Stewart Gardner Museum



Patient Population for all questions: Patients 16 years or older with opioid use disorder, who are being considered for MAT.

1. Is the evidence adequate to demonstrate that the net health benefit of the buprenorphine subcutaneous extended-release injection Sublocade™ (Indivior) is superior to that provided by transmucosal formulations of buprenorphine/naloxone?

A. Yes

B. No

2. Is the evidence adequate to demonstrate that the net health benefit of the buprenorphine subcutaneous extended-release injection CAM2038 (Braeburn) is superior to that provided by transmucosal formulations of buprenorphine/naloxone?

A. Yes

B. No

3. Is the evidence adequate to demonstrate that the net health benefit of buprenorphine implant Probuphine® (Titan Pharmaceuticals Inc.) is superior to that provided by transmucosal formulations of buprenorphine/naloxone?

A. Yes

B. No

4. Is the evidence adequate to demonstrate that the net health benefit of naltrexone intramuscular extended-release injection Vivitrol® (Alkermes) is superior to that provided by transmucosal formulations of buprenorphine/naloxone?

A. Yes

B. No

5. Is the evidence adequate to distinguish the net health benefit among the following interventions: (1) the two buprenorphine subcutaneous extended-release injections (Sublocade and CAM2038); (2) the buprenorphine implant (Probuphine); (3) naltrexone intramuscular extended-release injection (Vivitrol)?

A. Yes

B. No

6. Does treating patients with one of the extended-release interventions (CAM2038, Sublocade, Probuphine, or Vivitrol) offer one or more of the following potential "other benefits" vs. transmucosal formulations of buprenorphine/naloxone? (select all that apply)

A. CAM2038 and Sublocade offer reduced complexity

B. Probuphine offers reduced complexity

C. Vivitrol offers reduced complexity

D. Reduce important health disparities

E. Reduce caregiver or broader family burden

F. CAM2038 and Sublocade offer a novel mechanism of action or approach

G. Probuphine offers a novel mechanism of action or approach

H. Vivitrol offers a novel mechanism of action or approach

I. Significant impact on improving return to work/overall productivity

J. Other important benefits or disadvantages: _____.

7. Are any of the following contextual considerations important in assessing the long-term value for money of the extended-release interventions (CAM2038, Sublocade, Probuphine, or Vivitrol)? (Question 7 continues onto next slide)

A. Care of individuals with condition of high severity

B. Care of individuals with condition with high lifetime burden of illness

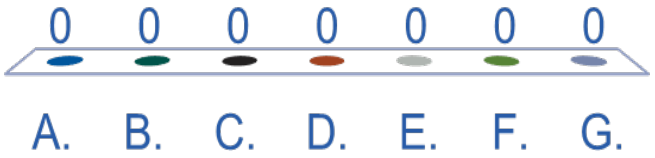
C. First to offer any improvement

D. Significant uncertainty about long-term risk of serious side effects of CAM2038

E. Significant uncertainty about long-term risk of serious side effects of Sublocade

F. Significant uncertainty about long-term risk of serious side effects of Probuphine

G. Significant uncertainty about long-term risk of serious side effects of Vivitrol



Question 7 continued from previous slide: Are any of the following contextual considerations important in assessing the long-term value for money of the extended-release interventions (CAM2038, Sublocade, Probuphine, or Vivitrol)?

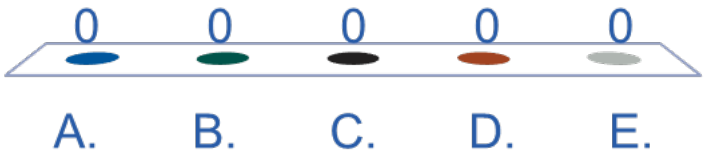
A. Significant uncertainty about magnitude or durability of long-term benefits of CAM2038

B. Significant uncertainty about magnitude or durability of long-term benefits of Sublocade

C. Significant uncertainty about magnitude or durability of long-term benefits of Probuphine

D. Significant uncertainty about magnitude or durability of long-term benefits of Vivitrol

E. Other important contextual considerations: _____.



Long-Term Value for Money

As described in ICER's recent update to its value assessment framework, questions on "long-term value for money" are subject to a value vote only when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis.

As shown in the Evidence Report, the estimates for Probuphine and Vivitrol exceed the higher end of the range and thus both interventions are deemed "low value" without a vote of the panel.

There is also no vote on Sublocade as we were not able to calculate an incremental cost-effectiveness ratio compared with sublingual buprenorphine/naloxone. CAM 2038 is not yet approved, and no price is available, so an incremental cost-effectiveness ratio could not be calculated; consequently, a value vote will not be taken.

Break
Meeting will resume at 2:15 pm

Policy Roundtable

Policy Roundtable Participants

Name	Title and Affiliation	COI Declaration
Barbara Henry, RPh	Lead Pharmacy Specialist, Harvard Pilgrim Health Care	Full-time employee of Harvard Pilgrim Health Care.
Kimberly Lenz, PharmD	Clinical Pharmacy Manager, MassHealth	Full-time employee of MassHealth.
Richard Malamut, MD	Chief Medical Officer, Braeburn	Full-time employee of Braeburn.
Michael Miller	Communications and Chapters Director, Young People in Recovery	None declared.
Lewis Nelson, MD	Professor and Chair, Department of Emergency Medicine; Chief, Division of Medical Toxicology, Rutgers New Jersey Medical School	None declared.
Amy K. O'Sullivan, PhD	Head of Health Economics and Outcomes Research, Alkermes	Full-time employee of Alkermes.
Maria Schiff	Senior Officer, Substance Use Prevention and Treatment Initiative, The Pew Charitable Trusts	None declared.
Ann Wheeler, PharmD, BCPP	National Director of Managed Care Medical Affairs; Head of Behavioral Health Medical Affairs, Indivior	Full-time employee of Indivior.
Joe Wright, MD, AAHIVS	Medical Director, Boston Health Care for the Homeless Program; Clinician, CareZone	Received consultancy fees from Massachusetts League of Community Health Centers.

NE CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about December 3
  - Includes description of NE CEPAC votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/topic/opioid-dependence/

Adjourn