Cost-Effectiveness Analysis of Extended-Release Medications for Opioid Use Disorder: Comparing Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

by

Jeremy Tyler Adams

BS, Nova Southeastern University, 1995

MPH, University of Utah, 1996

MD, University of Utah, 2007

MBA, George Washington University, 2012

Submitted to the Graduate Faculty of the

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2021

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

by

Jeremy Tyler Adams

It was defended on

April 14, 2021

and approved by

Cindy L. Bryce, PhD, Associate Professor, Department of Health Policy and Management

Julie W. Childers, MD, MS, Associate Professor, Department of Medicine

Kenneth J. Smith, MD, MS, Professor of Medicine and Clinical and Translational Science, Department of Medicine

Dissertation Director: Julie M. Donohue, PhD, Professor and Chair, Department of Health Policy and Management

Cost-Effectiveness Analysis of Extended-Release Medications for Opioid Use Disorder: Comparing Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

Jeremy Tyler Adams, PhD

University of Pittsburgh, 2021

Abstract

Extended-release medications for opioid use disorder (ERMOUD) are newer additions to combat the opioid epidemic. While more expensive than daily-administered formulations, they offer unique advantages. These include lessening the burden and constraints of daily adherence, improving treatment retention, and potentially improving long term remission, along with eliminating the risk of drug diversion and fatal accidental poisoning in children.

Opioid use disorder (OUD) is now viewed as a chronic medical condition, requiring long-term treatment, expectant of relapses and illicit reuse, and multiple treatment strategies and trials. Therefore, it is important to evaluate the cost-effectiveness of these newer extended-release medications, along with the daily-administered formulations, in the context of this newly adopted disease paradigm.

In **Chapter One**, we performed a cost-effectiveness analysis of ERMOUDs in both single-drug and multi-drug-in-sequence treatment strategies, allowing for readmission and transition to another drug regimen upon discontinuation or attrition due to illicit opioid use. Prior economic models did not allow treatment reentry nor switching. We found that ERMOUD multi-drug-in-sequence combination treatment strategies prove more cost-effective than single-drug ERMOUD treatment strategies and are a cost-effective alternative to daily administration MOUD regimens.

We triplicated our model in **Chapter Two** to compare three different drug pricing schedules: Wholesale Acquisition Costs (WAC), Drug Manufacturer's Net Price (DMN), and Medicaid Rebate-Adjusted Prices (MRA). We found that using MRA prices, which represents the majority of OUD patients, increases the viability and cost-effective competitiveness of ERMOUDs, while closer approximating real-world pricing conditions.

We further expanded our model in **Chapter Three** to include the original mainstays of MOUD, Methadone and Buprenorphine Maintenance Treatments, both singly and in multi-drug-in-sequence combinations. Thus, we were able to conduct a comprehensive cost-effectiveness analysis on essentially all available MOUD treatment strategies, allowing for readmission and drug switching. We found that, while the newer ERMOUDs are an important addition to the treatment options of OUD, and provide unique clinical advantages over the daily formulations, the single-drug BMT-only treatment strategy tested as the most cost-effective, at least until the price of both extended-release and daily formulations better align with their demonstrated benefits.

Table of Contents

List of Tables

List of Figures

1.0 Cost-Effectiveness of Extended-Release Medications for Opioid Use Disorder Treatment Strategies: Single-Drug and Multi-Drug-in-Sequence Regimens

1.1 Introduction

The United States continues to struggle with the opioid epidemic, deemed a Public Health Emergency in 2017.[1] As understanding of opioid use disorders (OUD), the disease driving the epidemic, evolves, treatment strategies do as well. OUD is now recognized as a chronic, relapsing condition, requiring longer episodes of continuous treatment like other chronic diseases. Treatment has therefore shifted away from an acute care paradigm, as abstinence achieved in the short-term is not predictive of long-term remission.[2] Although there are a number of "Medication-Assisted Treatment (MAT) Models of Care,"[3] these models focus more on the implementation of treatment. As OUD treatment changes to a chronic disease paradigm, one that expects periods of abstinence punctuated by relapses, and multiple treatment initiations and premature discontinuations,[4] we must evaluate Medications for Opioid Use Disorder (MOUD) use singularly, as well as in series with other MOUDs. In this Cost-Effectiveness Analysis of Extended-Release Medications for Opioid Use Disorder (ERMOUD), we evaluate both single-drug treatment strategies and multi-drug-in-sequence treatment strategies.

Three drugs are approved by the US Food and Drug Administration for MOUD: Methadone, Buprenorphine, and Naltrexone. MOUDs have been proven effective therapy, and widely-acknowledged as the gold-standard of care. In an effort to enhance retention, increase adherence, improve safety, and minimize drug diversion, long-acting or extended-release formulations of Buprenorphine and Naltrexone have been developed. Currently available in the

US are two once-monthly depot injections, one of buprenorphine (Sublocade) and one of Naltrexone (Vivitrol), and one 6-month subdermal implant of Buprenorphine (Probuphine). [Table 1.1]

Table 1.1 Scope of the Review

Name	Drug	Delivery	FDA Approval	FDA Recommended Dosing
Vivitrol	Naltrexone for Extended-Release Injectable Suspension	Monthly Intramuscular Injection	October 13, 2010	Minimum of 7-10 days of opioid withdrawal. 380 mg injections every four weeks or once a month.
Sublocade	Buprenorphine Extended-Release Injection for Subcutaneous Use	Monthly Subcutaneous Injection	November 30, 2017	Initiated 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	Buprenorphine Implant	6 Month Subdermal Implant	May 26, 2016	Initiated 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.

Prior economic models assume no treatment reentry after relapse to illicit opioid use or transitioning to other treatment regimens (a multi-drug-in sequence treatment strategy) following MOUD discontinuation. A cost-effectiveness model of Probuphine from a US societal perspective, including both direct medical costs and non-medical costs (such as criminal justice costs and lost productivity), with a 12-month time horizon found Probuphine to be cost-effective over sublingual buprenorphine with slightly increased QALY's, and lower overall costs.[5] Vivitrol cost-effectiveness was compared to methadone and buprenorphine maintenance treatments by estimating the incremental cost per opioid-free day over a 6-month time horizon. Vivitrol was found to cost $72/opioid-free-day compared to methadone maintenance treatment, without quality of life estimates, QALY calculations, or accounting for induction attrition due to illicit opioid use,

a significant issue particular to Vivitrol which requires an opioid-abstinent induction period of 7-12 days.[6]

The Institute for Clinical and Economic Review (ICER_*Report*) released a report on the cost-effectiveness of ERMOUDs that is most comparable to our study, with some important similarities and differences.[7] They compared four ERMOUDs (Vivitrol, Probuphine, Sublocade, and Brixadi) individually to generic Sublingual-Buprenorphine/Naloxone (gSL-Bup/Nal), using a Markov model from a U.S. health care perspective, with a 4-week cycle run over a 5-year time horizon, and treatment-specific efficacy and attrition rates derived from key relevant clinical trials, also used in our analysis. [Table 1.2] They found Vivitrol was dominated by gSL-Bup/Nal, Sublocade wasn't cost-effective even under unreasonably favorable assumptions, and Probuphine was dominant relative to gSL-Bup/Nal, only under a modified societal perspective. Their conclusion was that these ERMOUDs represented "low value for the money."[8] However, they stated that their analysis was limited by lacking the evidence on treatment pathways following MOUD discontinuation and how patients transition to different therapies.

Our model directly addresses these limitations by comparing ERMOUDs as single-drug treatment strategies and multi-drug-in-sequence treatment strategies, along with gSL-Bup/Nal. We hypothesize that multi-drug-in-sequence treatment strategies that follow patients cycling through different therapies, as in the real-world, will be deemed a cost-effective MOUD regimen, and warrant reconsideration from practitioners and policymakers alike in combatting the opioid epidemic, especially during this COVID-19 pandemic, when ERMOUDs could be particularly beneficial.

1.2 Methods

We developed a decision analytic model using individual Markov models of 15 MOUD drug treatment regimen strategies, including 3 single-drug strategies, and 12 multi-drug-in-sequence strategies that allowed switching to another drug and readmission upon discontinuation or attrition due to illicit opioid use. [Figure 1.1]

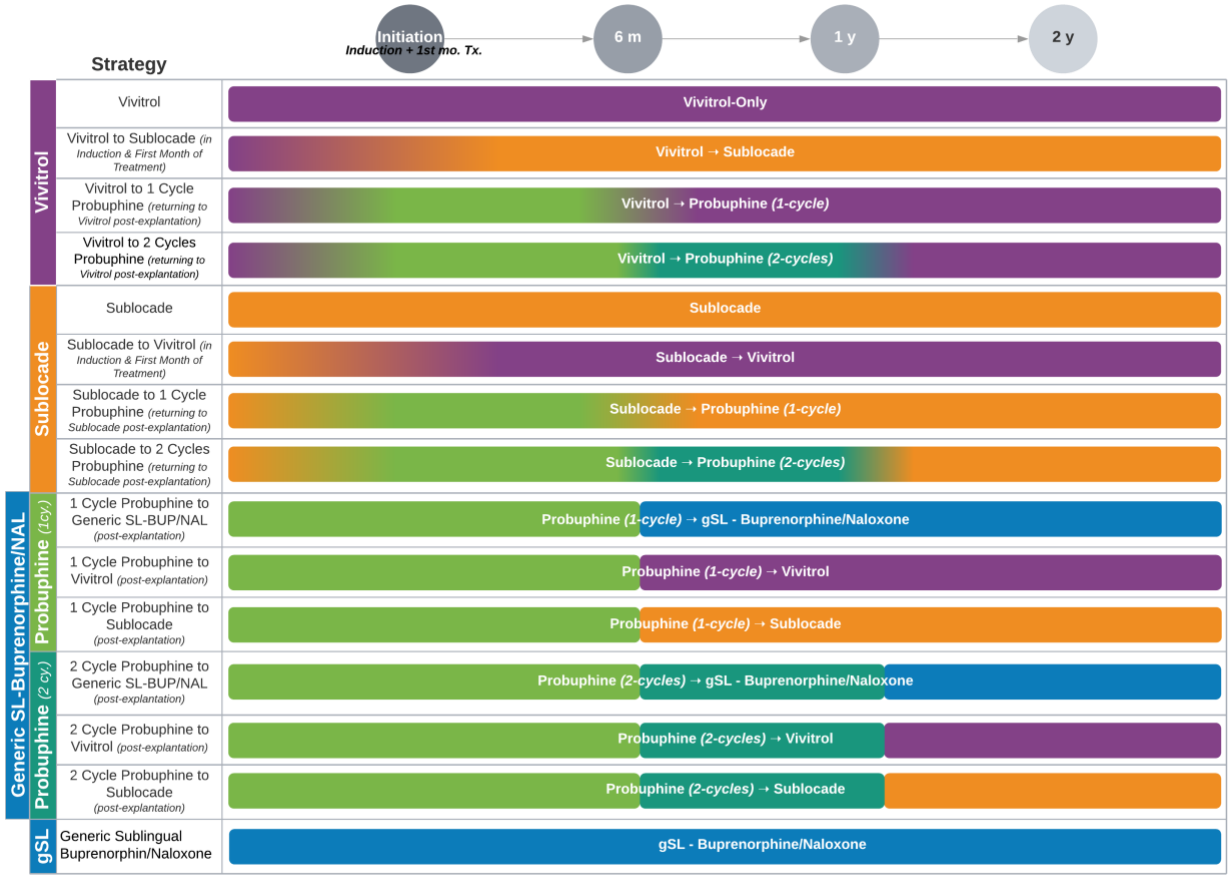


Figure 1.1 Tested Treatment Strategies

Model cycle length was one week, and the model was run for 4 separate time-horizons: 6-months, 1-year, 18-months, and 2-years. Our model was informed by, and measures of drug

efficacy and treatment attrition were gathered from, key clinical trials and relevant past economic models. [Tables 1.2 & 1.3]

Table 1.2 Key Clinical Trials

Drug	Trial	Study Design	Weeks	Detoxification/ Induction Period	Time of Randomization	Outcomes
Sublocade	Trial 13- 0001	Phase III RCT	24	**Detoxification**: none **Induction**: run-in induction phase with SL bup/nal film followed by open-label phase with 8 to 24 mg doses of bup/nal for four to 11 days	After induction	• Combination of urine samples and self-report used to assess abstinence • Outcome measured over 24 weeks
Probuphine	Rosenthal 2016	Phase III Non-inferiority	24	**Detoxification**: none **Induction**: stable dose of 8 mg/day or less of sublingual buprenorphine received for at least 24 weeks	After induction	• Urine samples and self-report used to assess abstinence • Outcome assessed over 24 weeks
Vivitrol	X-BOT	Phase IV		**Detoxification**: yes, protocols and length of time varied by site	Before induction	• Abstinence not reported • Time to relapse event reported
	Tanum 2017	Phase III RCT Non-inferiority	12	**Detoxification**: yes	After detoxification	• Urine samples used to assess abstinence • Outcome measured over 12 weeks

Table 1.3 Measurements of Efficacy

Drug Name	Trial	Induced	Abstinence	Attrition
Vivitrol	Lee (X:BOT)	72.08%	51.96%	52.94%
Sublocade*	Haight (Trial 13-0001)	60.84%	12.31%	37.13%
Probuphine	Rosenthal (PRO-814)	89.10%	80.46%	6.90%
gSL-Bup/Nal	Fudala (2003)	71.62%	53.00%	44.70%

*Statistics used from this study reflect individual's 100% abstinence, instead of participant's mean percentage abstinence, to match outcomes of the other two studies

We assumed direct transfer to the alternate drug regimen in our multi-drug-in-sequence strategies, however, a gap in time between treatment regimens, or a discontinuity of care, would not theoretically alter our model's results, as we chose to not modulate the second drug regimen's induction probability. Without any study statistics, to date, on multi-drug-in-sequence strategies, the effect of one MOUD preceding another, nor the temporal interruption in treatment, is unknown. Both an increase and decrease in the induction to the second drug or transfer regimen with an increasing gap between the two could be argued, as one may be more motivated to succeed at the second treatment option, or may be less dedicated to treatment upon discontinuation of the first regimen. We acknowledge that there likely is an influence from the first drug on the second, but until more data is available, our model will be unmodulated.

We took a health care perspective, and included drug prices using Wholesale Acquisition Cost (WAC, the most commonly used drug pricing benchmark[9]), and direct drug administration costs using CPT codes. [Table 1.4] Other health care costs, which are highly variable depending on geographic and demographic differences, healthcare provider and payor, were not included to ensure greater generalizability of results.

Table 1.4 Drug Costs

Name	Drug Costs*/wk	Admin. Costs/wk
Vivitrol	$327.25	$5.22**
Sublocade	$395.00	$5.22**
Probuphine	$190.38	$11.88§

**Costs based on Wholesale Acquisition Costs (WAC)*

***SC/IM Injection Administration (CPT Code: 96372)*

§Implant Insertion/Removal (CPT Code: 11981/11982)

Health utilities were sourced from the published literature, including a study that employed a cross-sectional online US survey.[10,11] [Table 1.5]

Table 1.5 Health Utilities

Health Utilities	Vivitrol	Sublocade	Probuphine
Induction	0.660	0.660	0.766÷
MAT w/o IUO	0.766	0.766	0.766
MAT w/ IUO*	0.660	0.660	0.660
OFF MAT w/o IUO	0.852	0.852	0.852
OFF MAT w/ IUO**	0.635	0.635	0.635
Death	0.000	0.000	0.000

**Combination of Prescription Opioid User & Intravenous Drug User Health Utilities: 0.700 & 0.618 at 50.7%/49.3% (Prescription/IVDU)*

***Combination of Prescription Opioid User and Intravenous Drug User Health Utilities: 0.694 & 0.574 at 50.7%/49.3% (Prescription/IVDU)*

÷Higher than other 2 Induction Utilities due to all cohort assumed to enter already on MAT (SL Buprenorphine) and clinically stable/abstinent

Each Markov Model has 6 health states, with the cohort entering the model in the Induction Health State. There are 4 health states denoting illicit opioid use or abstinence both in and out of treatment, and an absorbing death health state. Readmission or Switching to another drug treatment is allowed from the "Retained-Reused" (in treatment with illicit use of opioids) Health State in some tested strategies and returns to the Induction Health State. [Figure 1.2]

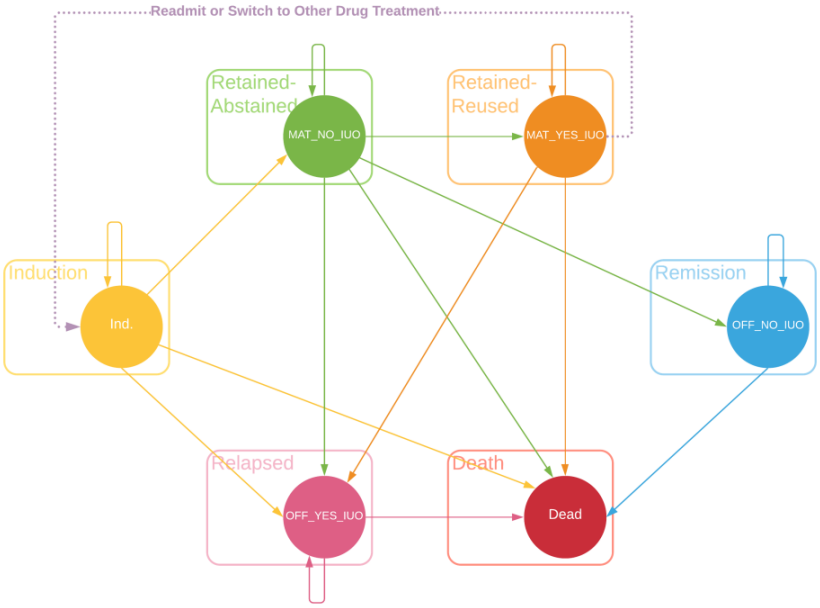


Figure 1.2 Markov Model Map

When to allow Readmissions for Vivitrol and Sublocade was determined by a sensitivity analysis. A pre-determined combination of varying time lengths of allowable readmission windows was tested, in both the induction phase and the first weeks of treatment. Accordingly, we allowed for readmission and switching drug treatments in the initiation (induction period and first weeks of treatment). Specifically, the single-drug treatment strategies did not allow for any readmission, whereas the multi-drug-in-sequence treatment strategies allowed for the minimum readmission windows for both the induction and treatment phases to permit transfer to another drug regimen upon discontinuation secondary to Illicit Use of Opioids (IUO).

A cost-effectiveness analysis was run to determine the undominated strategies in each chosen time-horizon, producing cost-effectiveness frontier graphs [Appendix A.1] with corresponding incremental cost-effectiveness ratios, at a Willingness-to-Pay (WTP) of $50,000. All 15 drug treatment regimen strategies were included in the 1-year and longer time-horizons, and 10 strategies (excluding the strategies that included a second Probuphine implant) were included in the 6-month time-horizon. The undominated strategies' Markov Models were individually run to evaluate the cohort's movement through the health states in all time-horizons. The proportion of the cohort in each health state both at the end of the time-horizon, as well as cumulative time spent during the time-horizon (AUC) was then compared amongst the other undominated strategies. [Appendix A.6]

Uncertainty was evaluated by both one-way and probabilistic sensitivity analysis. Model probability and health utilities were varied ±10%, with drug costs varying ±25%, and direct drug administration costs varying ±20%. Probabilistic sensitivity analysis was done using Monte Carlo simulations over 5,000 trials, with parameters assuming triangular distributions, producing cost-effectiveness scatterplots [Appendix A.2], acceptability curves [Appendix A.3], and strategy selection graphs [Appendix A.4] for all time-horizons. Further investigation of parameter uncertainty and key model economic drivers in the resulting predominant strategies was performed with one-way sensitivity analysis, by way of incremental cost-effectiveness scatterplots and tornado diagrams. [Appendix A.5]

1.3 Results

The "generic Sublingual-Buprenorphine/Naloxone" (*gSL-only*) treatment strategy was the least expensive and least effective strategy in all time-horizons (whereas Sublocade and Sublocade-containing strategies were always dominated, i.e., more costly and less effective than other strategies). The *gSL-only* cost-effectiveness ratio was the lowest and most advantageous, except for in the 2-year time-horizon, largely due to significantly lower costs compared to ERMOUDs and was used as the baseline for all comparative analyses. Our model found three undominated strategies when run over a 6-month time-horizon, and four undominated strategies when run over time-horizons of 1-year or more, all including the *gSL-only* treatment strategy. However, all drug treatment regimen strategies tested had cost-effectiveness ratios well below our WTP of $50,000 when compared individually to the common baseline *gSL-only* strategy, ranging from $3,884 – $34,651.

Table 1.6 Incremental Cost-Effectiveness Ratios of Undominated Strategies

Treatment Strategy	6-months	Treatment Strategy	1-year	18-months	2-years
gSL-Only	$0	**gSL-Only**	$0	$0	$0
PRO1 → VIV	**$21,595**	**PRO1 → gSL**	**$9,688**	**$5,655**	**$3,884**
VIV → PRO1	$470,387	VIV → PRO1	$138,627	$129,518	$110,233
		VIV → PRO2	$171,968	$306,087	$274,911

1.3.1 Readmission and Transfer Determination

Our one-way sensitivity analysis to determine the length of time in both the induction and treatment health states where treatment reentry or transfer to alternate treatment showed that no readmissions of any length, either in induction or treatment, were cost-effective. However, it did

show that while increasing the allowable weeks for readmission in the treatment health state became increasingly less cost-effective, increasing the allowable weeks for readmission in the induction health state was undominated, but more costly and more effective.

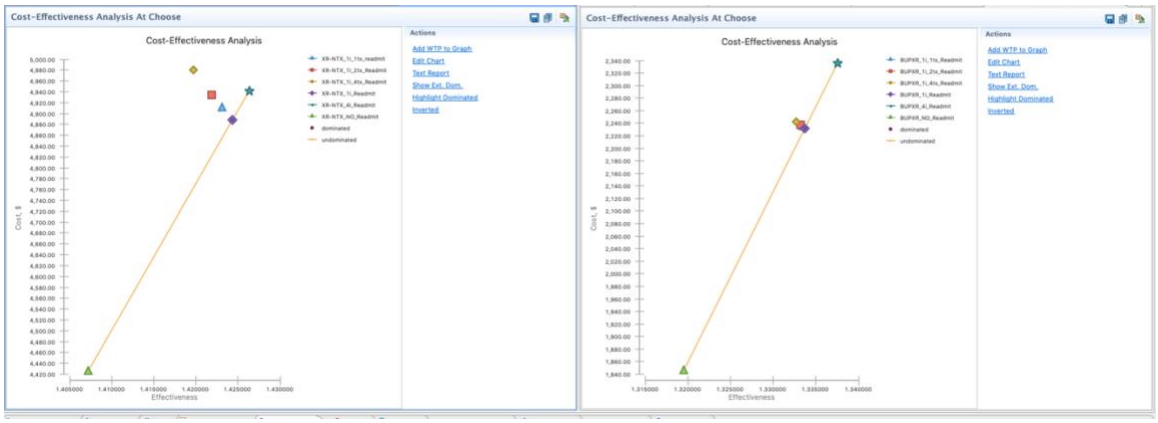


Figure 1.3 Readmission Sensitivity Analysis

A more thorough one-way sensitivity analysis was conducted wherein the readmission window was tested from 0 weeks allowed (meaning NO Readmission Allowed upon treatment discontinuation due to "Relapse" or IUO), to 10 weeks. Again, not allowing any readmissions, in any week tested, was most cost-effective for both the Induction Health State, and the Initial Treatment Health State.

1.3.2 6-Month Time-Horizon Results

1.3.2.1 Undominated Strategies & ICERs

Over a 6-month time-horizon, the "Probuphine *(1-cycle)* → Vivitrol" (*PRO1→VIV*) and its reverse "Vivitrol → Probuphine *(1-cycle)*" (*VIV→PRO1*) treatment strategies (where those in the cohort who used illicit opioids in the induction period or first few weeks of treatment were allowed to readmit or switch to the other drug in the treatment strategy) were found to be undominated strategies [Table 1.6], along with the baseline *gSL-only* strategy. Only the *PRO1→VIV* treatment strategy had an ICER below $50,000 (ICER = $21,595) when compared together with the other 8 strategies to *gSL-only* strategy. Further analysis was conducted to compare *gSL-only* to *PRO1→VIV*, the next most cost-effective undominated treatment strategy, as was performed in all time-horizons.

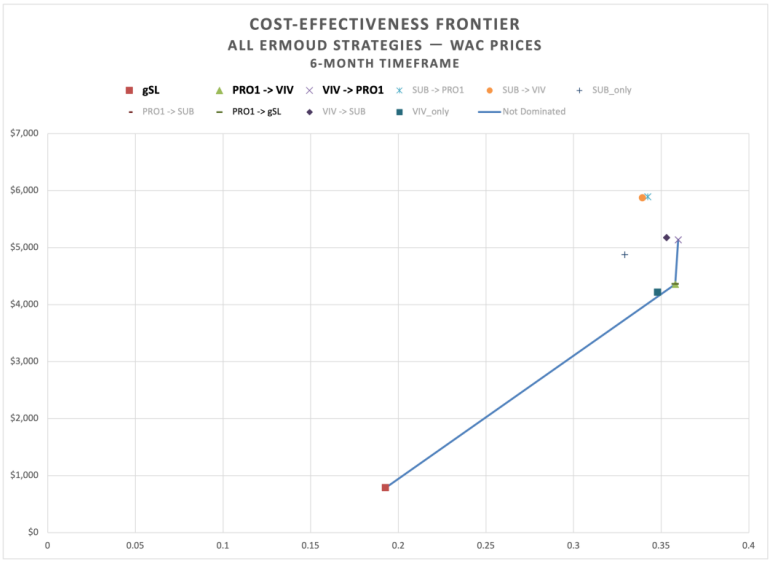


Figure 1.4 Cost-Effectiveness Frontier (6-month timeframe)

1.3.2.2 Health State Tracings & Comparisons

The *PRO1→VIV* strategy resulted in 3.3 times more of the cohort in the Retained-Abstained health state (those in treatment and not illicitly using opioids) compared to the *gSL-only* strategy. Whereas the *gSL-only* strategy resulted in 3.3 times more who Relapsed (those who left treatment illicitly using opioids), 1.4 times more Retained-Reused (those who are illicitly using opioids during treatment), and 2.8 times more Dead than the *PRO1→VIV* strategy. While the *gSL-only* strategy did result in a significantly higher proportion of the cohort in the Remission health state (those who left treatment without illicitly using opioids), this can be attributed to the fact that the Probuphine implant does not allow for treatment discontinuation as Sublingual-Buprenorphine/Naloxone does. This advantage in those in Remission disappears when comparing the overall abstinence rate both in and out of treatment (Retained-Abstained AND Remission combined), where the *PRO1→VIV* strategy results in 1.6 times more of the cohort abstaining from illicit opioid use. Conversely, the *gSL-only* strategy resulted in nearly 2 times the number of those who Relapsed or Reused (Retained-Reused AND Relapsed combined) compared to the *PRO1→VIV* strategy. [Appendix A.6]

1.3.2.3 Sensitivity Analysis

Monte Carlo probabilistic sensitivity analysis found that two strategies were most cost-effective: the *PRO1→VIV* strategy, and the "Probuphine → generic SL-Buprenorphine/Naloxone" (*PRO1→ gSL*) strategy. When the 10 strategies not containing a second cycle of Probuphine (2 ERMOUD single-drug strategies, 7 sequentially transitioning ERMOUD multi-drug-in-sequence strategies, and our comparator *gSL-only* strategy) were analyzed, the ERMOUD strategies were found to be more cost-effective over the daily formulation *gSL-only* strategy comparator at around the $15,000 WTP range. This decreased to around $7,000 WTP threshold when only the

undominated strategies (and predominate strategies from the Monte Carlo Sensitivity Analysis) were reanalyzed. After either of these thresholds, the *PRO1→VIV* strategy was consistently the preferred cost-effective drug regimen. In the 6-month time-horizon, the *PRO1→VIV* strategy was found to be the most cost-effective treatment strategy 51.9% of the time, compared to the *PRO1→ gSL* strategy, which was found to be the most cost-effective treatment strategy 46.3% of the time, with 5,000 Monte Carlo trials, at a WTP of $50,000. [Appendix A.4]

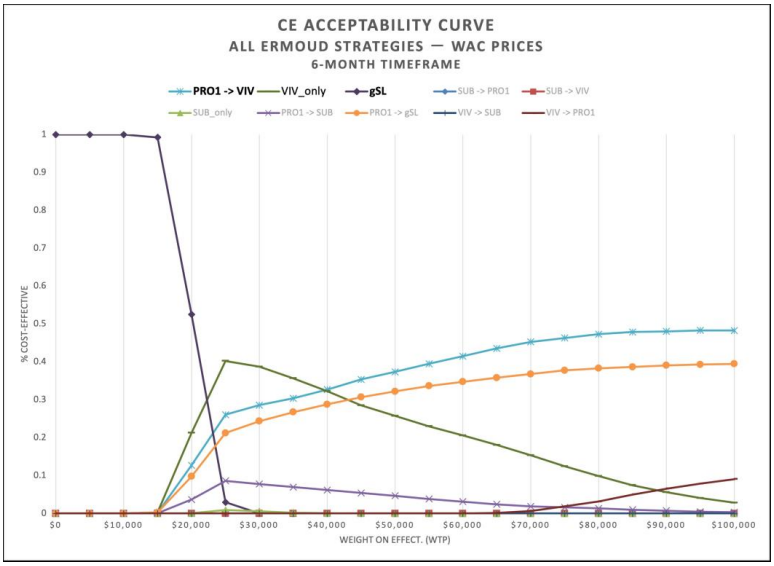


Figure 1.5 Monte Carlo Acceptability Curve (6-month timeframe)

Comparing these two strategies directly by incremental cost-effectiveness scatterplot resulted in the *PRO1→ gSL* strategy being either superior, or had both a higher cost and effectiveness, with an ICER less than $50,000, 46.3% of the time. [Appendix A.2] Further examination into the individual variable uncertainties of these two strategies with one-way sensitivity analysis, found that the model was only sensitive to Vivitrol-related parameters, led mostly by the probability of passing the induction period before entering into Vivitrol treatment, followed by the probability of discontinuing Vivitrol treatment, and the probability of using opioids while being treated with Vivitrol. [Appendix A.5]

1.3.3 Longer than 6-Months' Time-Horizon

1.3.3.1 Undominated Strategies & ICERs

The 1-year and longer (1-year, 18-months, and 2-years) time-horizons resulted in the same undominated strategies. Along with the *gSL-only* strategy, the next most cost-effective was the *PRO1→ gSL* strategy, followed by the "Vivitrol → Probuphine *(1-cycle)*" and the "Vivitrol → Probuphine *(2-cycles)*" (*VIV→PRO1* and *VIV→PRO2*). Only the *PRO1→gSL* treatment strategy had an ICER below $50,000 (ICERs = $9,688$_{1\text{-year}}$ - $3,884$_{2\text{-year}}$) when compared together with the other 13 strategies to the *gSL-only* strategy. [Table 1.6]

1.3.3.2 Health State Tracings & Comparisons

The *PRO1→ gSL* strategy resulted in much higher proportions of those who abstained from illicit use of opioids while in treatment (Retained-Abstained) compared to the *gSL-only* strategy, increasing from 5.1 times more in the 1-year time-horizon, to 13.2 times more in the 2-year time-horizon.

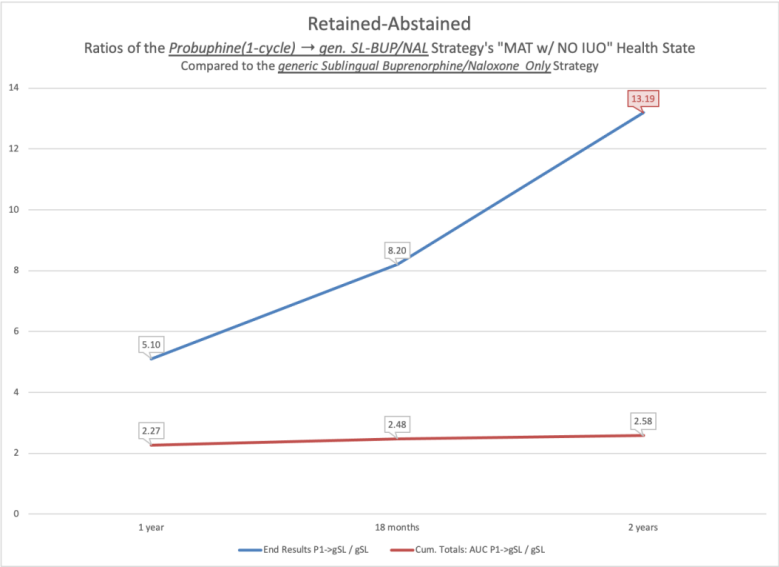


Figure 1.6 Retained-Abstained Health State Proportions Comparison

Conversely, the proportion of the cohort who reused illicit opioids while in treatment rose in the *gSL-only* strategy compared to the *PRO1→ gSL* strategy, from 3.1 times more in the 1-year time-horizon, to 5 times more in the 2-year time-horizon. Those leaving treatment abstinent of illicit opioid use (Remission) was higher in the *gSL-only* strategy, but not nearly as high as the *PRO1→VIV* strategy compared to the *gSL-only* strategy in the 6-month time-horizon, and decreased over time, from 1.5 times higher than the *PRO1→ gSL* strategy in the 1-year time-horizon, to close to even in the 2-year time-horizon. Similarly, those leaving treatment with illicit opioid use (Relapsed) and those Dead were higher in the *gSL-only* strategy compared to the *PRO1→ gSL* strategy, as they were compared to the *PRO1→VIV* in the 6-month time-horizon. However, these differences lowered over time, where those who Relapsed in the *gSL-only* strategy decreased from 1.4 times more compared to the *PRO1→ gSL* strategy in the 1-year time-horizon, to 1.1 times more; and mortality decreased from 2.1 times higher in the 1-year time-horizon, to 1.4 times higher in the 2-year time-horizon. Again, as we saw in the 6-month time-horizon, the ERMOUD-containing strategy (the *PRO1→ gSL* strategy), had higher overall abstinence rates both in and out of treatment (Retained-Abstained AND Remission combined) throughout the 1-year and longer time-horizons, ranging from 1.4 times higher in the 1-year time-horizon to 1.3 times higher in the 2-year time-horizon compared to the *gSL-only* strategy. Also, the overall illicit use of opioids (Retained-Reused AND Relapsed combined) was higher in the *gSL-only* strategy compared to the *PRO1→ gSL* strategy, ranging from 1.6 times higher in the 1-year time-horizon, to 1.3 times higher in the 2-year time-horizon. [Appendix A.6]

1.3.3.3 Sensitivity Analysis

Probabilistic Sensitivity Analysis using the Monte Carol method identified two strategies that were most cost-effective: the *PRO1→ gSL* strategy and the *VIV→PRO1* strategy. When all

15 strategies were analyzed (2 ERMOUD single-drug strategies, 12 sequentially transitioning ERMOUD multi-drug-in-sequence strategies, and our comparator *gSL-only* strategy), ERMOUD strategies were found to be more cost-effective over the daily formulation *gSL-only* strategy comparator at around the $3,000 WTP range in the 1-year time-horizon, falling to around the $2,500 WTP range in the 2-year time-horizon. This was similar when only the undominated strategies (and predominate strategies from the Monte Carlo Sensitivity Analysis) were reanalyzed. After either of these thresholds, the *PRO1→ gSL* strategy was largely the preferred cost-effective drug regimen when the WTP was less than around $63,000 in the 1-year time-horizon, falling to less than around $49,000 in the 2-year time-horizon. Above these thresholds the *VIV→PRO1* strategy was found most cost-effective, meaning that in the 2-year time-horizon, with a WTP of $50,000, the *VIV→PRO1* strategy was preferred. [Appendix A.3] The *PRO1→ gSL* strategy was most cost-effective treatment strategy $55.0\%_{\text{1-year}}$, $56.2\%_{\text{18-months}}$, and $45.9\%_{\text{2-year}}$ of the time, compared to the *VIV→PRO1* strategy, which was most cost-effective treatment strategy $28.9\%_{\text{1-year}}$, $41.7\%_{\text{18-month}}$, and $52.4\%_{\text{2-year}}$ of the time in their respective time-horizons, with 5,000 Monte Carlo trials, at a WTP of $50,000. [Appendix A.4]

Direct comparison of these two strategies by Incremental Cost-Effectiveness Scatterplots showed that the *VIV→PRO1* strategy was either inferior, less effective, or had an ICER more than $50,000, 63.6% and 57.8% of the time in the 1-year and 18-month time-horizons respectively, but was either superior, or had both a higher cost and effectiveness, with an ICER less than $50,000, 53.3% of the time in the 2-year time-horizon. One-way sensitivity analysis used for Tornado Diagrams showed that results of the model in all tested time-horizons longer than 6-months were most sensitive to the same top 3 variables, starting with Vivitrol discontinuation rates, Probuphine

induction success rates, and Vivitrol relapse rates, followed by, in different orders, the induction success rates of Vivitrol and generic Sublingual-Buprenorphine/Naloxone. [Appendix A.5]

Table 1.7 One-Way Sensitivity Analysis Tornado Diagram Variable Comparison

6-months	1-year	18-months	2-year
"Probuphine → gSL-Bup/Nal" vs. "Probuphine → Vivitrol"	**Weekly Probability of Leaving Vivitrol Treatment**		
Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	**Weekly Probability of Passing Probuphine Induction and Entering MAT with Probuphine**		
Weekly Probability of Leaving Vivitrol Treatment	**Weekly Probability of Illicitly Using Opioids While on Vivitrol MAT**		
Weekly Probability of Illicitly Using Opioids While on Vivitrol MAT	Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	Weekly Probability of Passing gSL-Bup/Nal Induction and Entering MAT with gSL-Bup/Nal	
	Weekly Probability of Passing gSL-Bup/Nal Induction and Entering MAT with gSL-Bup/Nal	Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	
	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT	Weekly Probability of Discontinuing gSL-Bup/Nal following Probuphine Explantation	
	Weekly Probability of Discontinuing gSL-Bup/Nal following Probuphine Explantation	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT
	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT
	Weekly Probability of Dying While on Vivitrol MAT	Weekly Probability of Discontinuing Probuphine Treatment	
	Weekly Probability of Discontinuing Probuphine Treatment	Weekly Probability of Dying While on Vivitrol MAT	
		Weekly Probability of Dying After Probuphine MAT with NO Illicit Use of Opioids	

1.4 Discussion

Understanding of opioid use disorders and the opioid epidemic continues to develop, as do approaches to treatment and new pharmaceutical formulations. Evidence of greater treatment success with longer MOUD retention lengthen the expected treatment timeline as perceptions of OUD changes to a chronic medical condition. In this view, it is inevitable that patients will be treated with multiple MOUD regimens, or receive the same ones multiple times. Thus, it is important to expand the research and cost-effectiveness analyses to include these treatment strategies, in order to further inform clinical guidance.

Including these new treatment strategies, with different combinations in sequence of available ERMOUDs and daily administered buprenorphine, we found that two multi-drug-in-sequence treatment strategies performed better than all others, including the single-drug ERMOUD treatment strategies. These were the *PRO1→VIV* strategy in the 6-month time-horizon, and the *PRO1→ gSL* strategy in longer time-horizons.

In short term treatment, there is a 3.3-times higher probability of relapse (leaving treatment with IUO), and a 2.8-times higher probability of death, after 6-months with daily buprenorphine treatment compared to the *PRO1→VIV* strategy. In longer term treatment, there is a 5-times$_{(1\text{-}year)}$ - 13-times$_{(2\text{-}years)}$ higher probability of treatment retention without IUO with the *PRO1→ gSL* strategy compared to daily buprenorphine alone (the *gSL-only* strategy). Conversely, there is a 3-times$_{(1\text{-}year)}$ – 5-times$_{(2\text{-}years)}$ higher probability of IUO in treatment, a higher probability of relapse, and over 2-times$_{(1\text{-}year)}$ higher probability of death with daily buprenorphine compared to the *PRO1→ gSL* treatment strategy. Although there is almost a 1.5-times higher chance of discontinuing daily buprenorphine treatment without IUO after 1 year of treatment, this evens out to nearly even odds after 2-years compared to the *PRO1→ gSL* strategy. In general, daily

buprenorphine treatment, in comparison, was associated with lower retention, higher relapse in and out of treatment, higher mortality, and only slightly higher in remission.

All 14 strategies when compared individually and only to the *gSL-only* strategy as a common baseline were considered cost-effective with ICERs well below a WTP of $50,000, and became increasingly more cost-effective the longer the time-horizon. The *SUB→VIV* (Sublocade switching to Vivitrol upon discontinuation due to illicit opioid use in the induction phase or first weeks of treatment) treatment strategy, our least cost-effective and dominated strategy, had an ICER of $34,651.16 compared to the *gSL-only* strategy with a time-horizon of 6-months, to the *PRO1→ gSL* strategy, our most cost-effective and undominated strategy, which had an ICER of $3,883.63 in the 2-year time-horizon.

Our model only considered direct drug administration costs, and WAC drug prices, as they are a widely-used publicly available benchmark, and represent the drug price ceiling, or out-of-pocket cost expected. Actual drug costs are a variable and opaque, determined by a complex drug supply and payment chain, which is moving payments and price benchmarks closer to actual pharmacy acquisition costs,[12] inclusive of rebates, discounts and lowered negotiated prices. Therefore, we expect that the accurate drug prices paid either by private-insurance, or for CMS beneficiaries are lower than modeled here, resulting in an even greater cost-effectiveness of ERMOUDs, and in particular the undominated multi-drug-in-sequence treatment strategies identified herein.

Aside from the cost-effectiveness measures, there are other significant benefits not accounted for in our model. ERMOUDs lessen the burden and constraints of daily adherence to other MOUD formulations, improving treatment retention, and thus potentially improving long term remission. They also reduce visits to providers, decreasing time spent away from work,

home, and school, transportation time and costs. This is an especially critical feature during the COVID-19 pandemic, where access to healthcare is limited by shutdowns, quarantines, and social distancing, leading to a dramatic increase in opioid-related overdoses and an exacerbated opioid epidemic.[13] Consequently it lessens the burden on an already stressed healthcare system and providers.[8] These extended-release formulations have no risk for diversion, unintended use for those they were not prescribed, or potential for accidental and fatal poisoning in children which currently occurs with daily MOUD formulations,[14] especially now with household members spending more time at home.

There were some important limitations in both our model inputs and design. Since there is no single source of clinical evidence for drug efficacy, model inputs for efficacy and attrition were cited from the latest research or most well-known studies, and gathered from the same sources as were used in the ICER_*Report* on ERMOUDs.[7] Nevertheless, the individual research study sources were limited by variations in study design, populations, measures of success, duration, and study induction. One important drawback and difference between the drugs in our model is that Vivitrol initiation requires an induction period of complete abstinence. Our model accommodated for this by incorporating a separate induction phase health state, as both of the other drugs also had some form of initiation criteria prior to treatment entry. We also chose weekly cycles for our model, as the induction period was shorter than the other health states' periods, and consequently adjusted our model inputs to weekly figures, except for Probuphine attrition, which remained at 6-month intervals, as it is an implant, and there are no reports in the literature of premature explantation. The health utility estimates used were not specific to each treatment or strategy, and as already mentioned, we acknowledge that the costs used in the model do not necessarily reflect the actual cost of drugs, nor did we include other important indirect medical costs, as we chose to

include the most stable and standard figures available. We further realize that there are significant issues with generalizability, which not only carry through from the sources used, but also by not accounting for individualization in the model construction, including demographic differences, opioid use patterns and preferences, and patient use and prior treatment history.

1.5 Conclusion

Extended-release formulations of MOUD drugs, when used in a multi-drug-in-sequence combination treatment strategy, prove more cost-effective than single-drug ERMOUD treatment strategies, and are a cost-effective alternative to daily administration MOUD regimens, with significant additional benefits, especially during the COVID-19 pandemic. Further research should include readmissions and switching MOUD treatments matching more real-world clinical experiences, using newer efficacy measures as the research develops, and more accurate pricing data as it becomes available.

2.0 Comparing Different Drug Pricing Schedules in Cost-Effectiveness Analyses of Extended-Release Medications for Opioid Use Disorder: Including Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

2.1 Introduction

Extended-Release Medications for Opioid Use Disorder (ERMOUDs) are used to combat the ongoing US opioid epidemic, lending unique benefits over existing Medications for Opioid Use Disorders (MOUD) options, especially during the COVID pandemic. Despite reducing the burden and constraints of daily MOUD formulations, increasing treatment adherence and retention, and improving long term remission, the use and dissemination of extended-release buprenorphine formulations, in particular, have been comparatively scant.

There are three FDA approved ERMOUDs currently available in the US. Probuphine, a six-month subdermal implant, and Sublocade, a once-monthly subcutaneous depot injection, are both formulations of buprenorphine, an opioid agonist/antagonist. Vivitrol, a once-monthly subcutaneous depot injection, is a formulation of naltrexone, a full opioid antagonist. Medicaid paid for nearly 30-times more prescriptions for buprenorphine than naltrexone, of which only 0.06% were extended-release formulations; 93.7% of naltrexone prescriptions were extended-release in 2018.[15] Extended-release buprenorphine use was similarly scant for those covered by commercial health insurance, with only 0.2% and 0.01% of all buprenorphine prescriptions being for Sublocade and Probuphine, respectively.[16] Vivitrol's market penetration may be partially due to earlier availability, or because of its lower cost and higher rebates and discounts.

Drug pricing is a complex process involving multiple stakeholders, distribution systems, governmental regulations, and confidential negotiations. Generally, drug manufacturers sell to drug wholesalers who then sell to pharmacies that dispense the drugs. Payments are negotiated back up the chain based on the Wholesale Acquisition Cost (WAC), which is publicly available, whereas the negotiated prices are not. Medicaid programs, which finance most MOUD (approximately 55%[17]), reimburses pharmacies for drugs based on the lowest of either the Actual Acquisition Cost (AAC; Medicaid's determination of pharmacies' actual price paid for the drug), the Federal Upper Limit (FUL; the federal reimbursement limit for some generic drugs), or the Maximum Allowable Cost (MAC; a state's reimbursement limit in addition to FUL).

In exchange for Medicaid drug coverage, a manufacturer agrees to pay a rebate to the state Medicaid agency, which in turn shares a portion with the Centers for Medicare & Medicaid Services (CMS). This arrangement, the Medicaid Drug Rebate Program (MDRP), established by the Omnibus Reconciliation Act of 1990, has greatly reduced drug prices for Medicaid. In 2018, Medicaid spent $60 billion on drugs, and received $36 billion in drug manufacturer's rebates, resulting in 60% savings.[18]

This significant savings to Medicaid was not accounted for by previous economic models used to evaluate ERMOUDs. In particular, the cost-effectiveness analysis of ERMOUDs conducted by the Institute for Clinical and Economic Review,[7] which included net drug prices as reported by the drug manufacturers, concluded that ERMOUDs provide "low value for the money."[8] After finding that the Medicaid rebate-adjusted prices for these drugs studied were significantly lower than accounted for in the models, the Urban Institute asserted that the cost-effectiveness of ERMOUDs could potentially be better than previously determined.[15]

Our study builds upon our previous research of different ERMOUD treatment strategies, to test this assertion and reevaluate the cost-effectiveness of ERMOUDs, utilizing the Medicaid rebate-adjusted prices, and compare them to both the drug manufacturer's net price as used in the ICER Study, and to the WAC benchmark price. Clinically this roughly translates to reassessing the value of ERMOUDs for Medicaid beneficiaries, who are the majority of those treated for opioid-related abuse and misuse, compared to those in treatment with private insurance, represented by the drug manufacturer's net price, and those out-of-pocket paying patients, characterized by WAC prices.

2.2 Methods

We expanded our model from our previous study, *"Cost-Effectiveness of Extended-Release Medications for Opioid Use Disorder Treatment Strategies: Single-Drug and Multi-Drug-in-Sequence Regimens,"* by triplicating it with 2 additional arms, each using a separate drug pricing schedule. One arm of the model applied DMN prices, another MRA prices, and the third, our prior research model, with WAC prices. Each arm comprised 15 individual Markov models of different drug treatment regimen strategies containing extended-release medications for opioid use disorder (ERMOUD). These included 3 single-drug strategies and 12 multi-drug-in-sequence strategies that allowed switching to another drug and readmission upon discontinuation or attrition due to illicit opioid use. [Figure 2.1]

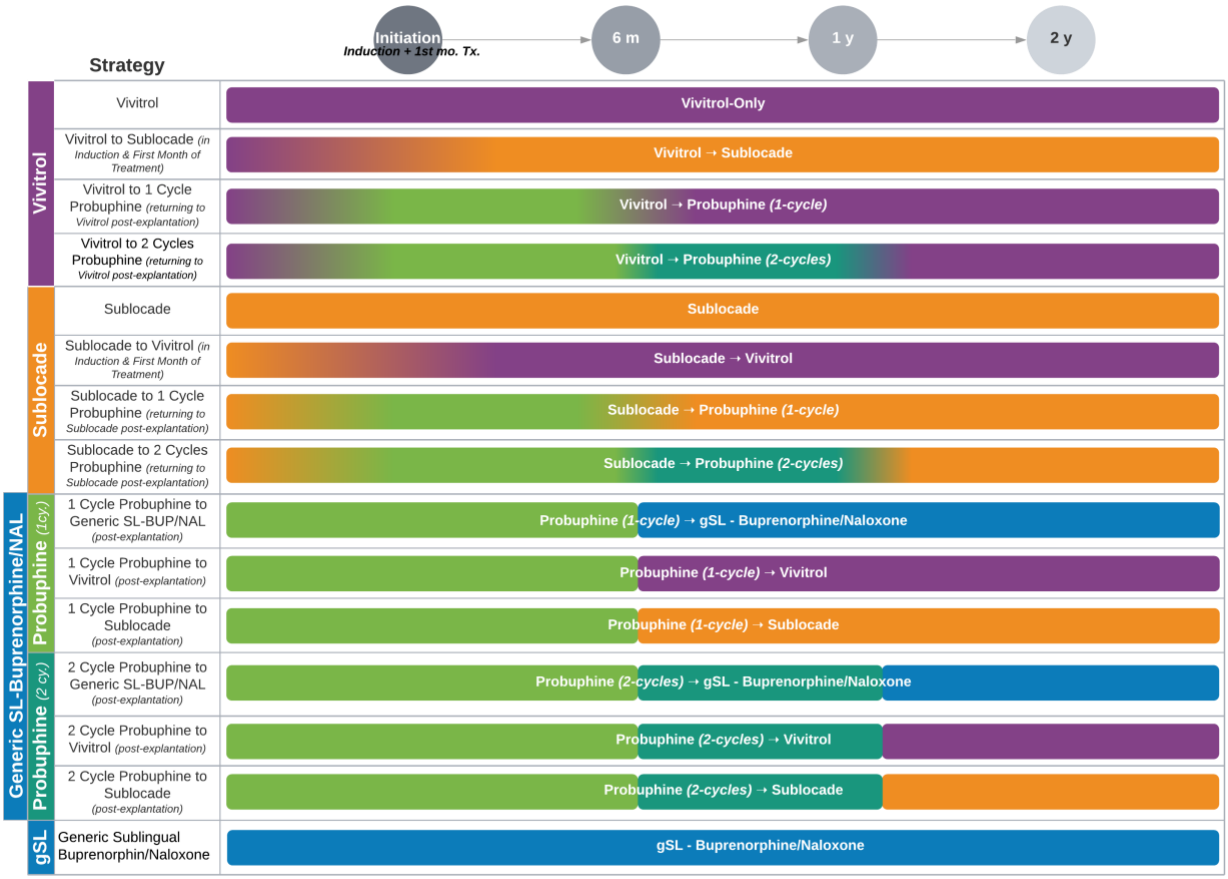


Figure 2.1 Tested Treatment Strategies for Each Pricing Schedule

Model cycle length was one week, and the model was run for 4 separate time-horizons: 6-months, 1-year, 18-months, and 2-years. Our model took a health care perspective, and was informed by, and populated with measures of drug efficacy and treatment attrition [Table 2.2] gathered from key clinical trials and relevant past economic models. [Table 2.1] Health utilities were sourced from the published literature, including a study that employed a cross-sectional online US survey. [Table 2.3]

Table 2.1 Key Clinical Trials

Drug	Trial	Study Design	Weeks	Detoxification/ Induction Period	Time of Randomization	Outcomes
Sublocade	Trial 13- 0001	Phase III RCT	24	**Detoxification**: none **Induction**: run-in induction phase with SL bup/nal film followed by open-label phase with 8 to 24 mg doses of bup/nal for four to 11 days	After induction	• Combination of urine samples and self-report used to assess abstinence • Outcome measured over 24 weeks
Probuphine	Rosenthal 2016	Phase III Non-inferiority	24	**Detoxification**: none **Induction**: stable dose of 8 mg/day or less of sublingual buprenorphine received for at least 24 weeks	After induction	• Urine samples and self-report used to assess abstinence • Outcome assessed over 24 weeks
Vivitrol	X-BOT	Phase IV		**Detoxification**: yes, protocols and length of time varied by site	Before induction	• Abstinence not reported • Time to relapse event reported
	Tanum 2017	Phase III RCT Non-inferiority	12	**Detoxification**: yes	After detoxification	• Urine samples used to assess abstinence • Outcome measured over 12 weeks

Table 2.2 Measurements of Efficacy

Drug Name	Trial	Induced	Abstinence	Attrition
Vivitrol	Lee (X:BOT)	72.08%	51.96%	52.94%
Sublocade*	Haight (Trial 13-0001)	60.84%	12.31%	37.13%
Probuphine	Rosenthal (PRO-814)	89.10%	80.46%	6.90%
gSL-Bup/Nal	Fudala (2003)	71.62%	53.00%	44.70%

*Statistics used from this study reflect individual's 100% abstinence, instead of participant's mean percentage abstinence, to match outcomes of the other two studies

Table 2.3 Health Utilities

Health Utilities	Vivitrol	Sublocade	Probuphine
Induction	0.660	0.660	0.766÷
MAT w/o IUO	0.766	0.766	0.766
MAT w/ IUO*	0.660	0.660	0.660
OFF MAT w/o IUO	0.852	0.852	0.852
OFF MAT w/ IUO**	0.635	0.635	0.635
Death	0.000	0.000	0.000

**Combination of Prescription Opioid User & Intravenous Drug User Health Utilities: 0.700 & 0.618 at 50.7%/49.3% (Prescription/IVDU)*

***Combination of Prescription Opioid User and Intravenous Drug User Health Utilities: 0.694 & 0.574 at 50.7%/49.3% (Prescription/IVDU)*

÷Higher than other 2 Induction Utilities due to all cohort assumed to enter already on MAT (SL Buprenorphine) and clinically stable/abstinent

Each Markov Model has 6 health states, with the cohort entering the model in the Induction Health State. [Figure 2.2] There are 4 health states denoting illicit opioid use or abstinence both

in and out of treatment, and an absorbing death health state. Readmission or Switching to another drug treatment is allowed from the "Retained-Reused" (in treatment with illicit use of opioids) Health State in some tested strategies and returns to the Induction Health State. Readmission and switching drug treatments was permitted in the initiation (induction period and first weeks of treatment). Specifically, the single-drug treatment strategies did not allow for any readmission, whereas the multi-drug-in-sequence treatment strategies allowed for the minimum readmission windows for both the induction and treatment phases to permit transfer to another drug regimen upon discontinuation secondary to Illicit Use of Opioids.

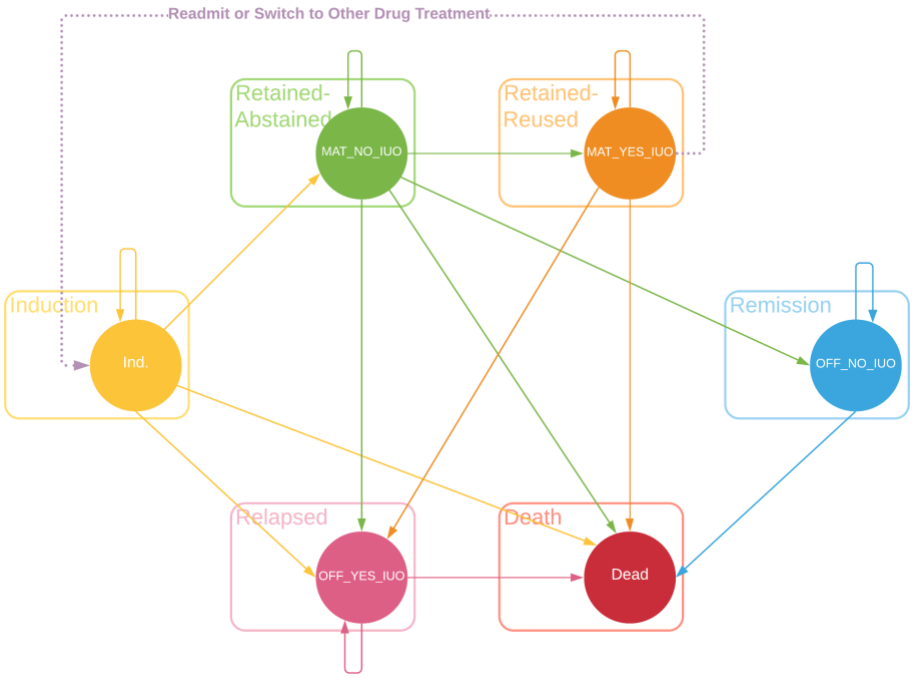


Figure 2.2 Markov Model Map

For this study, this model was triplicated to compare three different pricing schedules of the ERMOUDs tested, keeping drug administration costs and all other inputs unchanged. The model arm containing WAC prices, the highest drug costs of the three models, represented out-of-pocket payers. The WAC pricing schedule is an important publicly-available benchmark price

from which other lower prices are negotiated. The other model arm containing DMN prices, as reported in the Institute for Clinical and Economic Review's Report on ERMOUDs,[7] were sourced from the 2018 Federal Supply Schedule (FSS), or from the drug company (Alkermes) directly for Vivitrol. These prices represent those commercially insured. The third model was populated with Medicaid Rebate-Adjusted (MRA) prices, as reported in the Urban Institute's Study on Medicaid and ERMOUDs.

The Urban Institute determined MRA prices by analyzing Medicaid State Drug Utilization Data from 2011 to 2018 to track prescriptions of ERMOUDs, their unit price, and the Medicaid spending after accounting for federally mandated drug manufacturer's rebates.[19] They found that Vivitrol provided the greatest rebate and price reduction by more than 51%, from $1,206 to $589. This was followed by Sublocade with a 25% price reduction ($1,522 to $1,147), and Probuphine with a 23% price reduction ($2,650 to $2,038).[15] MRA prices were the lowest of the three in our study, and importantly relevant as they closest approximate real-world drug expenditures for the majority of those receiving MOUD.[15] [Figure 2.3]

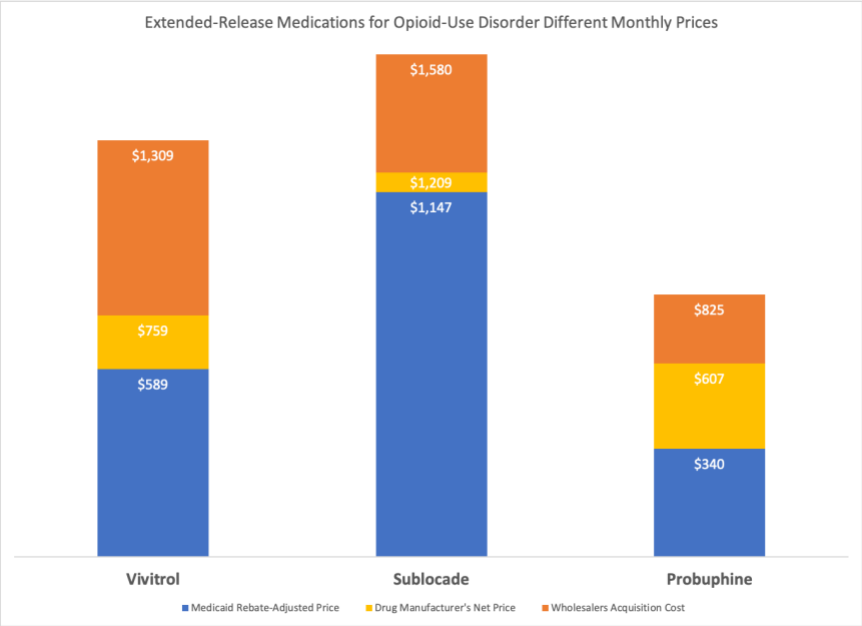


Figure 2.3 Drug Price Comparison

A cost-effectiveness analysis was run to determine the undominated strategies for all three pricing schedules, in each chosen time-horizon, producing cost-effectiveness frontier graphs with corresponding incremental cost-effectiveness ratios, at a Willingness-to-Pay (WTP) of $50,000. [Appendix B.2] All 15 drug treatment regimen strategies were included in the 1-year and longer time-horizons, and 10 strategies (excluding the strategies that included a second Probuphine implant) were included in the 6-month time-horizon. The undominated strategies' Markov Models were individually run to evaluate the cohort's movement through the health states in all time-horizons. The proportion of the cohort in each health state both at the end of the time-horizon, as well as cumulative time spent during the time-horizon (AUC) was then compared amongst the other undominated strategies.

Parameter uncertainty was evaluated by both one-way and probabilistic sensitivity analysis. Model probability and health utilities were varied ±10%, with drug costs varying ±25%, and direct drug administration costs varying ±20%. Probabilistic sensitivity analysis was performed using Monte Carlo simulations over 1,000 trials, with parameters assuming triangular distributions, producing cost-effectiveness scatterplots and acceptability curves. [Appendix B.3] Strategy selection charts at a WTP of $50,000 were constructed and included to compare the optimal treatment strategy for all time-horizons, depending on the pricing schedule. [Appendix B.4] Further investigation of parameter uncertainty and key model economic drivers in the resulting predominant strategies was performed with one-way sensitivity analysis, by way of incremental cost-effectiveness scatterplots and tornado diagrams. [Appendix B.5]

We performed a scenario analysis where all ERMOUDs in the model were afforded the same discount for Vivitrol as estimated in the Urban Institute report, or 48.8% of their pre-rebate price. The FSS price, as of September 2020, was used as the pre-rebate price, which was adjusted

to weekly costs, then discounted. This resulted in model price inputs of: 69.07_{Probuphine}$, 109.40_{Vivitrol}$, and 147.06_{Sublocade}$.

2.3 Results

More treatment strategies were found to be cost-effective at a WTP of $50,000 as the price of drugs decreased. There was only 1 cost-effective treatment strategy per time-horizon with WAC prices, 2 cost-effective treatment strategies in the 2-year time-horizon with DMN prices, and 2 treatment strategies in all time-horizons, except for in the 2-year time-horizon, with MRA prices. [Figure 2.4]

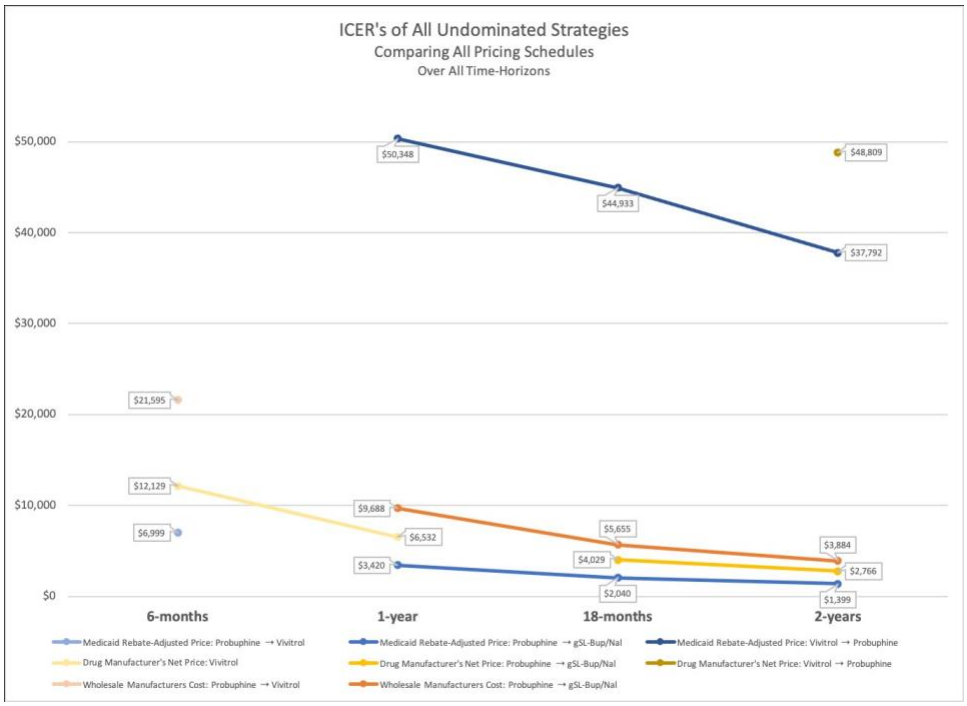


Figure 2.4 Incremental Cost-Effectiveness Ratios

While ICERs differed, the WAC pricing model shared the same dominant treatment strategies as the MRA pricing model, with the "Probuphine *(1-cycle)* → Vivitrol" (*PRO1→VIV*) treatment strategy dominating in the 6-month time-horizon, followed by the "Probuphine → generic SL-Buprenorphine/Naloxone" (*PRO1→ gSL*) strategy dominating in subsequent time-horizons. The DMN price schedule model resulted in the "Vivitrol-Only" (*VIV-only*) treatment strategy dominating in the 6-month and 1-year time-horizon, similarly followed by the

"Probuphine → generic SL-Buprenorphine/Naloxone" (*PRO1→ gSL*) strategy dominating in the later time-horizons. [Table 2.4]

Table 2.4 Prevailing Treatment Strategies by Drug Pricing Schedule

by ICER	6-months	1-year	18-months	2-years
Wholesale Acquisition Cost (WAC)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		
Drug Manufacturer's Net (DMN)	Vivitrol-Only		Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone	
Medicaid Rebate-Adjusted (MRA)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		

2.3.1 6-Month Time-Horizon Results

2.3.1.1 Undominated Strategies & ICERs

There were 2 undominated treatment strategies per pricing schedule (not including the comparator "generic Sublingual-Buprenorphine/Naloxone" treatment strategy (*gSL-only*), and only 1 strategy per pricing schedule under a WTP of $50,000 in the 6-month time-horizon. The MRA and WAC pricing schedule models were in concordance, finding the *PRO1→VIV* strategy cost-effective with ICERs of $6,999 and $21,595 respectively, followed by the reverse, "Vivitrol → Probuphine *(1-cycle)*" (*VIV→PRO1*) strategy. The DMN pricing schedule model found the *VIV-only* strategy cost-effective with an ICER of $12,129, also followed by the *VIV→PRO1* strategy. [Table 2.4]

Table 2.5 Incremental Cost-Effectiveness Ratios (6-month time-horizon)

6-months	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
Medicaid Rebate-Adjusted	*gSL-only*	$788		0.19278		
	PRO1→VIV	$1,945	$1,157	0.35808	0.16530	$6,999
	VIV→PRO1	$2,346	$401	0.35974	0.00166	$241,737
Drug Manufact. Net Price	*gSL-only*	$788		0.19278		
	VIV-only	$2,672	$1,884	0.34809	0.15531	$12,129
	VIV→PRO1	$3,357	$685	0.35974	0.01166	$58,795
Wholesale Acquisition Cost	*gSL-only*	$788		0.19278		
	PRO1→VIV	$4,358	$3,570	0.35808	0.16530	$21,595
	VIV→PRO1	$5,138	$780	0.35974	0.00166	$470,387

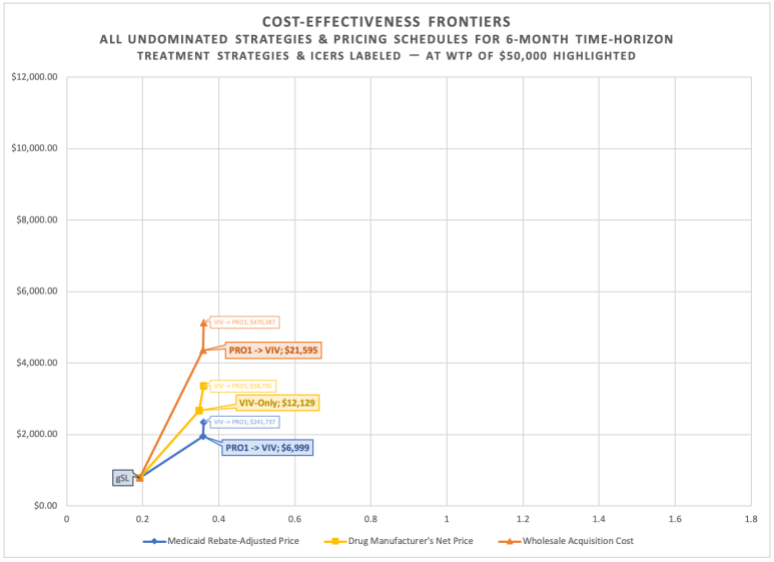


Figure 2.5 Cost-Effectiveness Frontiers (6-month time-horizon)

2.3.1.2 Sensitivity Analysis

Monte Carlo probabilistic sensitivity analysis found that two strategies were most cost-effective: the *PRO1→VIV* strategy, and the *VIV-Only* strategy. The Cost-Effectiveness Acceptability Curve of all three pricing schedules shows no overwhelmingly dominant strategy in the 6-month time-horizon. [Appendix B.3] In both the MRA and WAC pricing schedule models, the *PRO1→VIV* strategy was found most cost-effective 50% and 41% of the time out of 1,000 testing iterations, respectively, with at WTP of $50,000. The *VIV-Only* strategy was found most cost-effective in the DMN pricing schedule model 50% of the time. [Appendix B.4] When the Monte Carlo analysis was run including only undominated treatment strategies the selection was clearer, with the *PRO1→VIV* strategy selected 91% and 93% of the time in the WAC and MRA models, and the *VIV-Only* strategy selected 85% of the time.

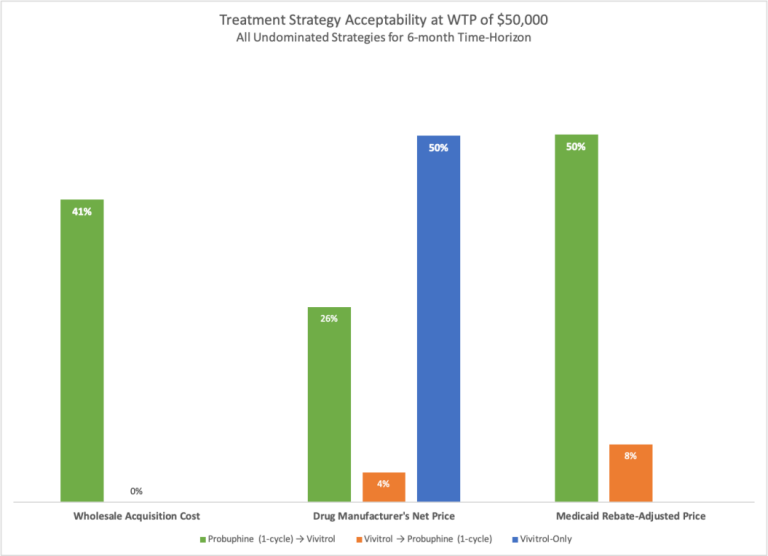


Figure 2.6 Probabilistic Analysis Strategy Selection (6-month time-horizon)

One-way sensitivity analysis comparing the *gSL-Only* strategy to the most cost-effective ERMOUD strategy in each pricing schedule is displayed in Tornado Diagrams showing that all models were most sensitive to the probability of passing the Induction phase of either regimen compared, followed by attrition in the treatment phase. [Appendix B.5]

2.3.1.3 Pricing Schedules Comparison

Comparing the two discounted pricing schedules to the WAC model significantly lowered the ICER cost, as well as changed the optimal treatment strategy selection in the DMN model. Both the MRA and WAC models resulted in the *PRO1→VIV* strategy being the most cost-effective with very different ICERs. While the average drug price difference between the MRA and WAC model being 45% lower, there is a 68% decrease in the ICER of the most optimal treatment strategy between these two pricing schedules. Even though the optimal treatment strategy selection is different between the DMN and MRA models, there is a significant difference between the two most optimal treatment strategies (42% decrease in ICERs). The *PRO1→VIV* treatment strategy

in the MRA pricing schedule was the most cost-effective regimen over all strategies and pricing schedules in the 6-month time-horizon, with an ICER of $6,999 compared to the *gSL-only* strategy.

2.3.2 Longer Than 6-Months' Time-Horizon

2.3.2.1 Undominated Strategies & ICERs

The 1-year and longer (1-year, 18-months, and 2-years) time-horizons, in all pricing schedules, resulted in similar undominated treatment strategies. There were three undominated treatment strategies, not including the comparator. These were the same for all pricing schedules in all time-horizons, with the exception of the DMN model in the 1-year time-horizon. The *PRO1→ gSL* treatment strategy was the most cost-effective overall, except for in the DMN pricing schedule model with a 1-year time-horizon, where the *VIV-only* strategy was found most optimal again, like in the 6-month time-horizon. This was followed by the *VIV→PRO1* and the "Vivitrol → Probuphine *(2-cycle)*" (*VIV→PRO2*) strategy. [Figure 2.7]

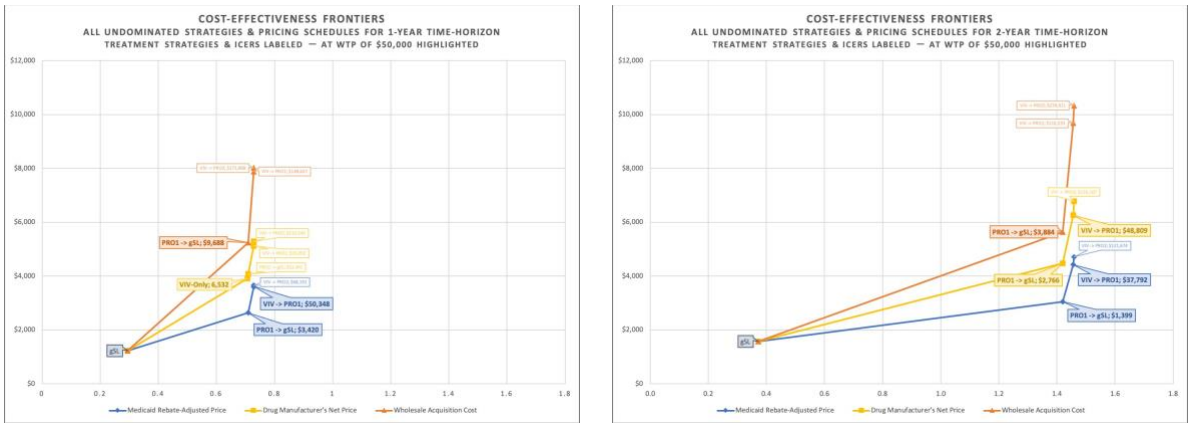


Figure 2.7 Cost-Effectiveness Frontiers (1-year and 2-year time-horizons)

At a WTP of $50,000, there were 2 cost-effective treatment strategies in the MRA model, and only 1 cost-effective treatment strategy in the DMN and WAC models, except for 2 in the DMN model with a 2-year time-horizon. ICERs decreased over time, with the most cost-effective strategy decreasing from $3,420 to $1,399 in the MRA model, $6,532 to $2,766 in the DMN

model, and $9,688 to $3,884 in the WAC model. Overall, the *PRO1→ gSL* treatment strategy in the MRA model was found to be the most cost-effective when compared to the *gSL-only* treatment option, with ICERs of $3,884 (1-year), $2,766 (18-months), and $1,399 (2-year time-horizon). [Tables 2.6 – 2.8]

Table 2.6 Incremental Cost-Effectiveness Ratios (1-year time-horizon)

1-year	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
Medicaid Rebate-Adjusted Price	*gSL-only*	$1,225		0.29400		
	PRO1→gSL	$2,644	$1,419	0.70891	0.41491	$3,420
	VTV→PRO1	$3,603	$959	0.72795	0.01904	$50,348
	VTV→PRO2	$3,655	$52	0.72871	0.00076	$68,191
Drug Manufact. Net Price	*gSL-only*	$1,225		0.29400		
	VTV-only	$3,915	$2,690	0.70586	0.41186	$6,532
	PRO1→gSL	$4,075	$160	0.70891	0.00305	$52,441
	VTV→PRO1	$5,122	$1,047	0.72795	0.01904	$55,002
	VTV→PRO2	$5,283	$161	0.72871	0.00076	$210,243
Wholesale Acquisition Cost	*gSL-only*	$1,225		0.29400		
	PRO1→gSL	$5,245	$4,020	0.70891	0.41491	$9,688
	VTV→PRO1	$7,884	$2,639	0.72795	0.01904	$138,627
	VTV→PRO2	$8,015	$131	0.72871	0.00076	$171,968

Table 2.7 Incremental Cost-Effectiveness Ratios (18-month time-horizon)

18-months	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
Medicaid Rebate-Adjusted Price	*gSL-only*	$1,455		0.34570		
	PRO1→gSL	$2,923	$1,468	1.06511	0.71941	$2,040
	VTV→PRO1	$4,174	$1,251	1.09295	0.02784	$44,933
	VTV→PRO2	$4,378	$204	1.09448	0.00153	$133,519
Drug Manufact. Net Price	*gSL-only*	$1,455		0.34570		
	PRO1→gSL	$4,354	$2,899	1.06511	0.71941	$4,029
	VTV→PRO1	$5,912	$1,558	1.09295	0.02784	$55,970
	VTV→PRO2	$6,308	$396	1.09448	0.00153	$259,076
Wholesale Acquisition Cost	*gSL-only*	$1,455		0.34570		
	PRO1→gSL	$5,523	$4,068	1.06511	0.71941	$5,655
	VTV→PRO1	$9,129	$3,606	1.09295	0.02784	$129,518
	VTV→PRO2	$9,597	$468	1.09448	0.00153	$306,087

Table 2.8 Incremental Cost-Effectiveness Ratio (2-year time-horizon)

2-years	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
Medicaid Rebate-Adjusted Price	*gSL-only*	$1,576		0.37249		
	PRO1→gSL	$3,041	$1,465	1.41935	1.04687	$1,399
	VTV→PRO1	$4,424	$1,383	1.45594	0.03659	$37,792
	VTV→PRO2	$4,714	$290	1.45832	0.00238	$121,674
Drug Manufact. Net Price	*gSL-only*	$1,576		0.37249		
	PRO1→gSL	$4,472	$2,896	1.41935	1.04687	$2,766
	VTV→PRO1	$6,258	$1,786	1.45594	0.03658	$48,809
	VTV→PRO2	$6,772	$514	1.45832	0.00238	$216,057
Wholesale Acquisition Cost	*gSL-only*	$1,576		0.37249		
	PRO1→gSL	$5,642	$4,066	1.41935	1.04687	$3,884
	VTV→PRO1	$9,675	$4,033	1.45594	0.03658	$110,233
	VTV→PRO2	$10,329	$655	1.45832	0.00238	$274,911

2.3.2.2 Sensitivity Analysis

Monte Carlo probabilistic sensitivity analysis showed that the *PRO1→ gSL* treatment strategy was the most cost-effective over all pricing schedules and in all time-horizons, except for in the MRA model with a 2-year time-horizon, where the *VIV→PRO1* treatment strategy was most cost-effective. [Appendix B.1] The WAC model, which only had one treatment strategy under the WTP in all three longer time-horizons, selected the *PRO1→ gSL* treatment strategy the vast majority of the time, ranging from $92\%_{\text{1-year}}$ to $98\%_{\text{2-years}}$ of the time over 1,000 iterations. When only undominated strategies were analyzed, the results were similar, around 98%. The DMN model selected the *PRO1→ gSL* treatment strategy the majority of the time, ranging from 57%-71% of the time, and 56%-67% when undominated strategies only were analyzed. The MRA model, however, had two strategies that switched preference, where the *PRO1→ gSL* treatment strategy declined in preference from $52\%_{\text{1-year}}$ to $41\%_{\text{2-years}}$, and the *VIV→PRO1* treatment strategy increased in preference from $32\%_{\text{1-year}}$ to $57\%_{\text{2-years}}$ of the time when tested over 1,000 iterations. [Appendix B.3] Similar results were found when undominated strategies only were analyzed.

One-way sensitivity analysis revealed that in all 3 pricing schedules, and over 3 time-horizons (1-year, 18-months, and 2-years), the models were most sensitive to the probability of passing the Probuphine Induction phase. This variable was the top result in 7 of the 9 Tornado Diagrams (3 pricing models × 3 time-horizons), occupying 78% of the number 1 spots, or 26% of the top 3 most sensitive variables. This combined with additional variables responsible for other drug's Induction Phase Passing Probability made up 78% of the top three, followed by Attrition from drug treatment (19%). Therefore, all models in all time-horizons were most sensitive to the probability of passing the Induction Phase, followed by the probability of discontinuing treatment. [Table 2.9]

Table 2.9 One-Way Sensitivity Analysis Tornado Diagram Variable Comparison

	6-month	1-year	18-months	2-years
MRA	Probuphine Induction Success			Probuphine Treatment Retention
	gSL-Only Induction Success	Success Transfer to gSL after Probuphine	gSL-Only Induction Success	Vivitrol Treatment Attrition
	gSL-Only Treatment Attrition	gSL-Only Induction Success	Successful Transfer to gSL after Probuphine	Vivitrol Induction Success
DMN	Vivitrol Induction Success		Probuphine Induction Success	
	gSL-Only Induction Success	Vivitrol Treatment Attrition	Successful Transfer to gSL after Probuphine	
	Vivitrol Treatment Attrition	gSL-Only Induction Success	gSL Treatment Attrition after Probuphine	gSL-Only Induction Success
WAC	gSL-Only Induction Success	Probuphine Induction Success		
	Probuphine Induction Success	gSL-Only Induction Success		Successful Transfer to gSL after Probuphine
	gSL-Only Treatment Attrition		Successful Transfer to gSL after Probuphine	gSL Treatment Attrition after Probuphine

2.3.2.3 Pricing Schedules Comparison

Similar to the 6-month time-horizon results, the MRA model was consistently and greatly more cost-effective than the other two models, with ICERs of the most cost-effective treatment strategies in all three time-horizons being approximately half of those in the DMN model, and only about a third of those in the WAC model. Out of all three pricing schedule models and all three time-horizons, the *PRO1→ gSL* treatment strategy in the MRA model over a 2-year time-horizon was found to be the most cost-effective, with an ICER of $1,399, and a Net Monetary Benefit of $67,926. [Table 2.8]

2.3.3 Scenario Analysis

Our scenario analysis, where all ERMOUDs prices in the model were subjected to the same discount as Vivitrol, or 48.8% of their pre-rebate price, resulted in the *PRO1→ gSL* treatment strategy being the most cost-effective in all time-horizons. The *PRO1→ gSL* strategy had lower ICERs than in any other model ($3,269$_{6\text{-months}}$-$764$_{2\text{-years}}$), compared to the *gSL-only* treatment option. At a WTP of $50,000, two additional treatment strategies were found cost-effective:

PRO1→VIV strategy in the 6-month time-horizon (ICER: $14,755) and the *PRO2→VIV* strategy in the 1-year time-horizon (ICER: $41,494). [Table 2.10]

Table 2.10 Scenario Analysis: All ERMOUDs at Vivitrol Discount Rate (48.8%)

Time-Horizon	Undom. Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
6-months	*gSL-only*	$788		0.19278		
	PRO1→gSL	$1,328	$540	0.35803	0.16524	$3,269
	PRO1→VIV	$1,329	$1	0.35808	0.00006	$14,755
	VIV→PRO1	$2,224	$895	0.35974	0.00166	$539,990
1-year	*gSL-only*	$1,225		0.29400		
	PRO1→gSL	$1,979	$754	0.70891	0.41491	$1,817
	PRO2→VIV	$2,632	$653	0.72464	0.01573	$41,494
	VIV→PRO2	$3,410	$779	0.72871	0.00407	$191,233
18-months	*gSL-only*	$1,455		0.34570		
	PRO1→gSL	$2,258	$802	1.06511	0.71941	$1,115
	VIV->PRO2	$4,106	$1,849	1.09448	0.02937	$62,948
2-years	*gSL-Only*	$1,576		0.37249		
	PRO1->gSL	$2,376	$800	1.41935	1.04687	$764
	VIV->PRO1	$4,273	$1,896	1.45594	0.03658	$51,835
	VIV->PRO2	$4,442	$169	1.45832	0.00238	$71,113

2.4 Discussion

Including the estimated drug price discounts and rebates increased the cost-effectiveness and comparable viability of ERMOUD treatment strategies, as expected with lower prices. However, this was not due to a mere cost shift, where we would expect to see similar prevailing cost-effective treatment strategies in all three pricing schedules. Instead, the most cost-effective strategies were different with DMN pricing in the first year, and the same with the WAC and MRA pricing (our most and least expensive pricing schedules), warranting further investigation. [Table 2.4] Additionally, more ERMOUD strategies were found to be cost-effective at a WTP of $50,000, thus increasing the economically practical MOUD clinical options, while better approximating real-world drug costs for the majority of those in treatment.

Drug costs are a complex and contentious issue, made even more confusing by the different pricing schedules used for the same drug by different classes of payers. Different pricing schedules may have their own proprietary formulas and methodologies. While recent legislation has attempted to make costs more transparent,[20] the increasing use of Pharmacy Benefit Managers (PBMs) to administer state's Medicaid contracts through Managed Care Organizations (MCOs) hinders these efforts. Approximately two-thirds of Medicaid beneficiaries receive their care through MCOs, and 40 state Medicaid agencies use MCOs, which are not subject to the same federal pricing rules and regulations. MCOs and PBMs are allowed to independently and confidentially negotiate prices directly with pharmacies, and keep some pricing information, including rebates and discounts, proprietary; thus, many drug prices are not known to state Medicaid agencies.[12]

The greater price rebate and savings of Vivitrol probably contributed to its overwhelming market share of ERMOUD prescriptions, although not solely. Vivitrol's drug manufacturer

Alkermes launched an aggressive marketing strategy that skirted conventional channels, bypassing skeptical healthcare providers and addiction specialists, and targeting public institutions, in particular drug courts, directly.[21] Leveraging political favor on the criminal justice population, Alkermes total revenues grew 656% since Vivitrol's approval in 2010, from $178.3 million in 2010[22] to $1.17 billion in 2019.[23] Vivitrol sales have increased 11% in 2019 from 2018, totaling $335.4 million.

Prescriptions of Vivitrol to Medicaid beneficiaries have likewise risen precipitously, nearly 30-fold from 7,474 prescriptions in 2011, to 216,561 prescriptions in 2018. That is 52-times higher the number of prescriptions for Sublocade in 2018 (4,134 prescriptions), and a staggering 14,437-times higher number than Probuphine in the same year. Since its FDA approval in 2016, Probuphine prescriptions have been covered by Medicaid twice in 2016, 34 times in 2017, and only 15 times in 2018. This discrepancy in prescription volume can be explained somewhat by the difference in Medicaid coverage of ERMOUDs by different state agencies. While Vivitrol is covered by Medicaid in all 50 states and DC, Sublocade and Probuphine were covered in 44 and 39 states including DC, respectively, in 2019. Vivitrol also was on 33 states' Preferred Drug List (PDL), and did not require prior authorization in 38 states, whereas Sublocade was on 17 states' PDL with no prior authorization in 13 states, and Probuphine was on 6 states' PDL with no prior authorization in 10 states. [Figure 2.8]

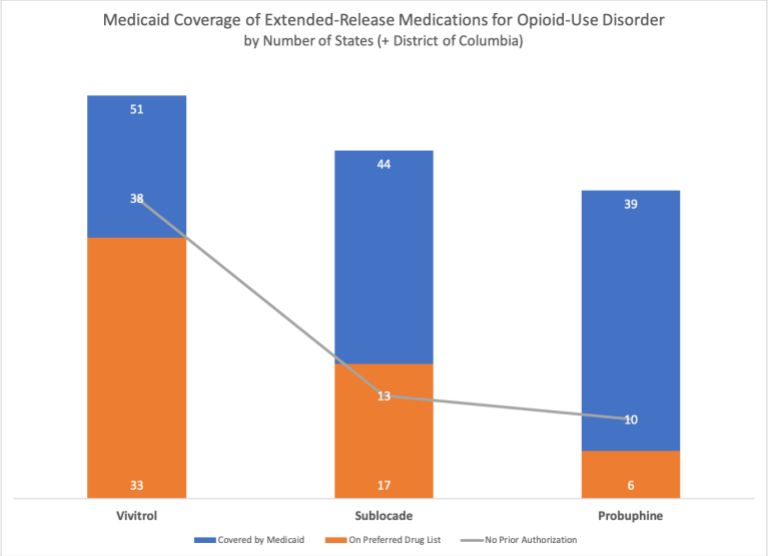


Figure 2.8 Medicaid ERMOUD Coverage

In addition to Medicaid coverage issues, there are other drug access concerns. In accordance with the Drug Addiction Treatment Act of 2000 (DATA 2000), a qualified healthcare provider must be specially trained, and FDA approved to prescribe buprenorphine. Additionally, a healthcare provider must be specially certified to prescribe, insert and remove Probuphine. These stipulations do not apply when prescribing Vivitrol. Probuphine has a unique reimbursement process called the "Buy & Bill" program, whereby the prescribing physician purchases Probuphine, takes ownership *(it is shipped to the physician office directly and must be signed for)* and then collects reimbursement through insurance companies or the patient in a self-pay scenario. It can be returned within 30 days if the patient changes their mind.

In light of the COVID-19 pandemic, it is important to consider the additional benefits that ERMOUDs provide that are not captured by this cost-effectiveness analysis, including easing the burden and constraints attached to daily formulation of medications for opioid-use disorder (MOUD). This improves treatment retention, thus potentially improving long term remission. They can reduce visits to providers, especially in the case of Probuphine. Recently there have been some concessions made in the regulations governing buprenorphine prescribing during

COVID-19 which theoretically could extend the period between patient-physician appointments longer than 1 month *(the duration between Vivitrol and Sublocade injections)*, depending on the technological capabilities of the telemedicine at specific clinics and patients, reimbursement and administrative procedures, and state and local policies. ERMOUDs also have no risk of diversion,[24] possibility of unintended use or accidental exposure and poisoning.[14]

Our model had some important limitations involving the model inputs. As previously mentioned, drug prices, except for the publicly available WAC price, are difficult to confirm. The prices for the DMN model were reported by the drug manufacturer's themselves, and the MRA prices do not specify state discrepancies in prices, fees, or MCO association. The health utility model inputs were not specific to each ERMOUD or treatment strategy. Measurements of efficacy and attrition were not from a single source, and subject to individual study design, measurement, administration, and reporting differences. Measures were taken in our model to mitigate any publication bias by using similar statistics from the cited studies' data, instead of their respective outcome results. For example, our model used complete individual abstinence during the therapeutic intervention as the measurement of efficacy, as opposed to average days abstinent reported in some studies. However, some potential selection bias due to trial participant selection in some studies could artificially increase their reported efficacy, as in the Probuphine study, where enrolled participants were more clinically stable than the other RCTs.

The research studies cited all shared the same 24-week study duration. It is therefore recognized that extrapolating those data over a 2-year time-horizon may not produce reliable results, but exploring longer model duration is important, as OUD is considered a chronic medical condition, requiring long-term, if not life-long, medical care. Furthermore, our longer time-

horizon results were consistently stable, oftentimes resulting in the same treatment strategies carrying over several time-horizons.

We understand that there is a difference between the theoretical cost-effectiveness of our treatment strategies and individual ERMOUD selections, and the practical real-world clinical concerns with implementing favored model strategies through use of some of these medications. Although Sublocade-containing treatment strategies were consistently dominated in all pricing schedules and time-horizons, it may be the most advantageous clinical treatment option for some patients. Conversely, despite Probuphine-containing treatment strategies performing better than other treatment options, due to Probuphine's extra training, added regulations, and unique reimbursement "Buy & Bill" program, it may not be a clinically feasible option for some physicians. Therefore, this cost-effectiveness analysis cannot be used as a sole criterion for clinical guidance, however it can provide evidence necessary to reexamine ERMOUD use and the steps necessary to use them clinically on par with daily formulation MOUD, as they are economically favorable, especially when analyzed with Medicaid Rebate-Adjusted Prices, lending additional benefits and special advantages while we continue to combat the worsening opioid epidemic during the coronavirus pandemic.

2.5 Conclusion

Using Medicaid Rebate-Adjusted Prices when analyzing the cost-effectiveness of ERMOUDs not only closer approximates the actual drug costs paid for the majority of those taking these uniquely beneficial medicines but increases their viability and cost-effective competitiveness when compared to daily formulation MOUDs. By significantly reducing ICERs, these lower prices add more ERMOUD treatment strategy deemed cost-effective at a WTP of $50,000, compared to other pricing schedules tested.

3.0 Comparing Methadone & Buprenorphine Maintenance Treatments with Extended-Release Medications for Opioid Use Disorder: Including Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

3.1 Introduction

The United States remains in an opioid epidemic resulting in millions of Americans with an Opioid-Use Disorder (OUD). OUD is considered a chronic disease, which like other chronic medical conditions, is characterized by cycles of relapse and remission. This often requires longer episodes of continuous treatment, and multiple trials of the same or different treatment strategies. Currently there are 3 drugs approved by the US Food & Drug Administration to treat OUD: Methadone, Buprenorphine, and Naltrexone. Each drug is available in different formulations and is subject to different regulations.

From 1974, with Methadone, until the approval of Vivitrol in 2010, these medications were only available in daily-administered formulations, or daily medications for opioid-use disorder (DMOUD). Since the introduction of Vivitrol, a monthly injection of extended-release naltrexone, two other extended-release medications for opioid-use disorder (ERMOUD) have been approved, both being forms of buprenorphine. Probuphine is a sub-dermal buprenorphine implant lasting 6 months, and Sublocade is a monthly depot injection of buprenorphine.

Prior economic models have analyzed some of these drugs for comparative cost-effectiveness, including Buprenorphine/Naloxone vs. no treatment,[25] Methadone vs. Buprenorphine,[26] Vivitrol vs. Methadone and Buprenorphine,[6] Probuphine vs. sublingual-Buprenorphine/Naloxone,[5] and several ERMOUDs vs. sublingual-Buprenorphine/Naloxone.[27]

However, no cost-effectiveness analysis has compared all these drugs together, nor have any of these models allowed for treatment reentry after relapse to illicit opioid use or transitioning to other treatment strategies (a multi-drug-in-sequence treatment strategy) following treatment discontinuation or attrition.

Our study builds upon our previous research of different ERMOUD treatment strategies, which compared Vivitrol, Buprenorphine, Probuphine, and sublingual-Buprenorphine/Naloxone, by adding DMOUD treatment strategies, including Methadone and Buprenorphine Maintenance Treatment single-drug strategies and their multi-drug-in sequence transition permutations, allowing for treatment reentry and switching to another treatment strategy, as seen in real-world conditions.

3.2 Methods

We expanded the decision analytic model of our previous study, "Cost-Effectiveness of Extended-Release Medications for Opioid Use Disorder Treatment Strategies: Single-Drug and Multi-Drug-in-Sequence Regimens," from 15 to 34 individual Markov Models. [Appendix C.1] These 34 individual Markov Models represent 5 single-drug treatment strategies and 29 multi-drug-in-sequence treatment strategies that allowed switching to another drug and readmission upon discontinuation or attrition due to illicit opioid use. [Figure 3.1] Model cycle length was one week, and the model was run for 4 separate time-horizons: 6-months, 1-year, 18-months, and 2-years. Our model took a health care perspective, and was informed by, and populated with measures of drug efficacy and treatment attrition gathered from key clinical trials and relevant past economic models. [Tables 3.1 & 3.2] Health utilities were sourced from the published literature, including a study that employed a cross-sectional online US survey. [Table 3.3]

Table 3.1 Key Clinical Trials

Drug Name	Trial	Year	Study Design	Duration (in weeks)	Outcomes
Vivitrol	Lee *(X:BOT)*	2018	Phase IV	24	Combination of urine toxicology and self-report used to assess Relapse
Sublocade	Haight *(Trial 13-0001)*	2019	Phase III RCT	24	Combination of urine toxicology and self-report used to assess Abstinence
Probuphine	Rosenthal *(PRO-814)*	2016	Phase III Non-Inferiority	24	Combination of urine toxicology and self-report used to assess Abstinence
Methadone (MMT) **Buprenorphine (BMT)**	Mattick (Cochrane DB of System. Revs.)	2014	Meta-Analysis & Systematic Review	-	-

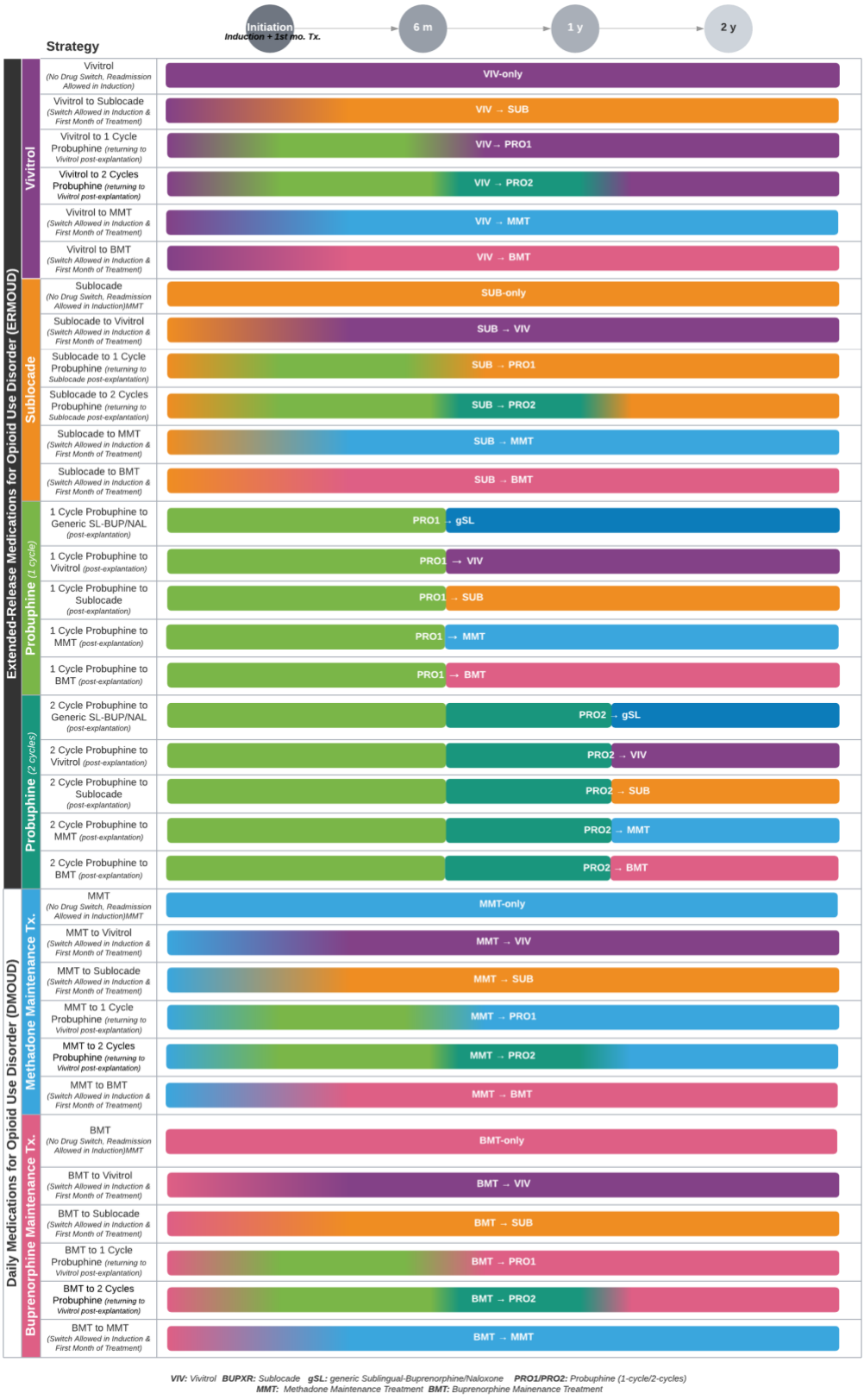


Figure 3.1 Tested Treatment Strategies

Table 3.2 Measurements of Efficacy

Drug Name	Trial	Induced	Abstinence	Attrition
Vivitrol	Lee *(X:BOT)*	72.08%	51.96%	52.94%
Sublocade*	Haight *(Trial 13-0001)*	60.84%	12.31%	37.13%
Probuphine	Rosenthal *(PRO-814)*	89.10%	80.46%	6.90%
gSL-Bup/Nal	Fudala *(2003)*	71.62%	53.00%	44.70%
Methadone	Mattick** *(Cochrane Database of Systematic Reviews)*		63.19%	51.61%
Buprenorphine			57.07%	60.29%

**Statistics used from this study reflect individual's 100% abstinence, instead of participant's mean percentage abstinence, to match outcomes of the other two studies*

***Statistics used from this study are from a meta-analysis, where induction probabilities were not separate*

Table 3.3 Health Utilities

Health Utilities	Vivitrol	Sublocade	Probuphine	MMT	BMT
Induction	0.660	0.660	0.766÷	0.660	0.660
MAT w/o IUO	0.766	0.766	0.766	0.766	0.766
MAT w/ IUO*	0.660	0.660	0.660	0.660	0.660
OFF MAT w/o IUO	0.852	0.852	0.852	0.852	0.852
OFF MAT w/ IUO**	0.635	0.635	0.635	0.635	0.635
Death	0.000	0.000	0.000	0.000	0.000

**Combination of Prescription Opioid User & Intravenous Drug User Health Utilities: 0.700 & 0.618 at 50.7%/49.3% (Prescription/IVDU)*

***Combination of Prescription Opioid User and Intravenous Drug User Health Utilities: 0.694 & 0.574 at 50.7%/49.3% (Prescription/IVDU)*

÷Higher than other 2 Induction Utilities due to all cohort assumed to enter already on MAT (SL Buprenorphine) and clinically stable/abstinent

Each Markov Model has 6 health states, with the cohort entering the model in the Induction Health State. [Figure 3.2] There are 4 health states denoting illicit opioid use or abstinence both in and out of treatment, and an absorbing death health state. Readmission or Switching to another drug treatment is allowed from the "Retained-Reused" (in treatment with illicit use of opioids) Health State in some tested strategies and returns to the Induction Health State. Readmission and switching drug treatments was permitted in the initiation (induction period and first weeks of treatment).

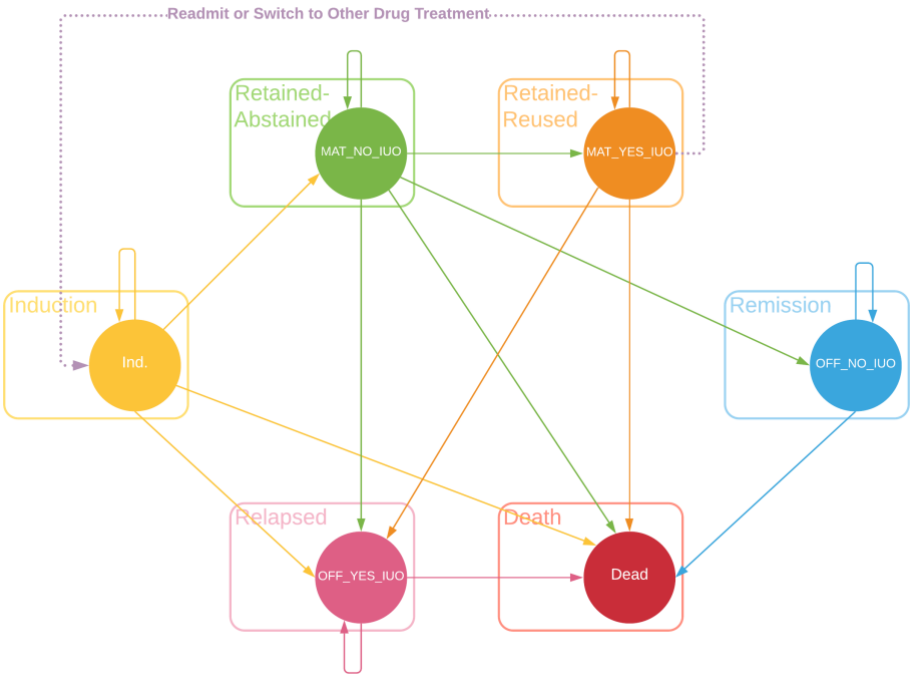


Figure 3.2 Markov Model Map

For this model, measures of drug efficacy and treatment attrition for the added DMOUD treatment strategies, Methadone Maintenance Treatment (MMT) and Buprenorphine Maintenance Treatment (BMT), came from a Cochrane Database of Systematic Reviews meta-analysis of 31 trials. More specifically, measures of drug efficacy came from 4 randomized-controlled trials (RCTs) and retention in treatment from 7 RCTs. These measures for the ERMOUD treatment strategies came from single RCTs. [Table 3.2] Health Utilities were kept the same, for simplicity, despite acknowledgment of reported differences showing MMT resulting in lower health-related quality of life than BMT.[10] Drug prices [Table 3.4] for DMOUDs included drug administration costs, which were proportionally larger than the ERMOUD model prices, as they include requisite Opioid Treatment Program costs for MMT administration and office-visit costs for BMT. Whereas ERMOUD drug prices included the Federal Supply Schedule (FSS) drug price as of

September 2020, and the direct administration cost (i.e., injection or implant cost) as priced by corresponding CPT codes.

Table 3.4 Drug Costs

Drug Name	Treatment Costs*/mo.	Administration Costs/mo.
Vivitrol	$897	$20.88**
Sublocade	$1,205	$20.88**
Probuphine	$566	$47.54§
gSL-Bup/Nal	$250	
Methadone	$504	included in tx. $
Buprenorphine	$450	

** Costs based on Federal Supply Schedule (09/2020)*

***SC/IM Injection Administration (CPT Code: 96372)*

§Probuphine Implant Insertion/Removal (CPT Codes: 11981/11982)

A cost-effectiveness analysis determined the undominated strategies for all 34 drug treatment strategies, in each chosen time-horizon, producing cost-effectiveness frontier graphs with corresponding incremental cost-effectiveness ratios, at a Willingness-to-Pay (WTP) of $50,000. [Appendices C.2-3] All 34 drug treatment regimen strategies were included in the 1-year and longer time-horizons, and 25 strategies (excluding the strategies that included a second Probuphine implant) were included in the 6-month time-horizon. This same analysis was repeated with only the single-drug treatment strategies for illustrative purposes. The undominated strategies' Markov Models were individually run to evaluate the cohort's movement through the health states in all time-horizons. The proportion of the cohort in each health state both at the end of the time-horizon, as well as cumulative time spent during the time-horizon (AUC) was then compared amongst the other undominated strategies.

3.2.1 Sensitivity Analysis

Uncertainty was evaluated by both one-way and probabilistic sensitivity analysis. Model probability and health utilities were varied ±10%, with drug costs varying ±25%, and direct drug administration costs varying ±20%. Probabilistic sensitivity analysis was done using Monte Carlo simulations over 500 trials, with parameters assuming triangular distributions, producing cost-effectiveness scatterplots and acceptability curves. [Appendices C.4-7] Strategy selection charts at a WTP of $50,000 were constructed and included to compare the optimal treatment strategy for all time-horizons. [Appendices C.8-9] Further investigation of parameter uncertainty and key model economic drivers in the resulting predominant strategies was performed with one-way sensitivity analysis, by way of incremental cost-effectiveness scatterplots and tornado diagrams. [Appendix C.10]

3.2.2 Scenario Analysis

Our base-case analysis included measures of efficacy for the Methadone-containing and Buprenorphine-containing treatment strategies from the Cochrane meta-analysis and systematic review at a fixed-rate for medium-dosage, as the other treatment strategy drugs were tested at a fixed-rate. However, as stated in the meta-analysis, fixed-dose treatment of either methadone or buprenorphine is rarely seen in clinical practice, and therefore flexible-dose analyses are more relevant to real-world settings.[28] In scenario analysis, we added 2 additional treatment strategies (*MMT-only-flex* & *BMT-only-flex*) utilizing the measures of efficacy reported in the meta-analysis for flexible-dose methadone and buprenorphine.

Additionally, in better approximating real-world settings, we drew from our previous research ("Comparing Different Drug Pricing Schedules in Cost-Effectiveness Analyses of Extended-Release Medications for Opioid Use Disorder: Including Single-Drug and Multi-Drug-in-Sequence Treatment Strategies") on different pricing schedules for the drugs evaluated in our model. We utilized the FSS drug prices in this current study's base-case analysis, as they are publicly available, and approximate the Drug Manufacturer's Net (DMN) prices, which are not publicly disclosed. The DMN prices were used and reported in the model and paper on ERMOUDs cost-effectiveness released by the Institute for Clinical and Economic Review (ICER).[27] The Urban Institute, however, released a study stating ICER may have used inaccurate drug pricing, as the DMN price does not include the rebates and discounts afforded to Medicaid, the majority provider of OUD treatment.[15] In another scenario tested, we ran the base-case analysis with Medicaid Rebate-Adjusted (MRA) prices for the ERMOUDs, per the Urban Institute report, both with and without the added flexible-dose treatment strategies. The DMOUD drug prices remained the same, as they are not necessarily drug specific, but rather reflect the cost of MMT and BMT treatment, reported by the National Institute on Drug Abuse.[29]

Table 3.5 Scenario Analysis Drug Prices

$/dose	FSS	DMN	MRA
Vivitrol	$897	$759	$589
Sublocade	$1,205	$1,209	$1,147
Probuphine	$3,680	$3,640	$2,038

3.3 Results

The "Buprenorphine Maintenance Treatment" (*BMT-only*) strategy, followed by the "Methadone Maintenance Treatment" (*MMT-only*) strategy were the most cost-effective treatment strategies in all time-horizons when all 34 treatment strategies were included in the analysis (full analysis), as well as when only the single-drug treatment strategies (single-drug analysis) were tested. The other undominated strategies in both the full and single-drug analyses were Probuphine-containing multi-drug-in-sequence treatment strategies, except for "Vivitrol-Only" (*VIV-only*) treatment strategy in the single-drug analysis' 18-month time-horizon. [Table 3.6]

Table 3.6 Undominated Treatment Strategies

Undom. Ranked		6-months	1-year	18-months	2-years
ALL Strategies	1	BMT-only			
	2	MMT-only			
	3	MMT→PRO			
	4	PRO→SUB		PRO2→MMT	
	5			PRO2→VIV	
Single-Drug Strategies	1	BMT-only			
	2	MMT-only			
	3	PRO→gSL		VIV-only	

***PRO: 1-cycle in 6-month time-horizon; 2-cycles in >6-months*

***MMT-only in 2-year time-horizon has ICER<$50,000*

The *MMT-only* treatment strategy was the only other treatment strategy to be considered cost-effective with an incremental cost-effectiveness ratio (ICER) below a Willingness-to-Pay (WTP) of $50,000, and only in the 2-year time-horizon (ranging from $88,020$_{6\text{-months}}$ - $49,611$_{2\text{-years}}$). All other undominated treatment strategies' ICERs were significantly larger, ranging from the "Methadone Maintenance Treatment → Probuphine *(1-cycle)*" (*MMT→PRO1*) treatment

strategy in the full analysis at 6-months being $138,476, to the *VIV-only* treatment strategy in the single-drug analysis at 18-months being $2,614,033. [Table 3.7]

Table 3.7 Incremental Cost-Effectiveness Ratios

6-months	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
ALL Strategies	***BMT-only***	$1,305		0.34917		
	MMT-only	$1,732	$427	0.35402	0.00485	$88,020
	MMT→PRO1	$2,013	$281	0.35604	0.00203	$138,476
	PRO1→SUB	$3,644	$1,630	0.36375	0.00771	$211,539
Single-Drug Strategies	***BMT-only***	$1,305		0.34917		
	MMT-only	$1,732	$427	0.35402	0.00485	$88,020
	PRO1→gSL	$3,531	$1,799	0.36178	0.00777	$231,629

1-year	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
ALL Strategies	***BMT-only***	$1,813		0.71180		
	MMT-only	$2,563	$751	0.72197	0.01017	$73,767
	MMT→PRO2	$3,285	$722	0.72483	0.00286	$251,923
	PRO2→SUB	$7,204	$3,919	0.73566	0.01082	$362,171
Single-Drug Strategies	***BMT-only***	$1,813		0.71180		
	MMT-only	$2,563	$751	0.72197	0.01017	$73,767
	PRO2→gSL	$6,999	$4,435	0.73137	0.00940	$472,006

18-months	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
ALL Strategies	***BMT-only***	$1,999		1.07245		
	MMT-only	$2,942	$942	1.08808	0.01563	$60,275
	MMT→PRO2	$3,981	$1,039	1.09142	0.00334	$311,055
	PRO2→MMT	$8,178	$4,197	1.10089	0.00947	$443,310
	PRO2→VIV	$9,321	$1,143	1.10212	0.00123	$930,179
Single-Drug Strategies	***BMT-only***	$1,999		1.07245		
	MMT-only	$2,942	$942	1.08808	0.01563	$60,275
	VIV-only	$6,021	$3,079	1.08926	0.00118	$2,614,033

2-years	Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E
ALL Strategies	***BMT-only***	$2,068		1.43118		
	MMT-only	$3,114	$1,046	1.45227	0.02108	$49,611
	MMT→PRO2	$4,293	$1,179	1.45615	0.00388	$303,926
	PRO2→MMT	$8,727	$4,434	1.46724	0.01109	$399,798
Single-Drug Strategies	***BMT-only***	$2,068		1.43118		
	MMT-only	$3,114	$1,046	1.45227	0.02108	$49,611

There are notable differences between the *BMT-only* and *MMT-only* treatment strategies when comparing their health state tracings. [Appendices C.11-12] While both treatment strategies resulted in similar cohort proportions ending (Ending Results), as well as spending time throughout the study (Cumulative Totals) in Remission, or the OFF without Illicit Use of Opioids ("OFF w/o IUO") health state, the *MMT-only* treatment strategy resulted in higher Retention in treatment, and lower Relapse than the *BMT-only* treatment strategy. Retention in *MMT-only* over *BMT-only* grew with longer time-horizons, in both the In-treatment with and without Illicit Use of Opioids health states ("MAT w/o IUO" & "MAT w/ IUO"), as well as in both comparing the Ending Results and the Cumulative Totals. [Appendices C.13-14] This was seen especially in the Ending Results over a 2-year time-horizon, where Retention in *MMT-only* treatment without Illicit Use of Opioids was over 4-times higher that of the *BMT-only* treatment strategy. [Figure 3.3]

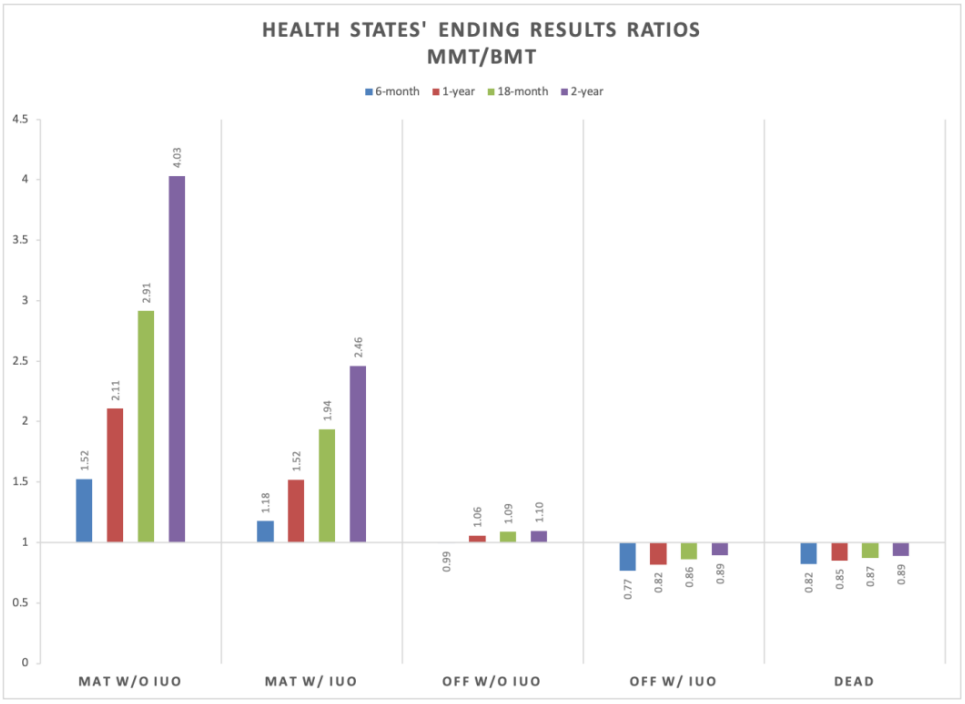


Figure 3.3 Health State Comparison: MMT/BMT

3.3.1 Sensitivity Analysis Results

Probabilistic Sensitivity Analysis using the Monte Carlo method, over 500 iterations, found the *BMT-only* treatment strategy to be the most cost-effective over all time-horizons, in both the full and single-drug models. [Appendices C.4-5] The cost-effectiveness scatterplots consistently show Sublocade-containing treatment strategies clustered and dominated. [Figure 3.4]

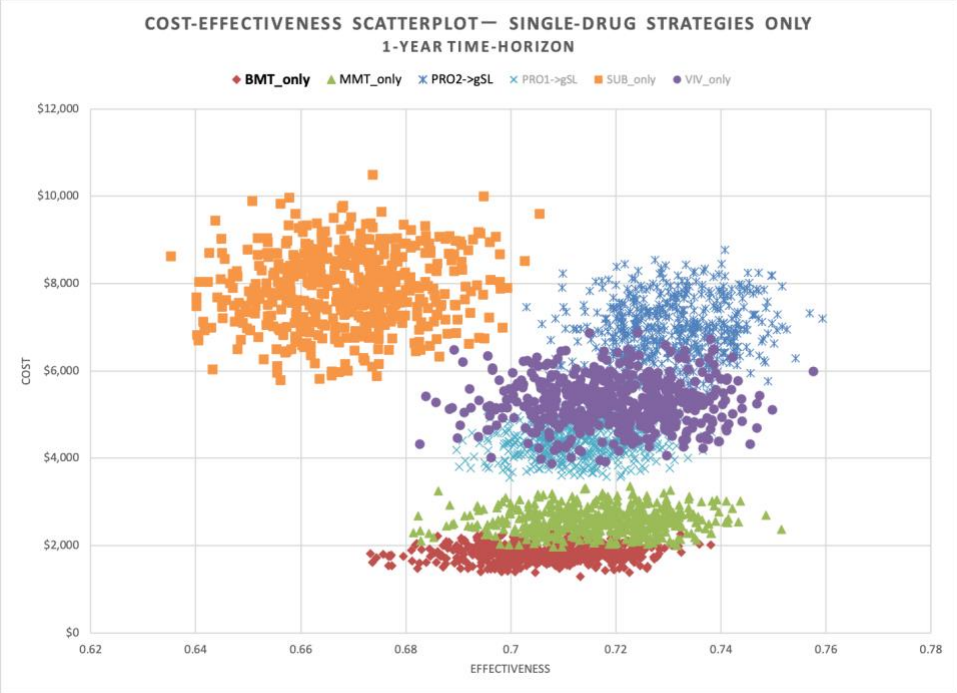


Figure 3.4 Scatterplot Showing Sublocade's Separation (orange)

The cost-effectiveness acceptability curves show the *BMT-only* treatment strategy being largely preferred, with the *MMT-only* treatment strategy being second. The *MMT-only* treatment strategy overtakes preference from the *BMT-only* treatment strategy at an intersection which decreases over time, from a WTP of around $90,000 in the 6-month time-horizon, to about $50,000 in the 2-year time-horizon. [Figure 3.5]

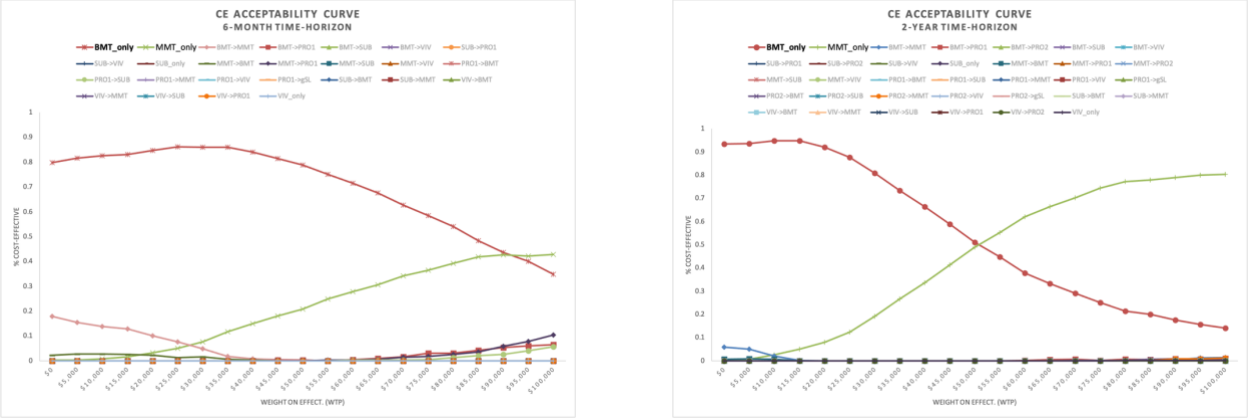


Figure 3.5 BMT Loses Dominance to MMT Over Time

This is reflected further in the strategy selection at a WTP of $50,000 charts, where the *BMT-only* treatment strategy is the preferred strategy 79%$_{\text{(full-model)}}$-82%$_{\text{(single-drug-model)}}$ in the 6-month time-horizon, decreasing to 51%$_{\text{(full-model)}}$-53%$_{\text{(single-drug-model)}}$ in the 2-year time-horizon. [Appendices C.8-9]

One-way sensitivity analysis revealed that the *BMT-only* and *MMT-only* treatment strategy models, when compared to each other, were most sensitive to variation of the same model parameters in all time-horizons tested. These treatment strategy models were most sensitive to the probability of entering into treatment, followed by the probability of leaving treatment, the probability of relapsing to illicit opioid use, and the probability of readmission or reentry following discontinuation due to illicit opioid use. [Appendix C.10]

	6-month	1-year	18-months	2-years
MMT v. BMT	MMT Induction Success			
	BMT Induction Success			
	MMT Treatment Attrition			

Figure 3.6 Tornado Diagram Variable Comparison Table

3.3.2 Scenario Analysis Results

The *BMT-only* treatment strategy's preference over the *MMT-only* treatment strategy decreased to nearly even odds (51% vs. 49%, respectively) in the base-case probabilistic analysis at the 2-year time-horizon, as reported above. When the flexible-dose Methadone and Buprenorphine treatment options were added, the flexible-dose Buprenorphine Maintenance Treatment (*BMT-only-flex*) strategy was the overwhelmingly preferred strategy selection ($79\%_{6\text{-months}}$-$100\%_{2\text{-years}}$), with the *BMT-only* strategy second and only.

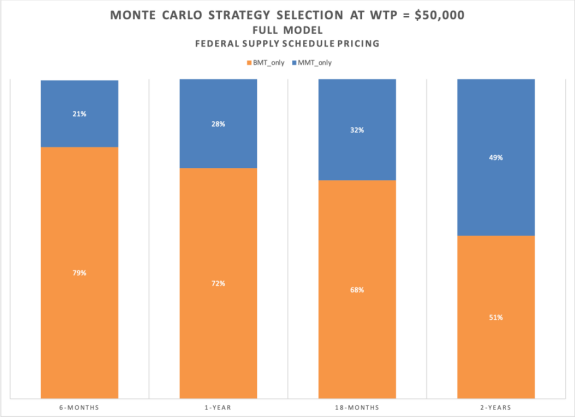


Figure 3.7 Base-Case Scenario Analysis with FSS Pricing

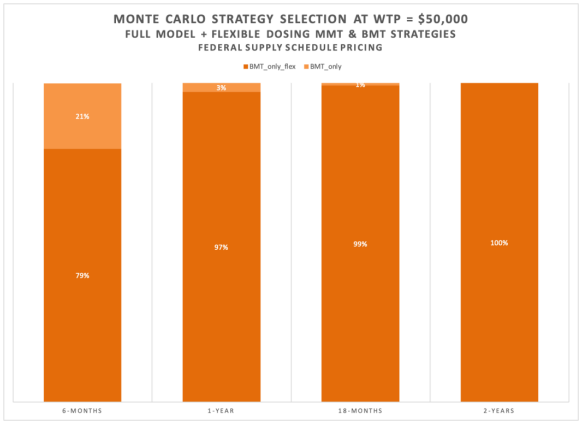


Figure 3.8 Scenario Analysis with Flexible Dosing and FSS Pricing

The *BMT-only-flex* treatment strategy was the preferred selection also in the Monte Carlo scenario analysis with Medicaid-Rebate Adjusted prices for the ERMOUDs and flexible-dose Methadone and Buprenorphine treatment options included. However, the *BMT-only-flex* treatment strategy's clear majority was not evident in the 6-month time-horizon, where the "Probuphine *(1-cycle)* → Sublocade" (*PRO1→SUB*) treatment strategy came second ($47\%_{BMT\text{-}only\text{-}flex}$ vs. $41\%_{PRO1\rightarrow SUB}$).

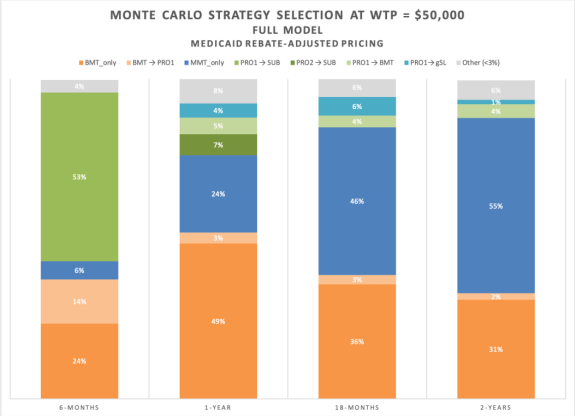


Figure 3.9 Base-Case Scenario Analysis with MRA Pricing

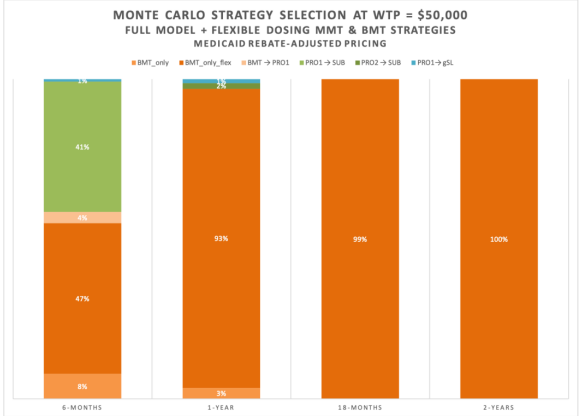


Figure 3.10 Scenario Analysis with Flexible Dosing and MRA Pricing

The use of MRA prices increased the likelihood of more treatment strategies being a viable cost-effective selection and decreased the predominant treatment strategy's majority position. This was shown in our previous research, and evident in our scenario analysis with MRA prices not including the flexible-dose strategies, where there were 16 treatment strategies with any selection preference percentage, compared to just 2 with FSS pricing. In the 6-month time-horizon, with MRA pricing, the *PRO1→SUB* treatment strategy was preferred over the *BMT-only* treatment strategy, 53% to 24%. [Appendices C.15-16]

3.4 Discussion

When comparing the cost-effectiveness of OUD treatment strategies, it is important to include MMT and BMT, the mainstays of Medications for Opioid Use Disorder (MOUD), previously known as MAT (Medication-Assisted Treatment), since the availability, adoption, and coverage for ERMOUDs remains comparatively minute. In 2018, Medicaid covered nearly 30-times more prescriptions for buprenorphine than naltrexone (93.7% being Vivitrol), of which only 0.06% were extended-release buprenorphine formulations.[15] Commercial health insurance coverage is similarly scant, with only 0.2% and 0.01% of all buprenorphine prescriptions, in 2018, being for Sublocade and Probuphine, respectively.[16]

ERMOUDs are becoming the preferred route of administration, according to some reports,[30] due to their ability in overcoming barriers such as patient non-compliance, missing doses, drug diversion, and even inadvertent overdose or accidental poisoning.[31] However, in our base-case analysis, over all time-horizons, the daily-formulation *BMT-only* treatment strategy was found to be the most cost-effective strategy in both our full model and single-drug model. This is similar to the results of the aforementioned Institute for Clinical and Economic Review (ICER) report, which modeled ERMOUDs compared to a daily-formulation of generic Sublingual-Buprenorphine/Naloxone (gSL-Bup/Nal), and found that the extended-release formulations were "judged to represent low value for the money."[8]

We expect the ERMOUD prices to decrease, as they are still comparatively new MOUD treatment options with no generic drug substitutes currently available, which will increase their cost-effective competitiveness. This was evident in our scenario analysis, where MRA prices were modeled, producing different outcomes, especially in the 6-month time-horizon. The *PRO1→SUB* treatment option was preferred over the *BMT-only* strategy, being not only a multi-drug-in-

sequence treatment strategy compared to a single-drug strategy, but also a combination of 2 different ERMOUDs. This not only shows the potential of extended-release formulations, but also supports the importance of testing multi-drug-in-sequence treatment strategies, as they better approximate real-world settings and OUD treatment clinical courses that follow a chronic medical condition, expectant of relapses and remissions. Furthermore, these 6-month time-horizon findings are significant, since nearly all of the model inputs are from 6-month duration studies, there is more confidence in the model's 6-month time-horizon results then longer extrapolations.

Along with perception changes in OUD to a chronic medical condition, the goals of treatment have likewise shifted away from a complete abstinence of illicit opioid use as recovery, to focus more on retention in treatment, and ongoing management of this complex disease. Treatment Retention not only increases the probability of long-term Remission, but also reduces the transmission of HIV and HCV, increases the likelihood of employment, decreases criminal behavior associated with drug use, and lowers the risk of overdose and death.[32] Therefore, it is important to analyze the health state tracings of the treatment strategies in this light. When comparing the *BMT-only* treatment strategy to the next most cost-effective option, the *MMT-only* treatment strategy, there are some important differences. The *MMT-only* strategy retained in treatment more of the cohort across all time-horizons, by up to 4-times more, than the *BMT-only* strategy, with more in treatment abstaining from illicit opioid use than using. Conversely, while the *BMT-only* treatment strategy resulted in slightly less of the cohort ending in, and occupying throughout, the Remission health state (denoted as Out of Treatment without Illicit Use of Opioids "OFF w/o IUO"), it also resulted in more Relapses (denoted as Out of Treatment with Illicit Use of Opioids "OFF w/ IUO") and Deaths. Thus, despite being the more cost-effective treatment

option, the *BMT-only* strategy may not be the best clinical choice. This may very well be the case for the other treatment strategies tested.

The global coronavirus pandemic has only exacerbated the ongoing opioid epidemic. Barriers to treatment have increased with efforts to mitigate the spread of COVID-19, including social distancing, quarantine, and an overwhelmed healthcare delivery system. To improve MOUD access, the federal government released new guidelines regarding MMT and BMT specifically. The Substance Abuse and Mental Health Services Administration (SAMHSA) released guidance on March 16, 2020, which permitted the federally approved Opioid Treatment Programs (OTP), the only dispensary of methadone for OUD, to dispense 28-day take-home supplies of methadone for clinically stable patients, and 14-day take-home supplies to less stable patients deemed safe by the OTP.[33] Although these take-home supplies are not extended to patients newly initiating MMT, or those in short-term or interim treatment (who are still required in-person visits), they do significantly change treatment for those already receiving treatment. Previously, a 28-day take-home supply was only permitted to those clinically stable, and in treatment for at least 2 years. A 14-day take-home supply was likewise only available after at least 1 year of treatment.

The Drug Enforcement Agency (DEA) released new guidance on March 31, 2020 regarding BMT, which allowed the initiation of treatment with buprenorphine via tele-medicine without an in-person exam.[34] Buprenorphine may be prescribed only by qualified providers who have undergone specialized training to obtain an "X-waiver" in accordance with the Drug Addiction Treatment Act of 2000 (DATA2000),[35] which regulates the number of patient's a prescriber can treat. However, the number of providers with an "X-waiver" is not nearly enough to match the clinical need, contributing to insufficient capacity.[36] Furthermore, the number of providers with an "X-waiver" who actually prescribe buprenorphine is even lower, and those who

do treat patients with BMT follow less than half the number of patients their "X-waiver" allows them to see.[37]

These new regulations regarding access and availability of MMT and BMT diminish one of the main advantages that ERMOUDs had over DMOUDs, being the ability to decrease provider contact. Under the new guidelines, those who are clinically stable and receiving MMT may only be required monthly in-person contact with their healthcare provider, just like those receiving Vivitrol or Sublocade monthly injections. Those receiving BMT may go longer than a month without contact, which may rival Probuphine's 6-month duration. Moreover, any follow-up care through an OTP for either MMT or BMT are allowed via tele-medicine, including phone only.

In the very last days of the Trump Administration, the US Department of Health and Human Services (HHS) released "Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder" which would eliminate the "X-waiver" requirement for DEA registered physicians treating up to 30 patients for OUD with buprenorphine.[38] These new guidelines, announced on January 14th 2021, were in response to provisional data released by the US Center for Disease Control and Prevention that reported over 83,000 overdose deaths from July 2019 to July 2020. This is the highest number of overdose deaths ever reported in one year, as well as a 24.2% increase from the previous year.[39] However, only one week into the new Biden Administration, these measures were reversed. A statement released by HHS, on January 27th 2021, stated that the guidelines were announced prematurely, and "cannot be issued at this time."[40]

We acknowledge the difference between the theoretical cost-effectiveness of our treatment strategies differ from the practical real-world clinical application and use of these regimens. Although the DMOUD treatment strategies were found to be more cost-effective over the ERMOUD options, the extended-release formulations still provide unique clinical advantages over

daily formulations, as in abating drug diversion (especially in certain populations including the criminal justice involved), increasing compliance, and potentially improving treatment retention. It is important to note that these results may be due, in part, to the model input probabilities used for the DMOUDs, as they were from a meta-analysis instead of from a single study source, as the ERMOUDs were. In fact, in our previous research, when the ERMOUDs were compared to generic Sublingual-Buprenorphine/Naloxone, using measures of efficacy from a single-source study,[41] the ERMOUDs were consistently more cost-effective.

There were some other important limitations in both our model inputs and design. The health utility model inputs were not specific to each treatment strategy. Measurements of efficacy and attrition were not from one single study, but rather from different single-source RCTs for the ERMOUDs, and a meta-analysis for the DMOUDs, which are all subject to individual study design, measurement, administration, and reporting differences. The single-source RCT research studies cited, as well as most studies comprising the meta-analysis, shared the same 24-week study duration. Therefore, we recognize that extrapolating that data over a 2-year time-horizon may not return as reliable results, however, it was important to extend our model duration, as OUD is now looked at as a chronic medical condition, requiring long-term, if not life-long, medical care. Nevertheless, we were reassured by our longer time-horizon results, as they were consistently stable and non-sporadic over time, oftentimes resulting in the same treatment strategies carrying over several time-horizons. We further realize that there are significant issues with generalizability, which not only carry through from the sources used, but also from not accounting for individualization in the model construction, including demographic differences, opioid use patterns and preferences, and patient use and prior treatment history.

This cost-effectiveness analysis is too premature to be used as clinical guidance, however it can provide the evidence necessary to examine the currently available MOUDs, and compare the cost-effectiveness of both daily and extended-release formulations.

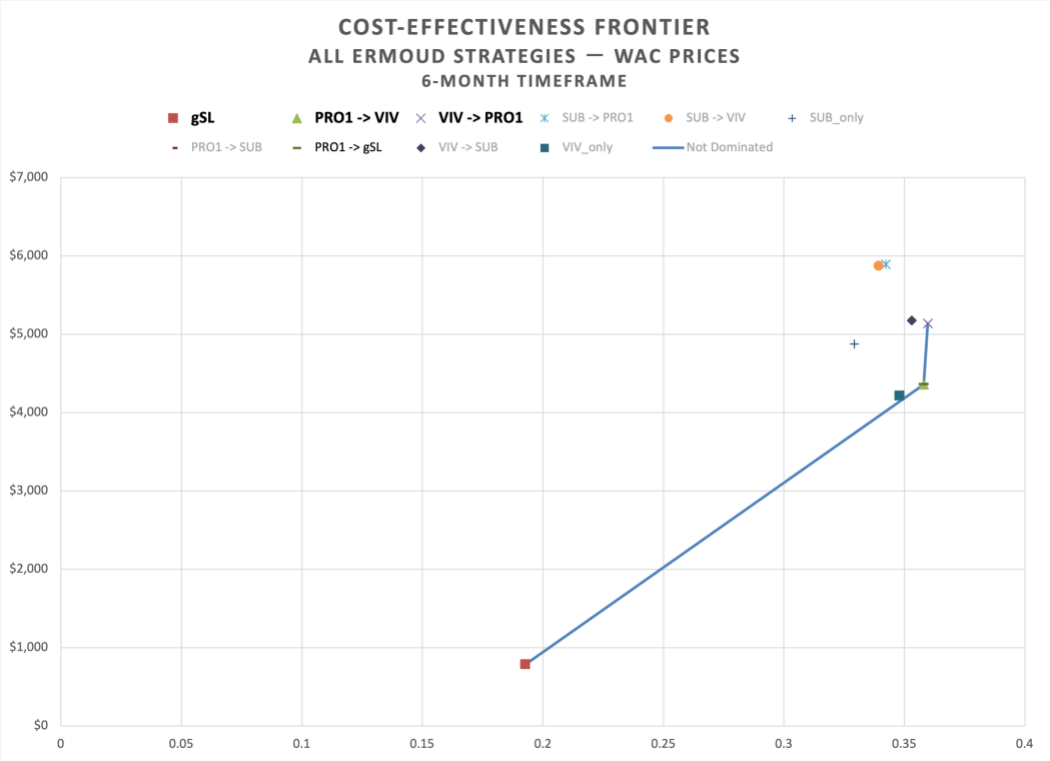
3.5 Conclusion

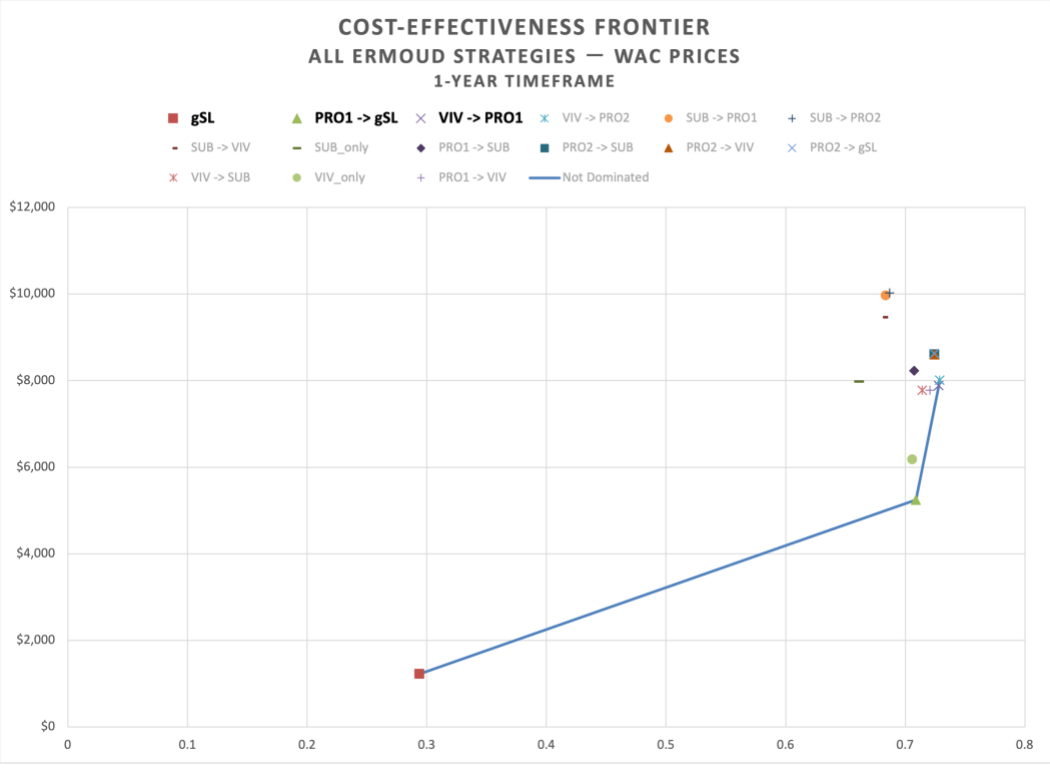
Daily formulations of Medications to treat Opioid Use Disorder, specifically the mainstays of BMT and MMT, may be more cost-effective treatment options over newer extended-release formulations until the price of both formulations better align with their demonstrated benefits. While the newer extended-release formulations are an important addition to the treatment options of OUD, and provide unique clinical advantages over the daily formulations, the single-drug BMT-only treatment strategy tested as the most cost-effective, especially with the newly released federal regulations on OUD treatment during the coronavirus pandemic.

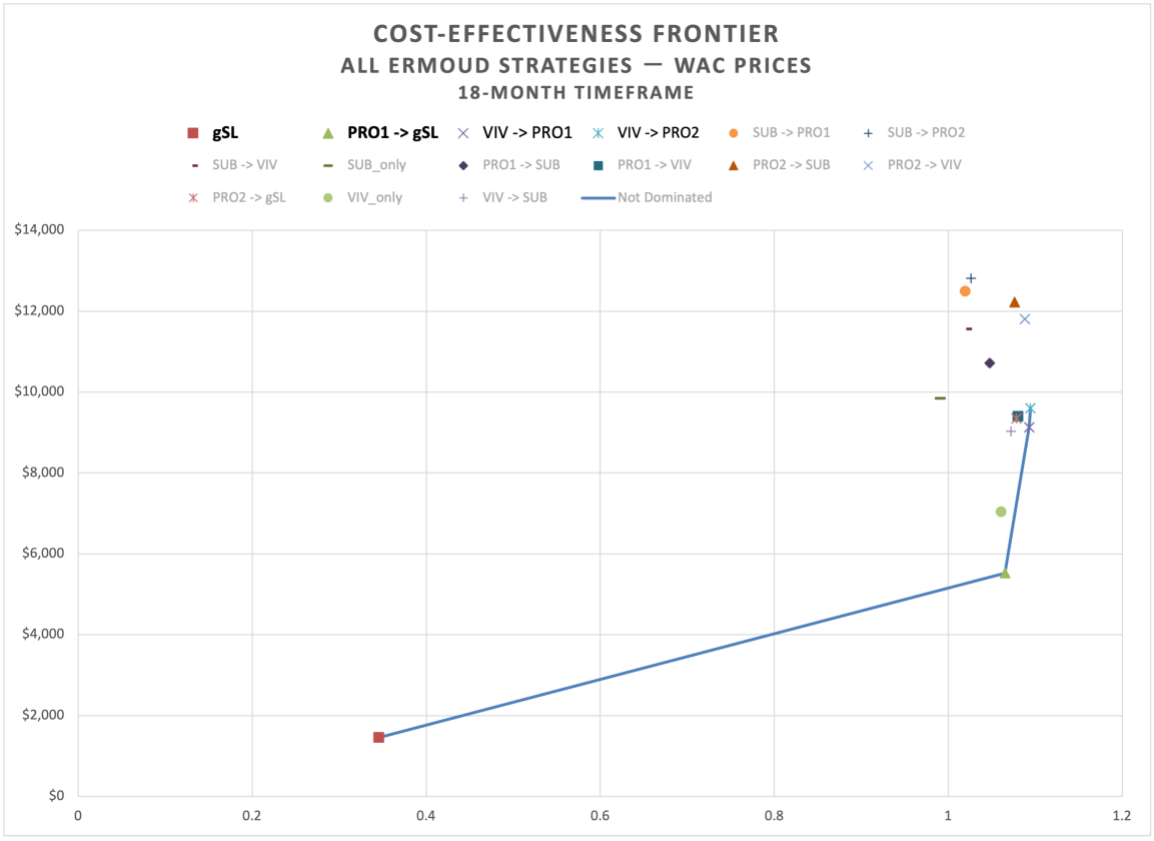
Appendix A Additional Tables and Figures for:

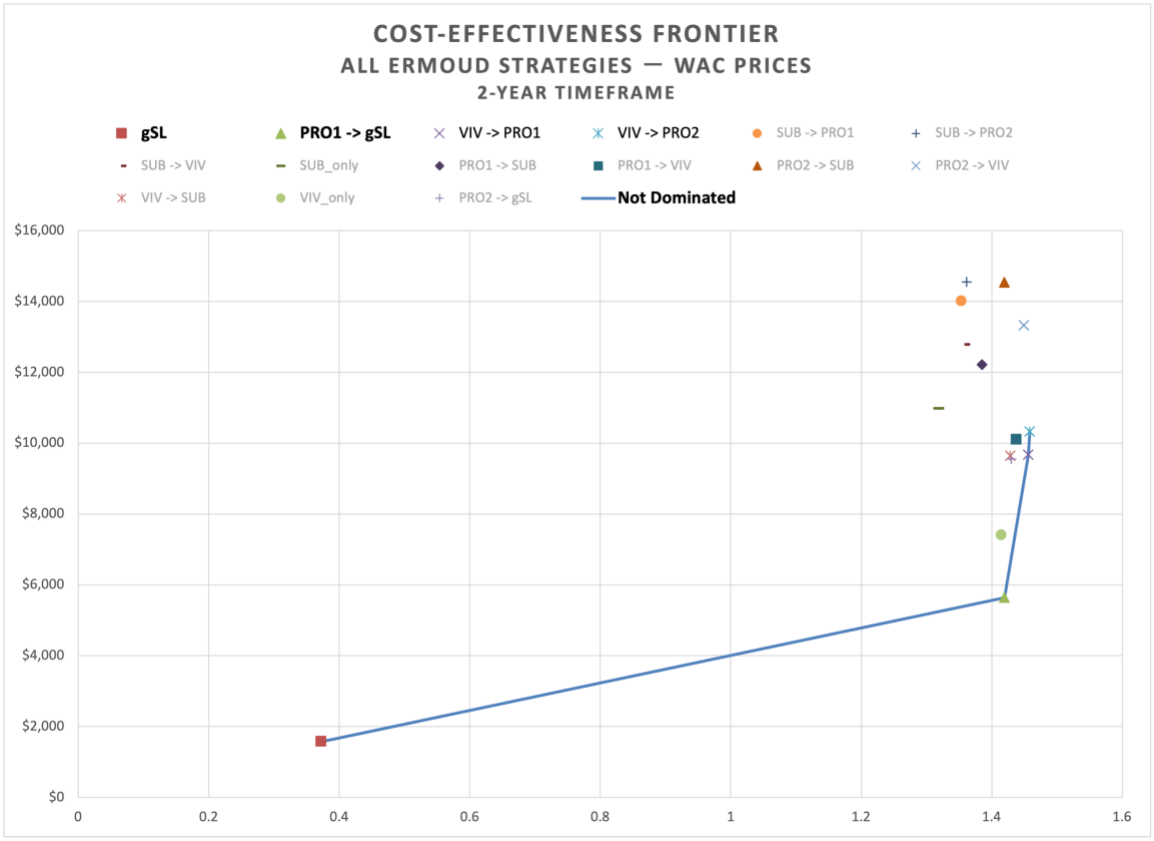
Cost-Effectiveness of Extended-Release Medications for Opioid Use Disorder Treatment Strategies: Single-Drug and Multi-Drug-in-Sequence Regimens

Appendix A.1 Cost-Effectiveness Frontiers

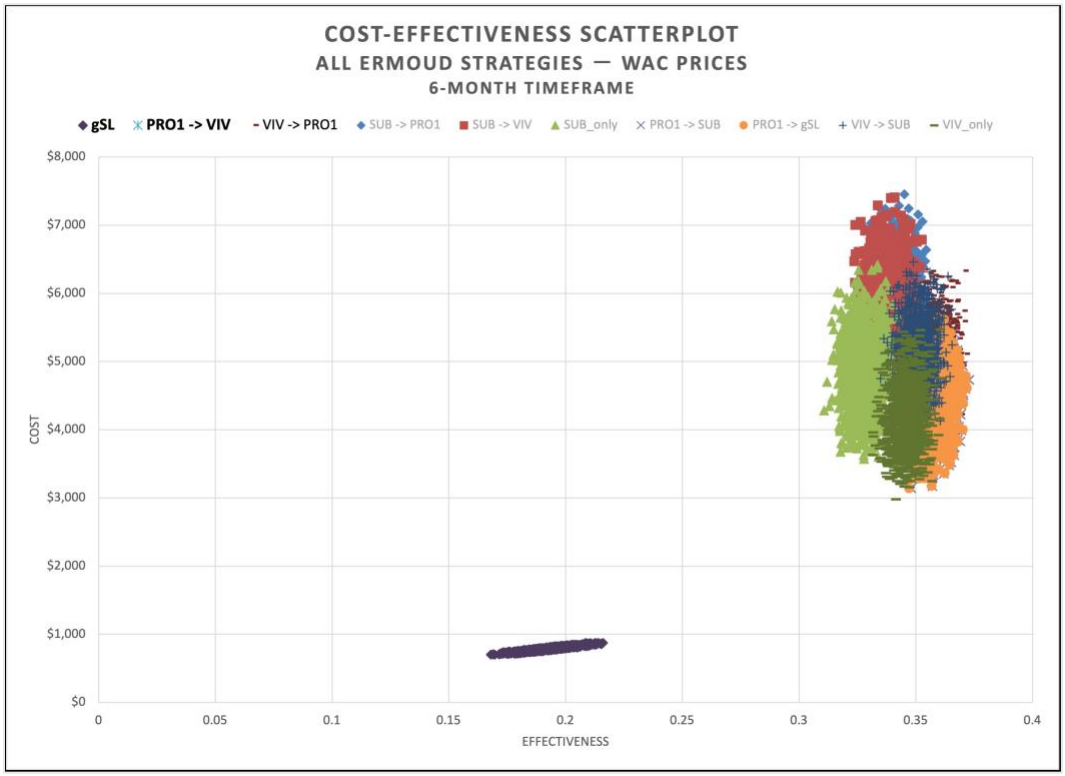


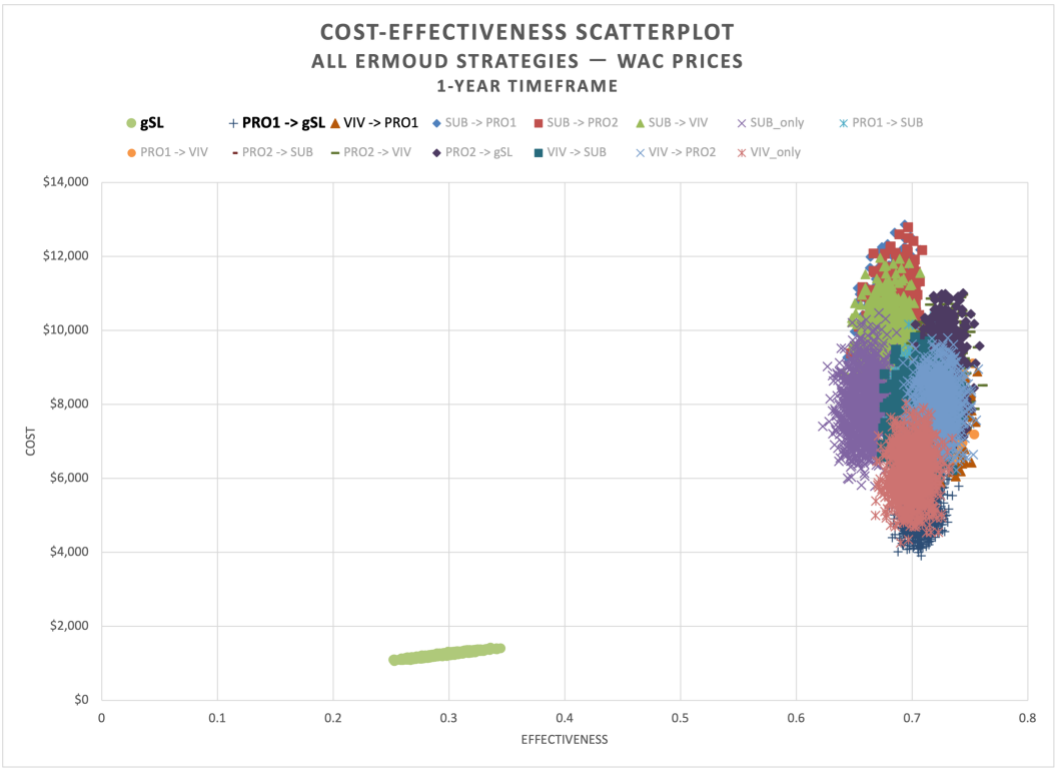


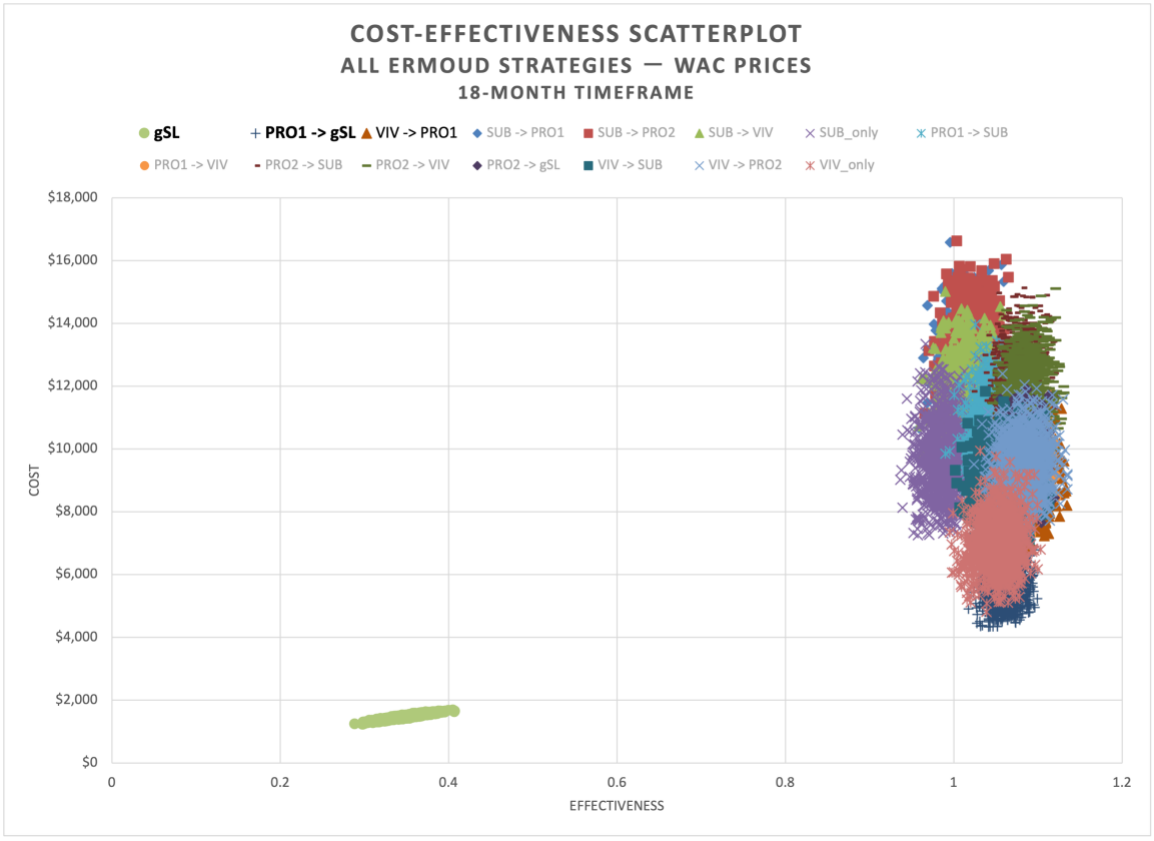

COST-EFFECTIVENESS FRONTIER
ALL ERMOUD STRATEGIES — WAC PRICES
18-MONTH TIMEFRAME
gSL
PRO1 -> gSL
VIV -> PRO1
VIV -> PRO2
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
PRO2 -> gSL
VIV_only
VIV -> SUB
Not Dominated
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
0
0.2
0.4
0.6
0.8
1
1.2

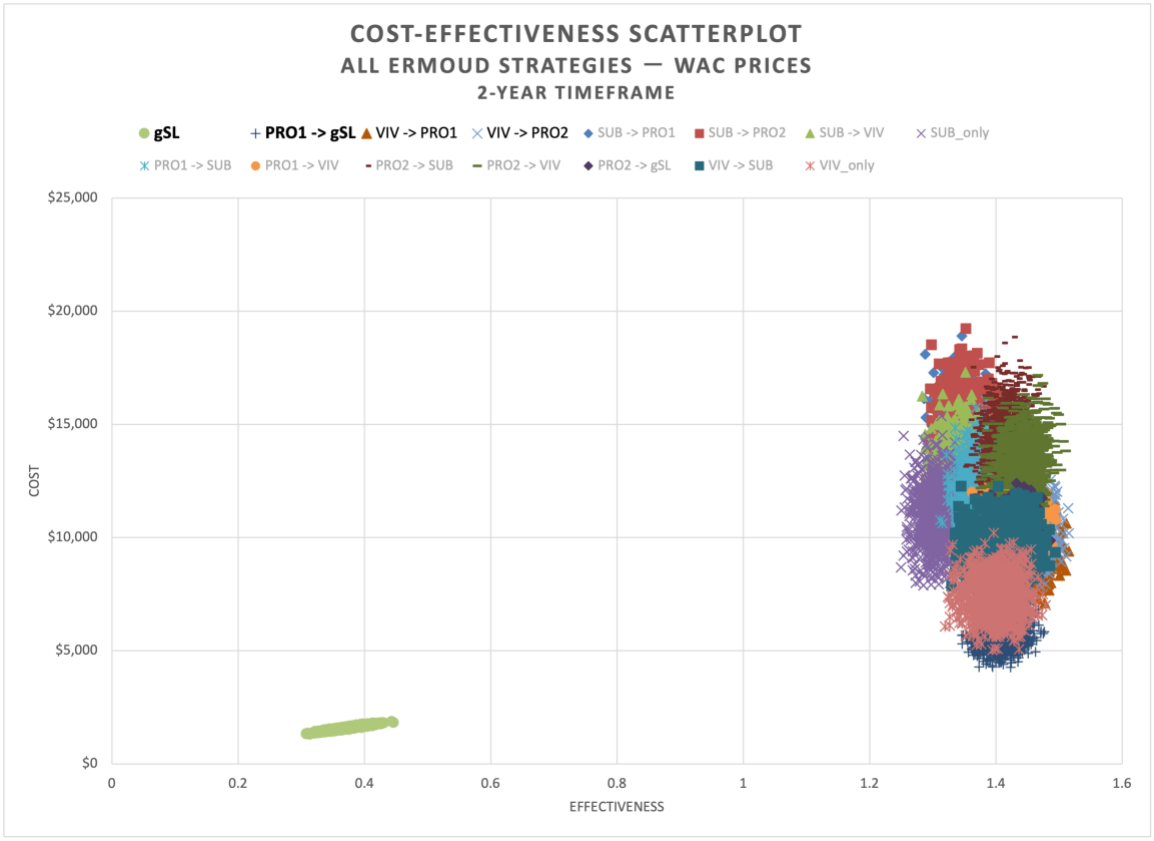

COST-EFFECTIVENESS FRONTIER
ALL ERMOUD STRATEGIES — WAC PRICES
2-YEAR TIMEFRAME
gSL
PRO1 -> gSL
VIV -> PRO1
VIV -> PRO2
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
VIV -> SUB
VIV_only
PRO2 -> gSL
Not Dominated
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6

Appendix A.2 Cost-Effectiveness Scatterplots

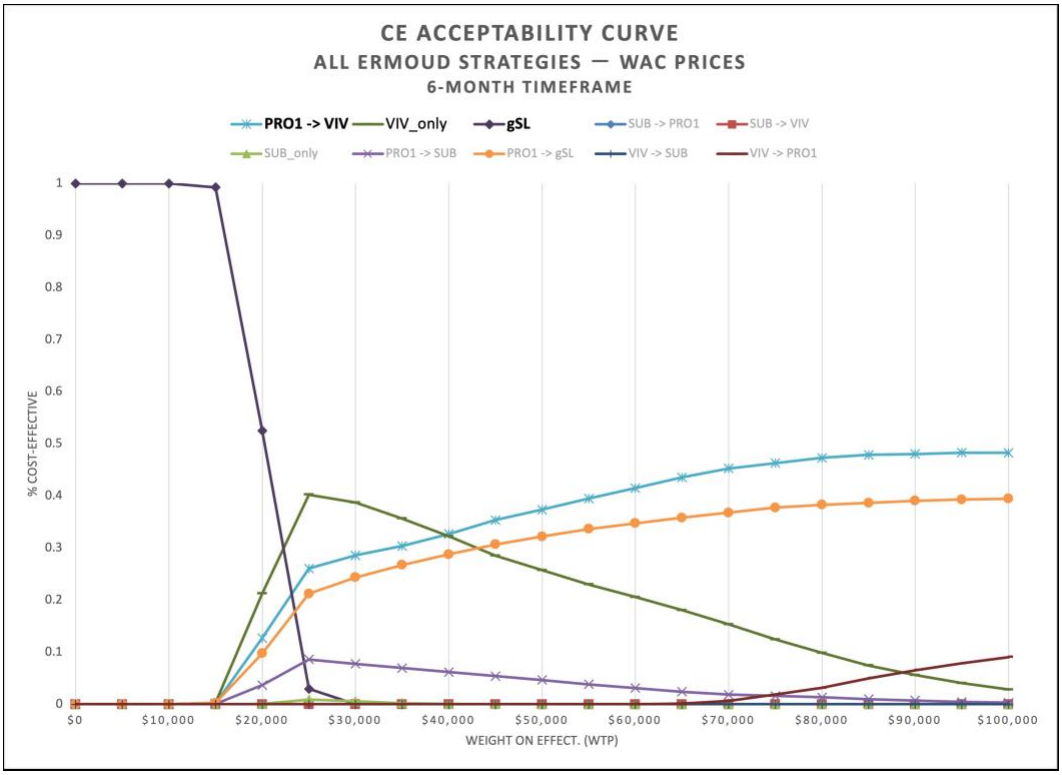


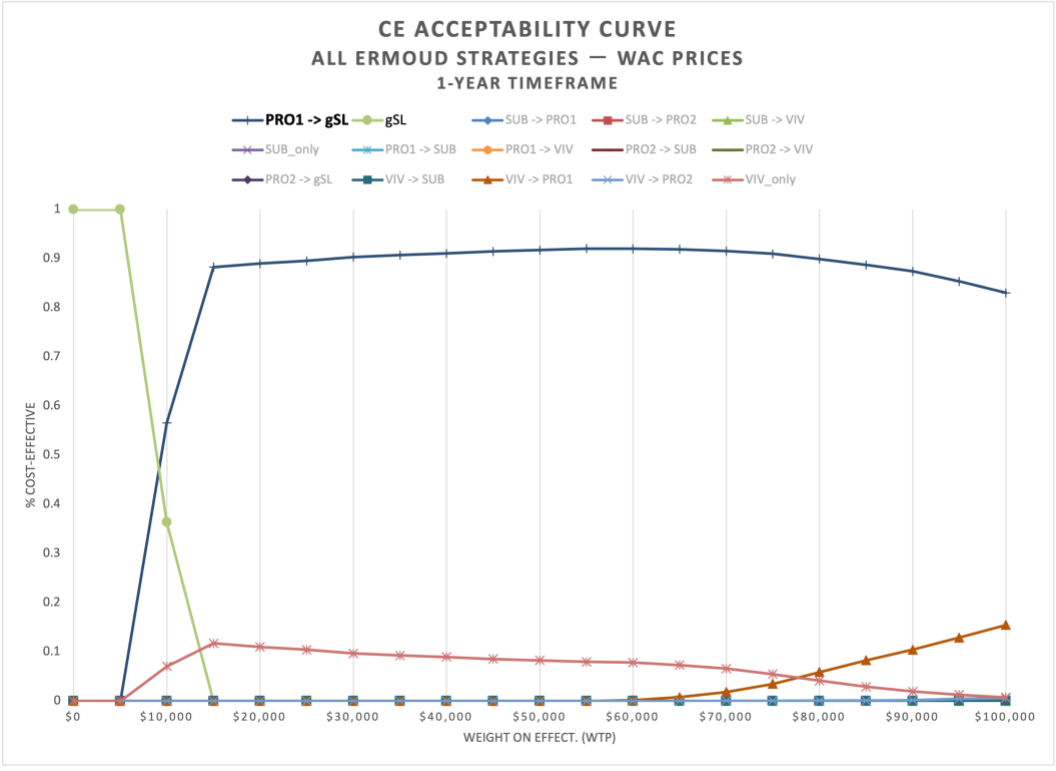


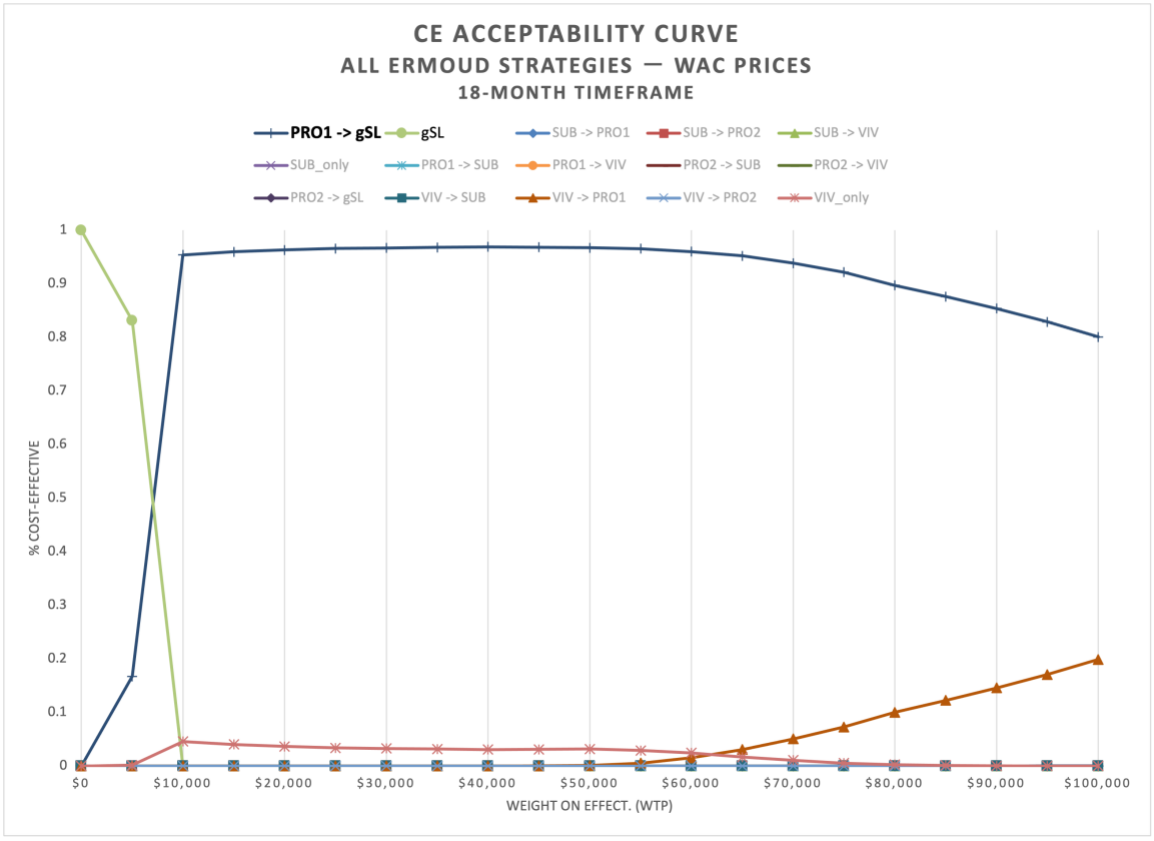

COST-EFFECTIVENESS SCATTERPLOT
ALL ERMOUD STRATEGIES — WAC PRICES
18-MONTH TIMEFRAME
gSL
PRO1 -> gSL
VIV -> PRO1
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
PRO2 -> gSL
VIV -> SUB
VIV -> PRO2
VIV_only
$18,000
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
COST
0
0.2
0.4
0.6
0.8
1
1.2
EFFECTIVENESS

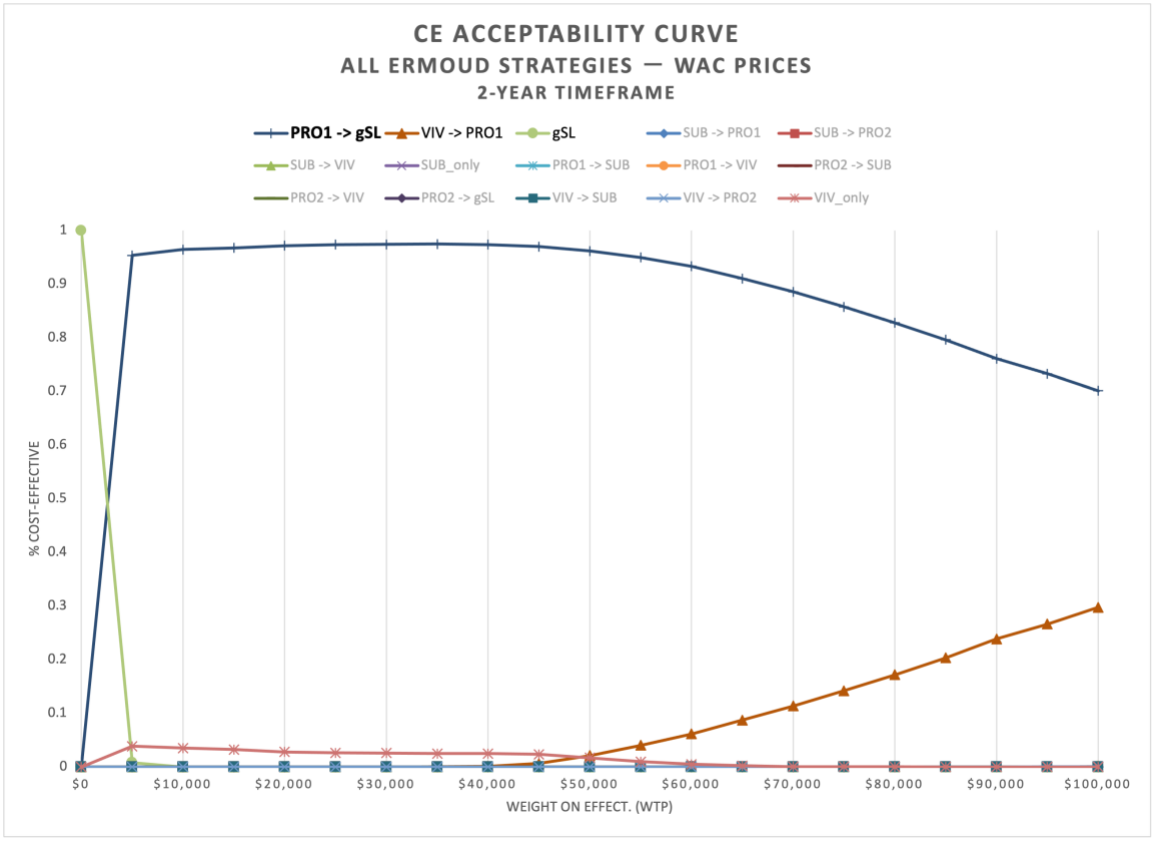

COST-EFFECTIVENESS SCATTERPLOT
ALL ERMOUD STRATEGIES — WAC PRICES
2-YEAR TIMEFRAME
gSL
PRO1 -> gSL
VIV -> PRO1
VIV -> PRO2
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
PRO2 -> gSL
VIV -> SUB
VIV_only
$25,000
$20,000
$15,000
$10,000
$5,000
$0
COST
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
EFFECTIVENESS

Appendix A.3 Monte Carlo Acceptability Curves

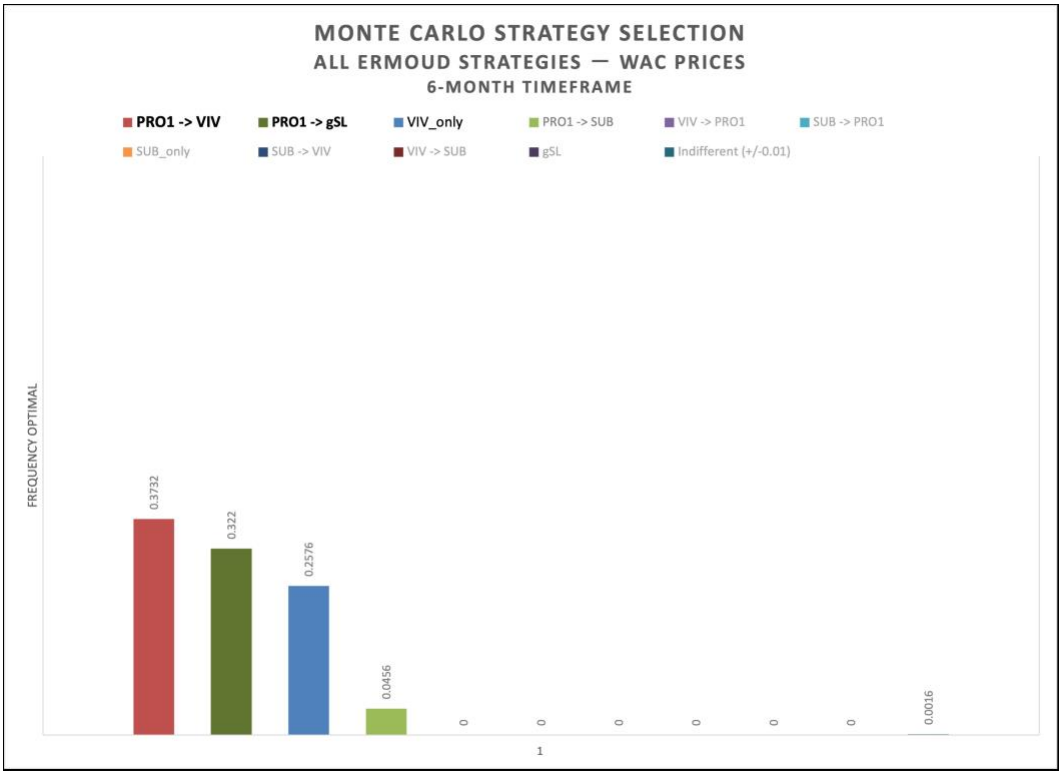


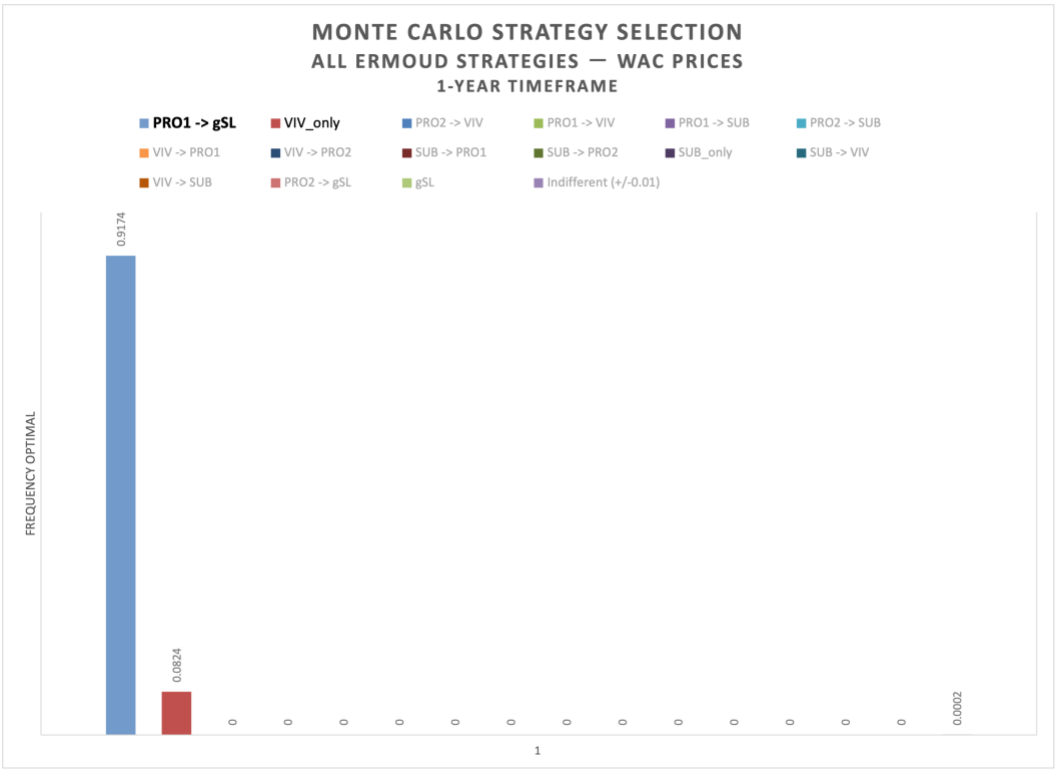


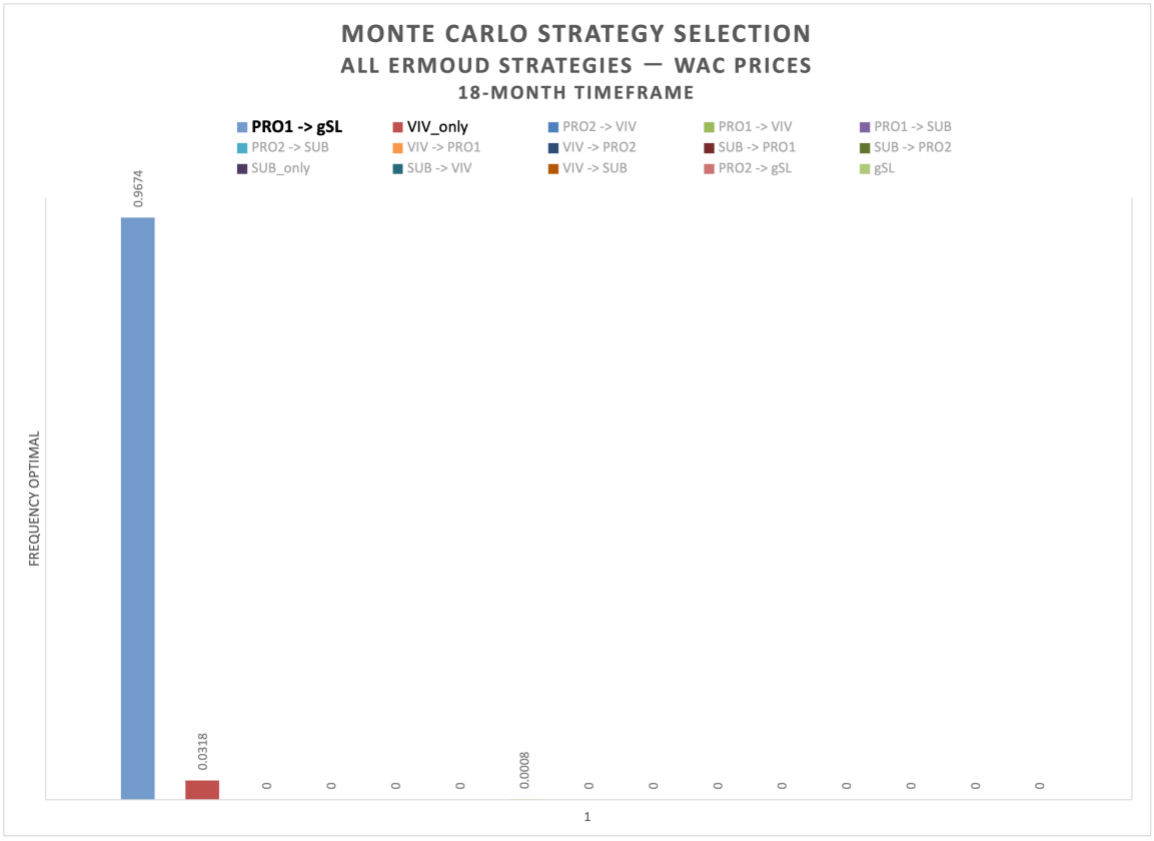

CE ACCEPTABILITY CURVE
ALL ERMOUD STRATEGIES — WAC PRICES
18-MONTH TIMEFRAME
PRO1 -> gSL
gSL
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
PRO2 -> gSL
VIV -> SUB
VIV -> PRO1
VIV -> PRO2
VIV_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
$0
$10,000
$20,000
$30,000
$40,000
$50,000
$60,000
$70,000
$80,000
$90,000
$100,000
WEIGHT ON EFFECT. (WTP)

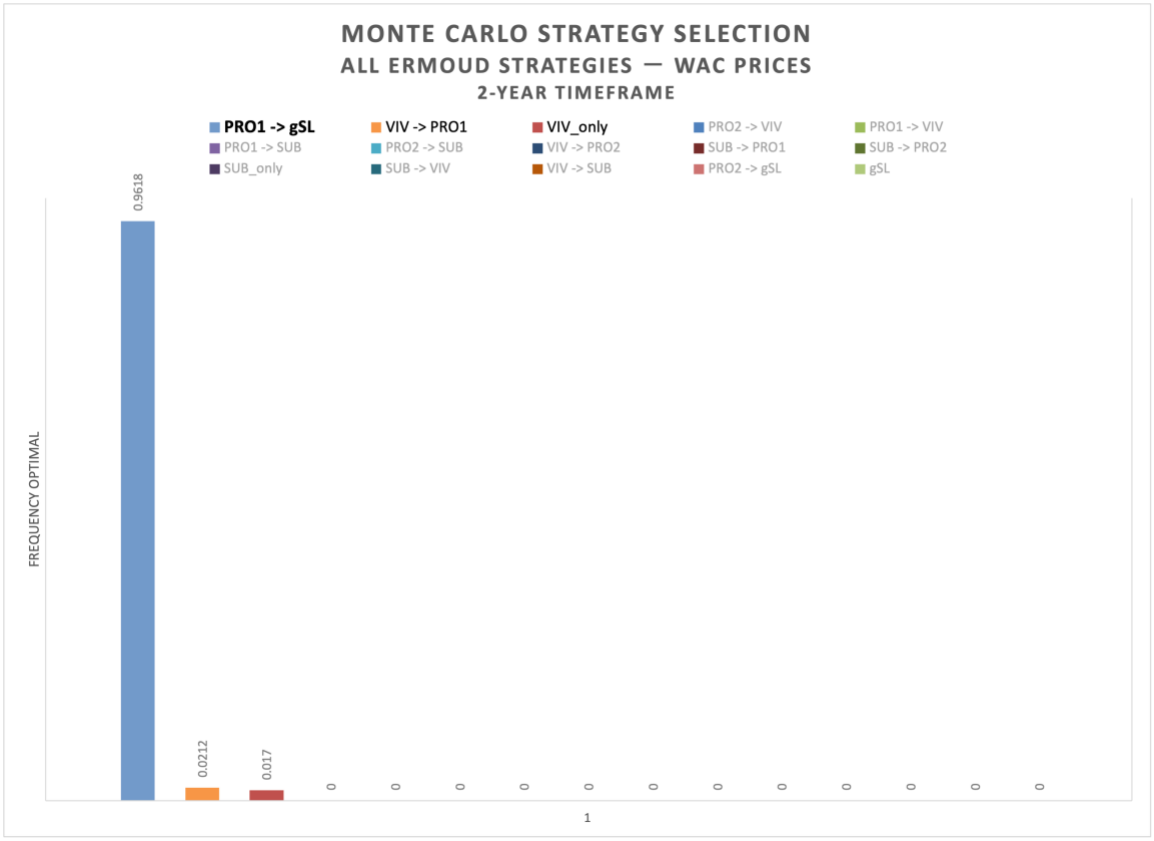

CE ACCEPTABILITY CURVE
ALL ERMOUD STRATEGIES — WAC PRICES
2-YEAR TIMEFRAME
PRO1 -> gSL
VIV -> PRO1
gSL
SUB -> PRO1
SUB -> PRO2
SUB -> VIV
SUB_only
PRO1 -> SUB
PRO1 -> VIV
PRO2 -> SUB
PRO2 -> VIV
PRO2 -> gSL
VIV -> SUB
VIV -> PRO2
VIV_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
$0
$10,000
$20,000
$30,000
$40,000
$50,000
$60,000
$70,000
$80,000
$90,000
$100,000
WEIGHT ON EFFECT. (WTP)

Appendix A.4 Probabilistic Analysis Strategy Selection





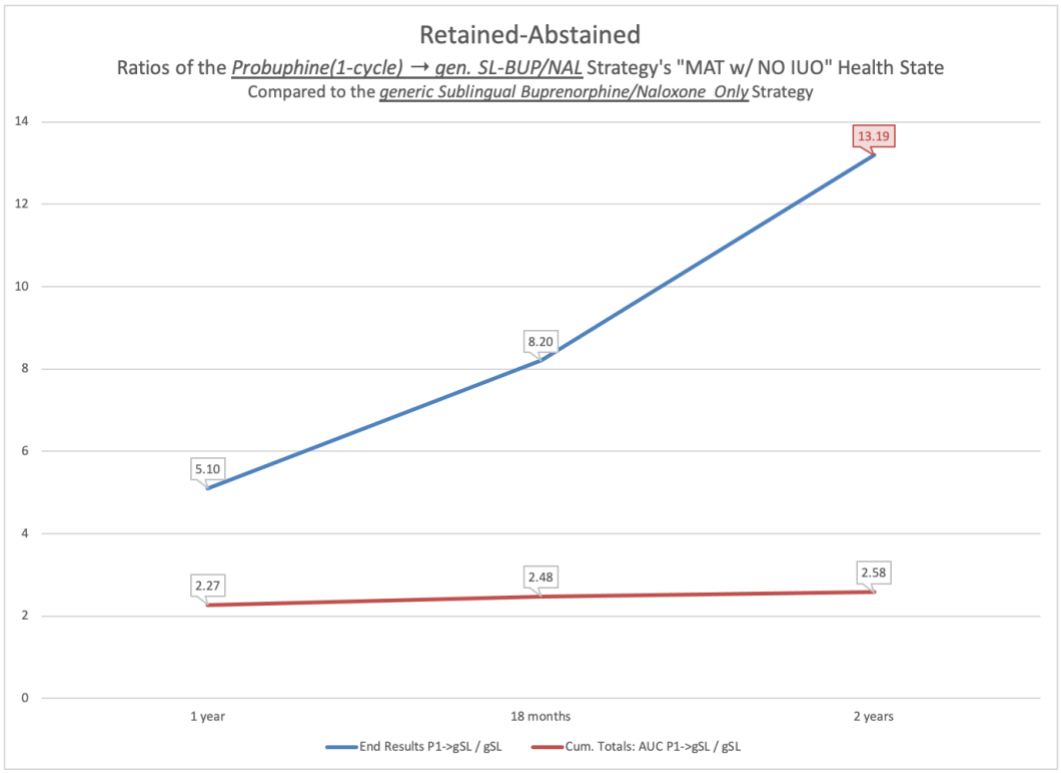

MONTE CARLO STRATEGY SELECTION
ALL ERMOUD STRATEGIES — WAC PRICES
18-MONTH TIMEFRAME
PRO1 -> gSL
VIV_only
PRO2 -> VIV
PRO1 -> VIV
PRO1 -> SUB
PRO2 -> SUB
VIV -> PRO1
VIV -> PRO2
SUB -> PRO1
SUB -> PRO2
SUB_only
SUB -> VIV
VIV -> SUB
PRO2 -> gSL
gSL
FREQUENCY OPTIMAL
0.9674
0.0318
0
0
0
0
0.0008
0
0
0
0
0
0
0
0
1

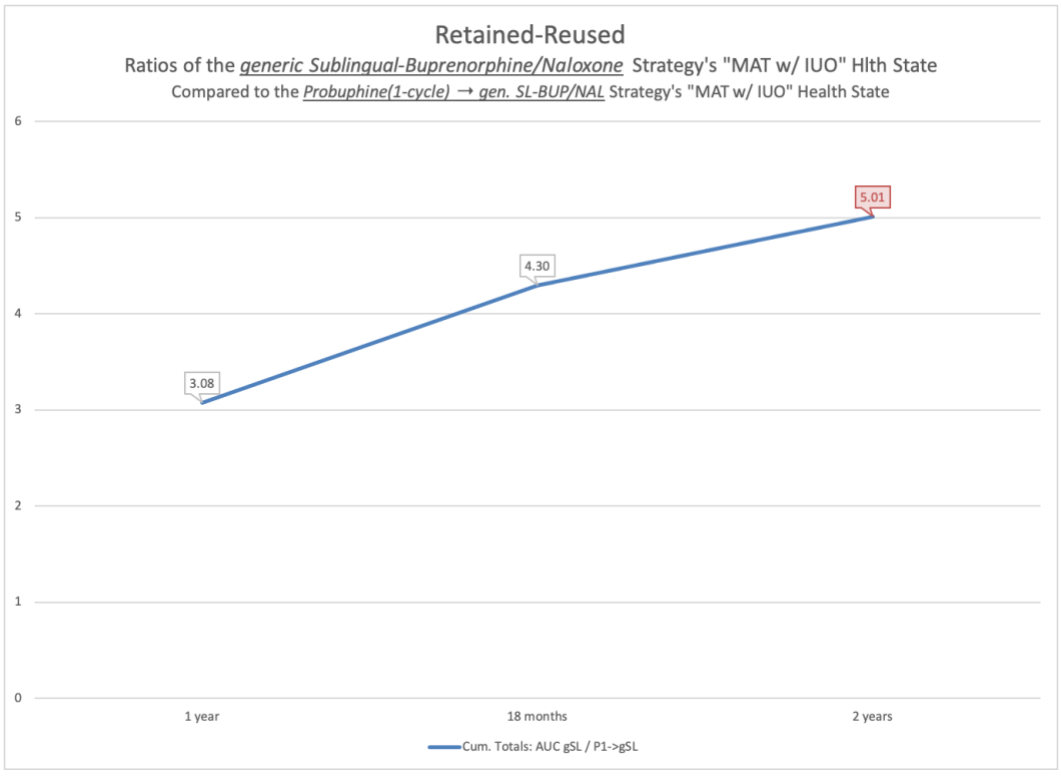

MONTE CARLO STRATEGY SELECTION
ALL ERMOUD STRATEGIES — WAC PRICES
2-YEAR TIMEFRAME
PRO1 -> gSL
VIV -> PRO1
VIV_only
PRO2 -> VIV
PRO1 -> VIV
PRO1 -> SUB
PRO2 -> SUB
VIV -> PRO2
SUB -> PRO1
SUB -> PRO2
SUB_only
SUB -> VIV
VIV -> SUB
PRO2 -> gSL
gSL
FREQUENCY OPTIMAL
0.9618
0.0212
0.017
0
0
0
0
0
0
0
0
0
0
0
0
1

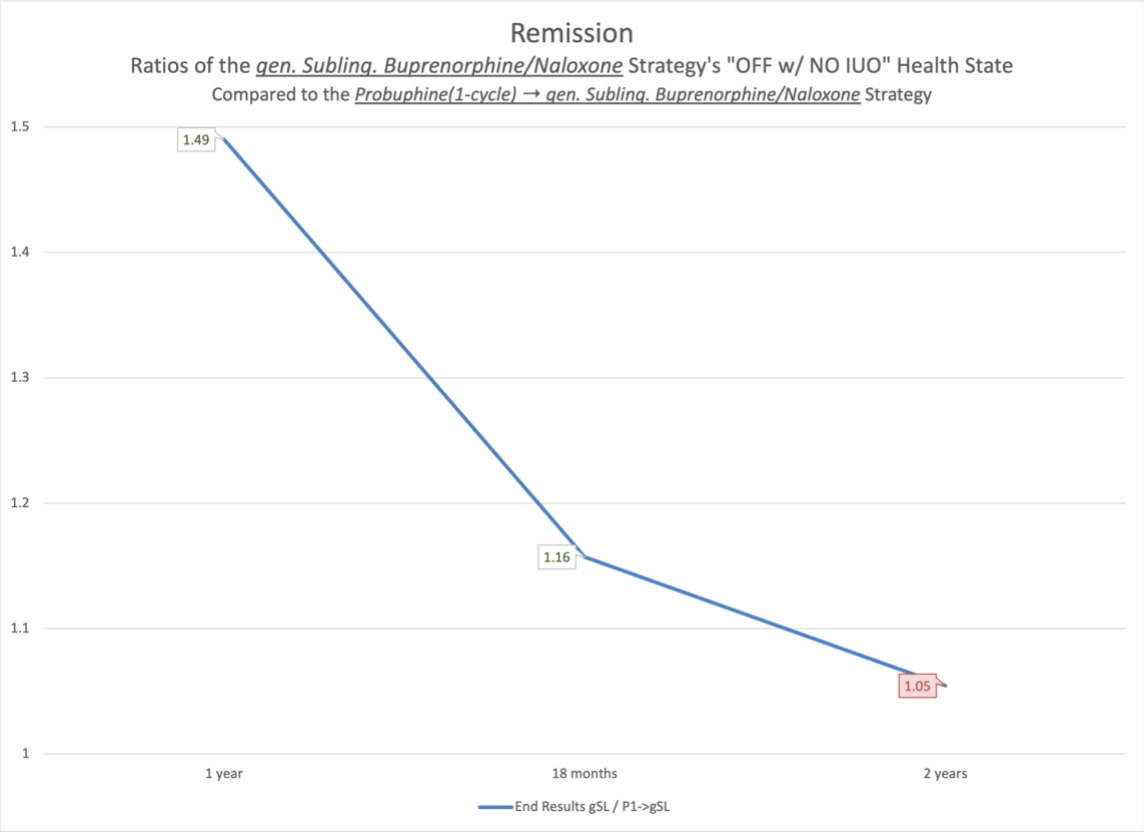
Appendix A.5 One-Way Sensitivity Analysis Tornado Diagram Variable Table

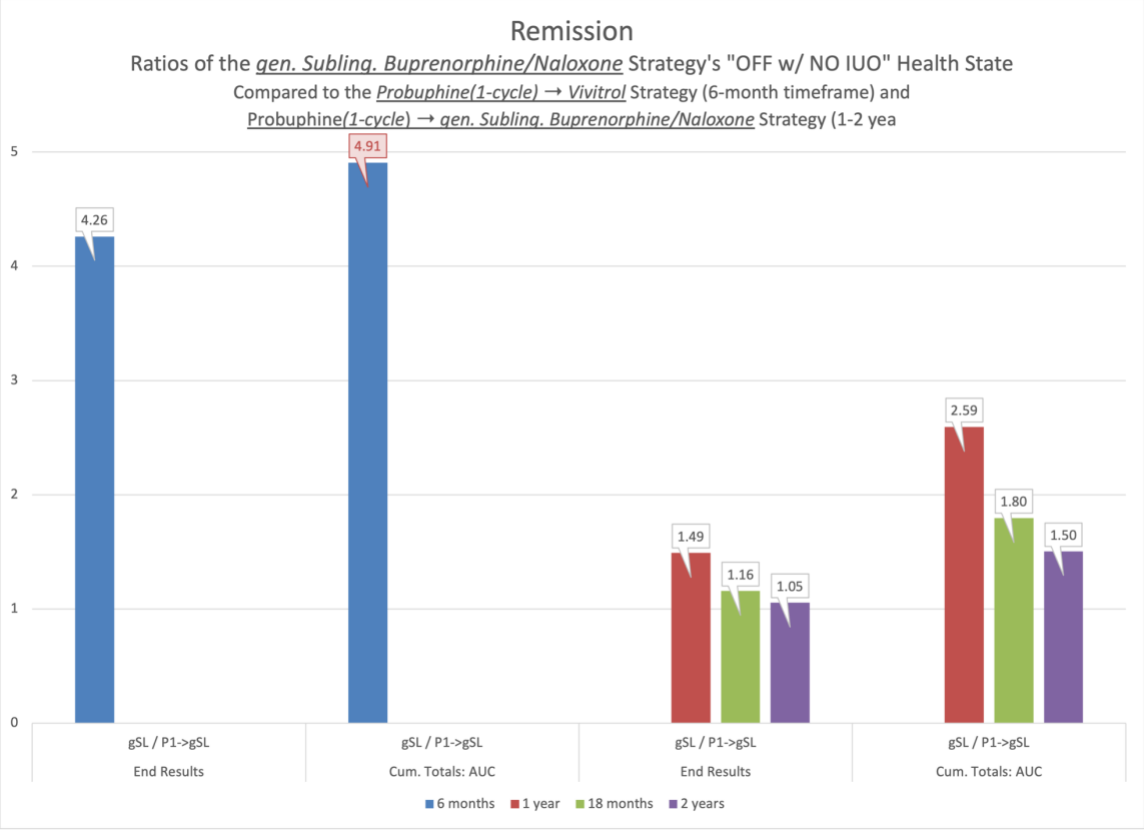
6-months	1-year	18-months	2-year
"Probuphine → gSL-Bup/Nal" vs. "Probuphine → Vivitrol"	**Weekly Probability of Leaving Vivitrol Treatment**		
Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	**Weekly Probability of Passing Probuphine Induction and Entering MAT with Probuphine**		
Weekly Probability of Leaving Vivitrol Treatment	**Weekly Probability of Illicitly Using Opioids While on Vivitrol MAT**		
Weekly Probability of Illicitly Using Opioids While on Vivitrol MAT	Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	Weekly Probability of Passing gSL-Bup/Nal Induction and Entering MAT with gSL-Bup/Nal	
	Weekly Probability of Passing gSL-Bup/Nal Induction and Entering MAT with gSL-Bup/Nal	Weekly Probability of Succeeding Vivitrol Induction and Entering MAT with Vivitrol	
	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT	Weekly Probability of Discontinuing gSL-Bup/Nal following Probuphine Explantation	
	Weekly Probability of Discontinuing gSL-Bup/Nal following Probuphine Explantation	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT
	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT	Weekly Probability of Illicitly Using Opioids While on Probuphine MAT	Weekly Probability of Illicitly Using Opioids While on gSL-Bup/Nal MAT
	Weekly Probability of Dying While on Vivitrol MAT	Weekly Probability of Discontinuing Probuphine Treatment	
	Weekly Probability of Discontinuing Probuphine Treatment	Weekly Probability of Dying While on Vivitrol MAT	
		Weekly Probability of Dying After Probuphine MAT with NO Illicit Use of Opioids	

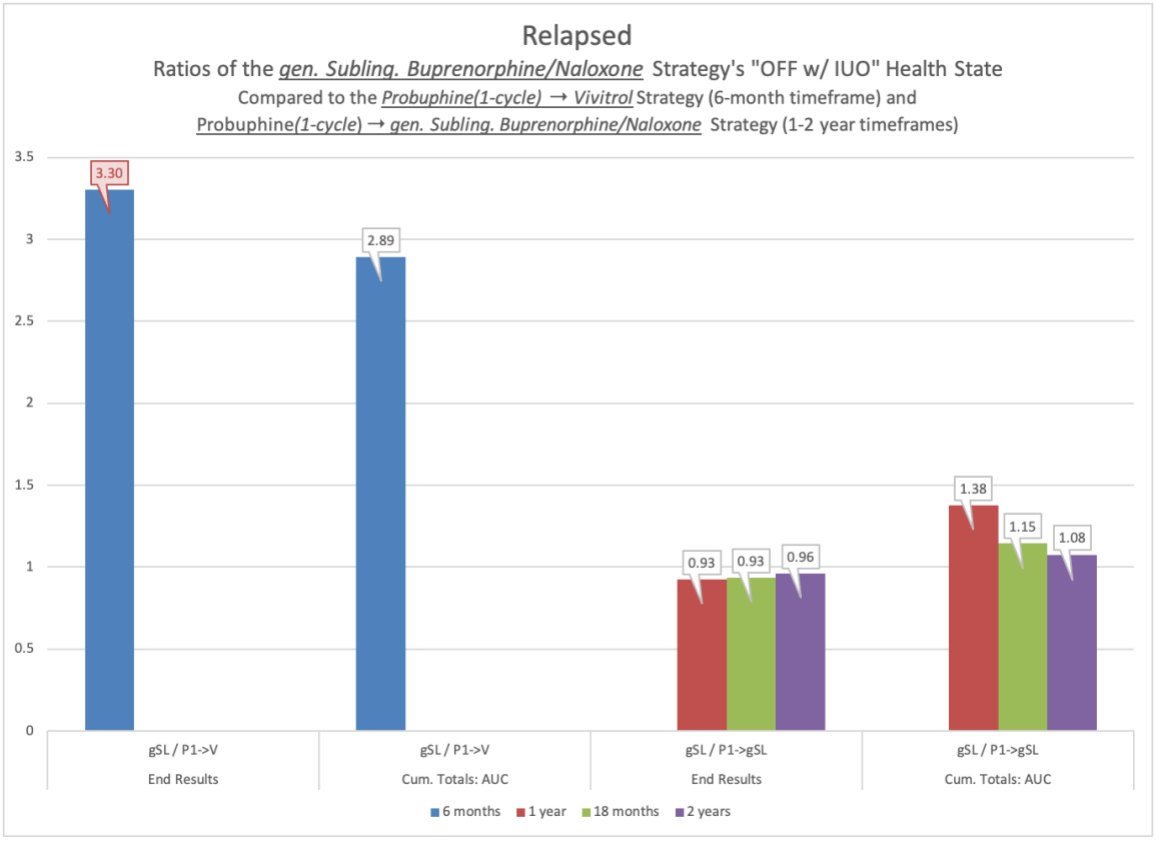
Appendix A.6 Health State Proportions Comparisons

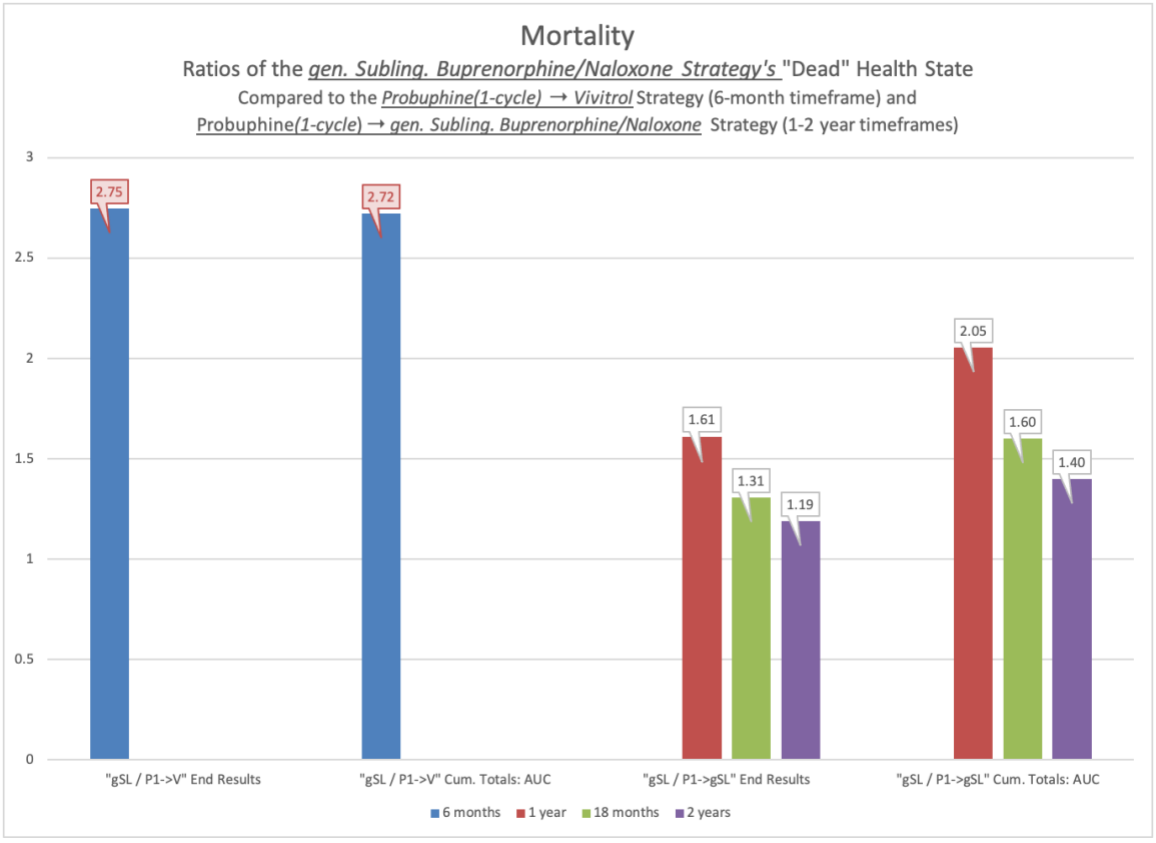





Remission
Ratios of the gen. Subling. Buprenorphine/Naloxone Strategy's "OFF w/ NO IUO" Health State
Compared to the Probuphine(1-cycle) → gen. Subling. Buprenorphine/Naloxone Strategy
1.5
1.4
1.3
1.2
1.1
1
1.49
1.16
1.05
1 year
18 months
2 years
End Results gSL / P1->gSL


Remission
Ratios of the gen. Subling. Buprenorphine/Naloxone Strategy's "OFF w/ NO IUO" Health State
Compared to the Probuphine(1-cycle) → Vivitrol Strategy (6-month timeframe) and
Probuphine(1-cycle) → gen. Subling. Buprenorphine/Naloxone Strategy (1-2 yea
5
4
3
2
1
0
4.26
4.91
1.49
1.16
1.05
2.59
1.80
1.50
gSL / P1->gSL
End Results
gSL / P1->gSL
Cum. Totals: AUC
gSL / P1->gSL
End Results
gSL / P1->gSL
Cum. Totals: AUC
6 months
1 year
18 months
2 years


Relapsed
Ratios of the gen. Subling. Buprenorphine/Naloxone Strategy's "OFF w/ IUO" Health State
Compared to the Probuphine(1-cycle) → Vivitrol Strategy (6-month timeframe) and
Probuphine(1-cycle) → gen. Subling. Buprenorphine/Naloxone Strategy (1-2 year timeframes)
3.5
3
2.5
2
1.5
1
0.5
0
3.30
2.89
0.93
0.93
0.96
1.38
1.15
1.08
gSL / P1->V End Results
gSL / P1->V Cum. Totals: AUC
gSL / P1->gSL End Results
gSL / P1->gSL Cum. Totals: AUC
6 months
1 year
18 months
2 years


Mortality
Ratios of the gen. Subling. Buprenorphine/Naloxone Strategy's "Dead" Health State
Compared to the Probuphine(1-cycle) → Vivitrol Strategy (6-month timeframe) and
Probuphine(1-cycle) → gen. Subling. Buprenorphine/Naloxone Strategy (1-2 year timeframes)
3
2.5
2
1.5
1
0.5
0
2.75
2.72
1.61
1.31
1.19
2.05
1.60
1.40
"gSL / P1->V" End Results
"gSL / P1->V" Cum. Totals: AUC
"gSL / P1->gSL" End Results
"gSL / P1->gSL" Cum. Totals: AUC
6 months
1 year
18 months
2 years

Appendix B Additional Tables and Figures for:

Comparing Different Drug Pricing Schedules in Cost-Effectiveness Analyses of Extended-Release Medications for Opioid Use Disorder: Including Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

Appendix B.1 Most Cost-Effective Treatment Strategies

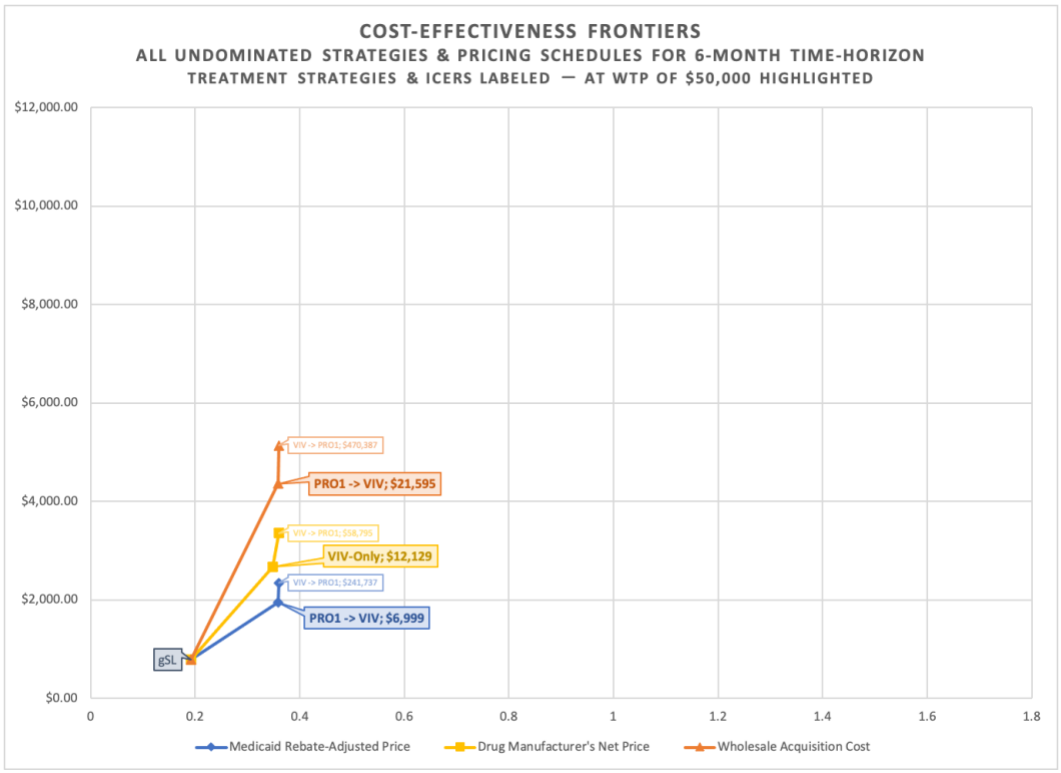
Appendix B.1.1 By Incremental Cost-Effectiveness Ratios

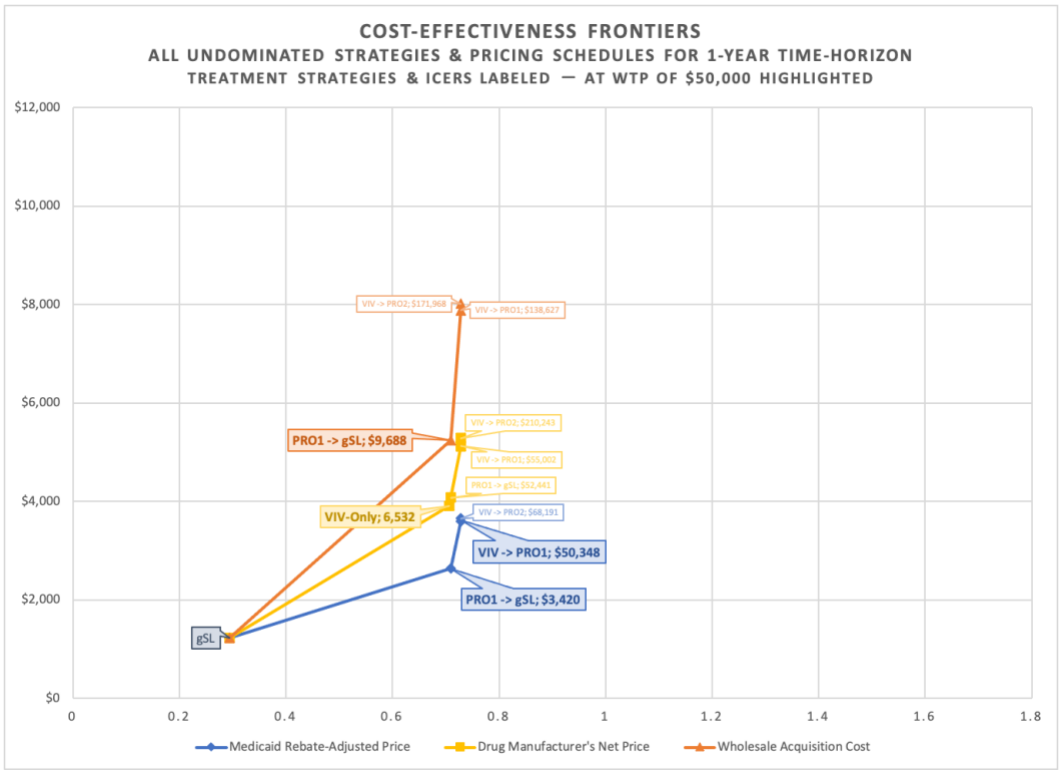
by ICER	6-months	1-year	18-months	2-years
Wholesale Acquisition Cost (WAC)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		
Drug Manufacturer's Net (DMN)	Vivitrol-Only		Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone	
Medicaid Rebate-Adjusted (MRA)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		

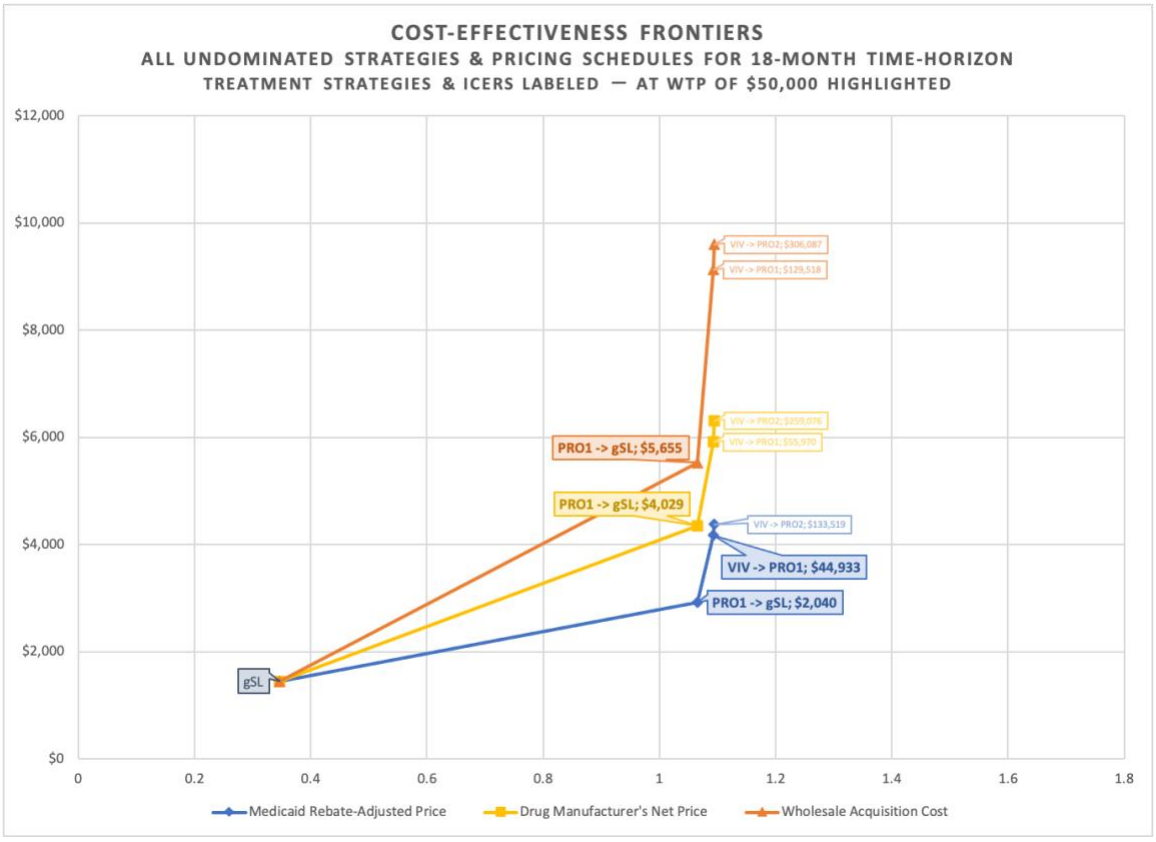
Appendix B.1.2 By Monte Carlo Strategy Selection

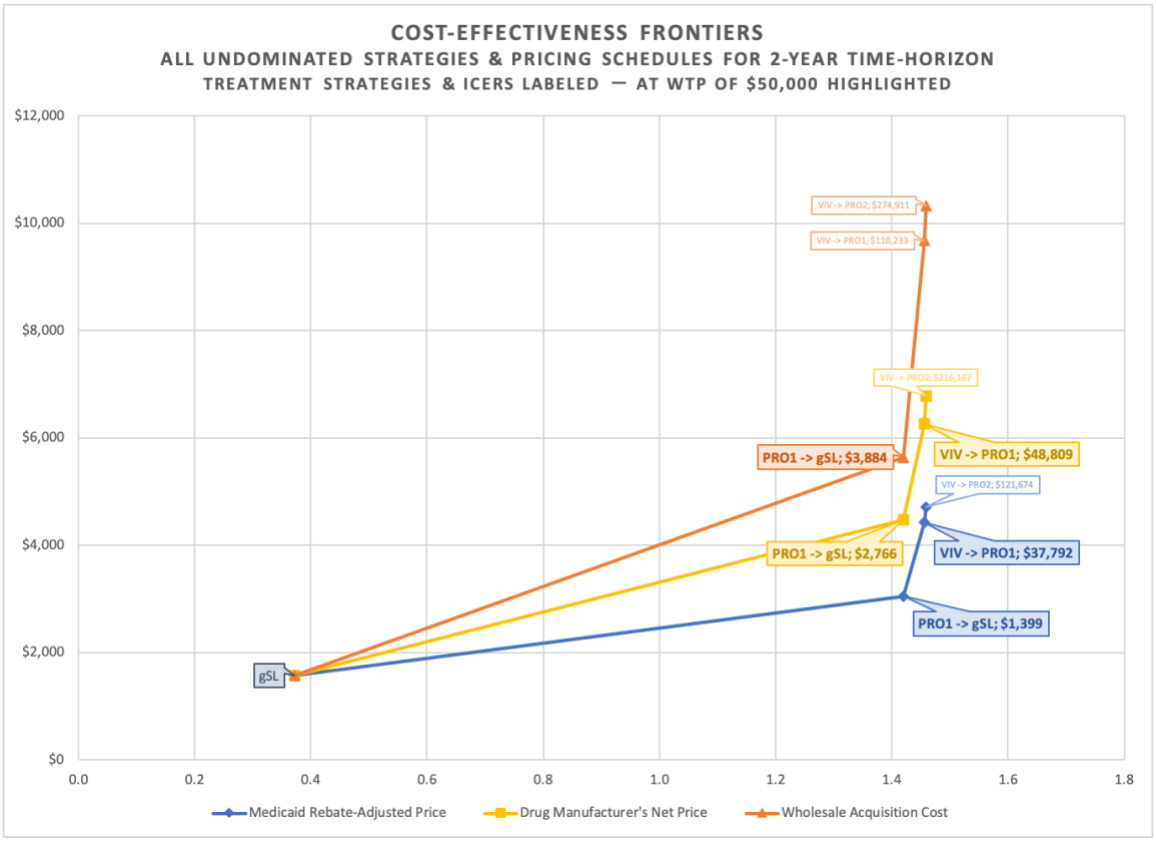
by Monte Carlo	6-months	1-year	18-months	2-years
Wholesale Acquisition Cost (WAC)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		
Drug Manufacturer's Net (DMN)	Vivitrol-Only	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		
Medicaid Rebate-Adjusted (MRA)	Probuphine (1-cycle) → Vivitrol	Probuphine (1-cycle) → generic Sublingual Buprenorphine/Naloxone		Vivitrol → Probuphine (1-cycle)

Appendix B.2 Cost-Effectiveness Frontiers



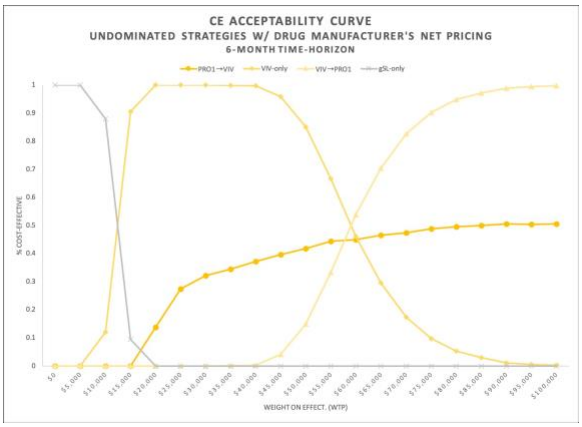


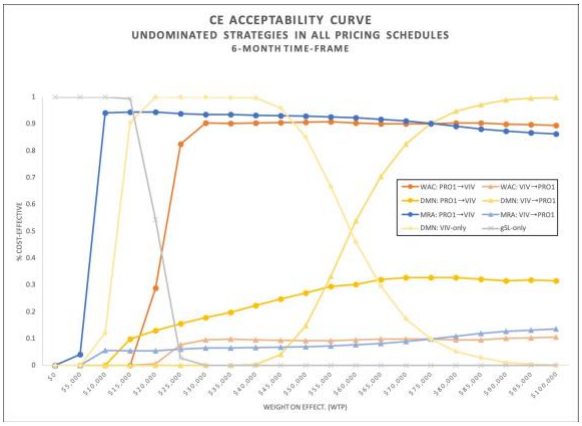

COST-EFFECTIVENESS FRONTIERS
ALL UNDOMINATED STRATEGIES & PRICING SCHEDULES FOR 18-MONTH TIME-HORIZON
TREATMENT STRATEGIES & ICERS LABELED — AT WTP OF $50,000 HIGHLIGHTED
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
VIV -> PRO2; $306,087
VIV -> PRO1; $129,518
VIV -> PRO2; $259,076
VIV -> PRO1; $55,970
PRO1 -> gSL; $5,655
PRO1 -> gSL; $4,029
VIV -> PRO2; $133,519
VIV -> PRO1; $44,933
PRO1 -> gSL; $2,040
gSL
Medicaid Rebate-Adjusted Price
Drug Manufacturer's Net Price
Wholesale Acquisition Cost


COST-EFFECTIVENESS FRONTIERS
ALL UNDOMINATED STRATEGIES & PRICING SCHEDULES FOR 2-YEAR TIME-HORIZON
TREATMENT STRATEGIES & ICERS LABELED — AT WTP OF $50,000 HIGHLIGHTED
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
VIV -> PRO2; $274,911
VIV -> PRO1; $110,233
VIV -> PRO2; $216,167
PRO1 -> gSL; $3,884
VIV -> PRO1; $48,809
VIV -> PRO2; $121,674
PRO1 -> gSL; $2,766
VIV -> PRO1; $37,792
PRO1 -> gSL; $1,399
gSL
Medicaid Rebate-Adjusted Price
Drug Manufacturer's Net Price
Wholesale Acquisition Cost

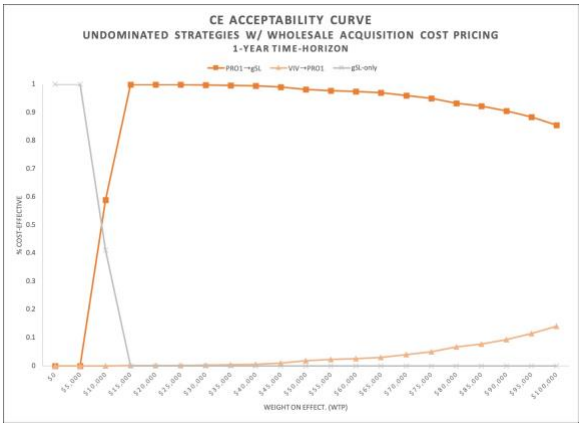
Appendix B.3 Monte Carlo Acceptability Curves

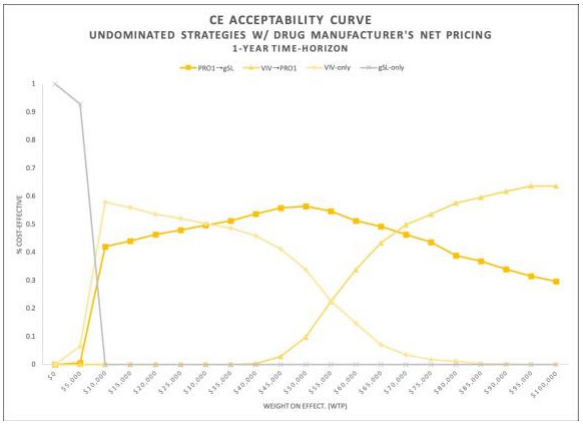
Appendix B.3.1 6-month timeframe

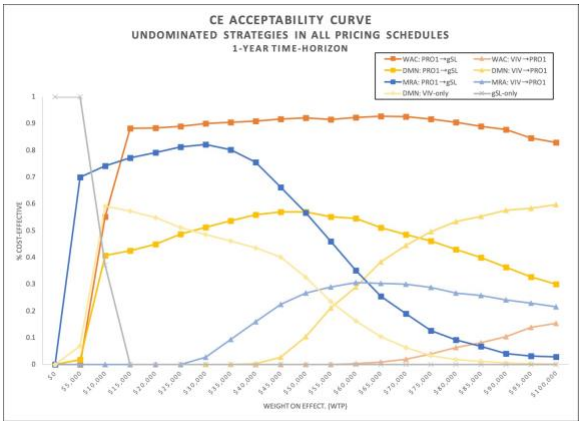




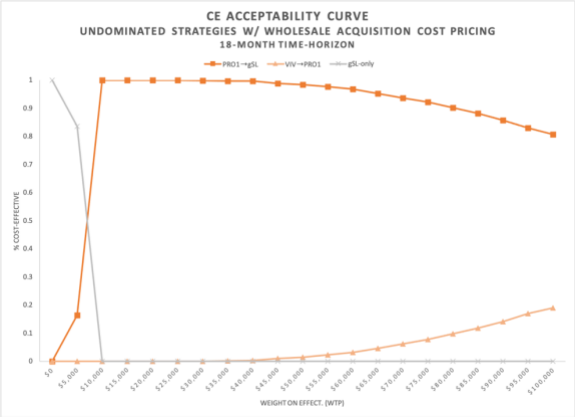
Appendix B.3.2 1-year timeframe

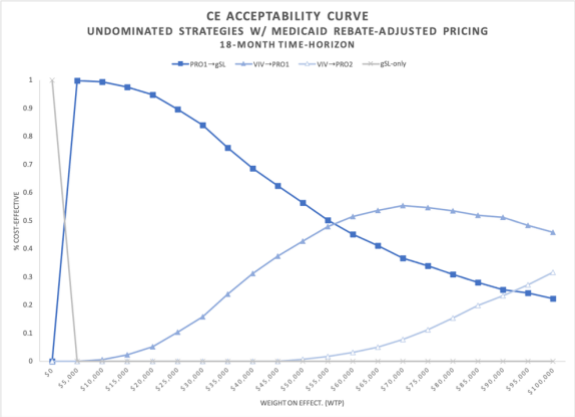


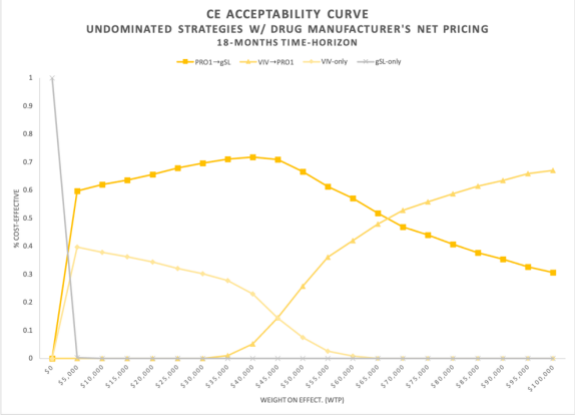


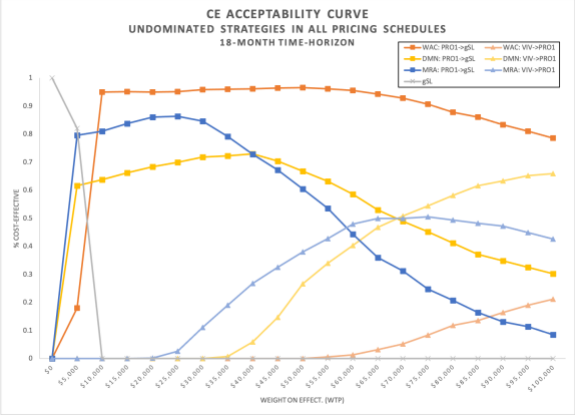


Appendix B.3.3 18-month timeframe

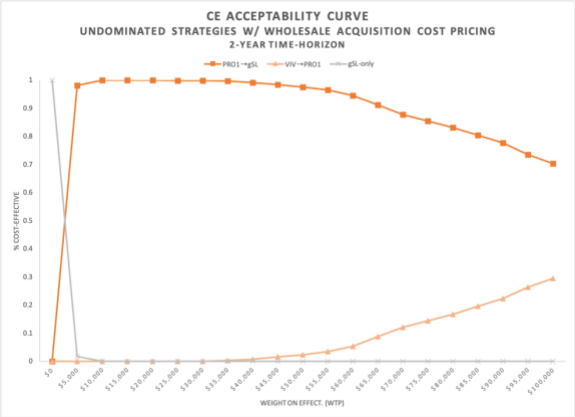


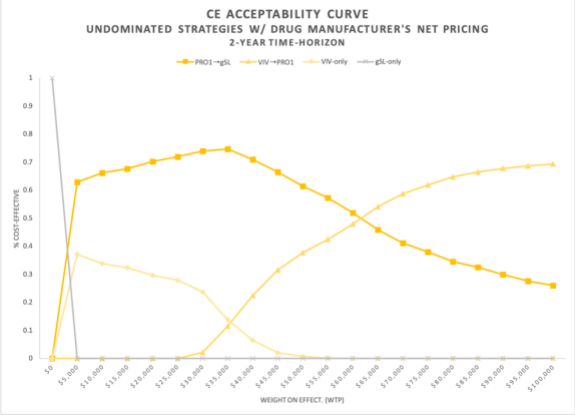


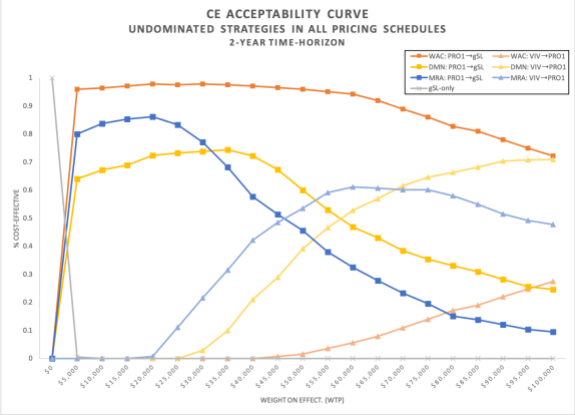




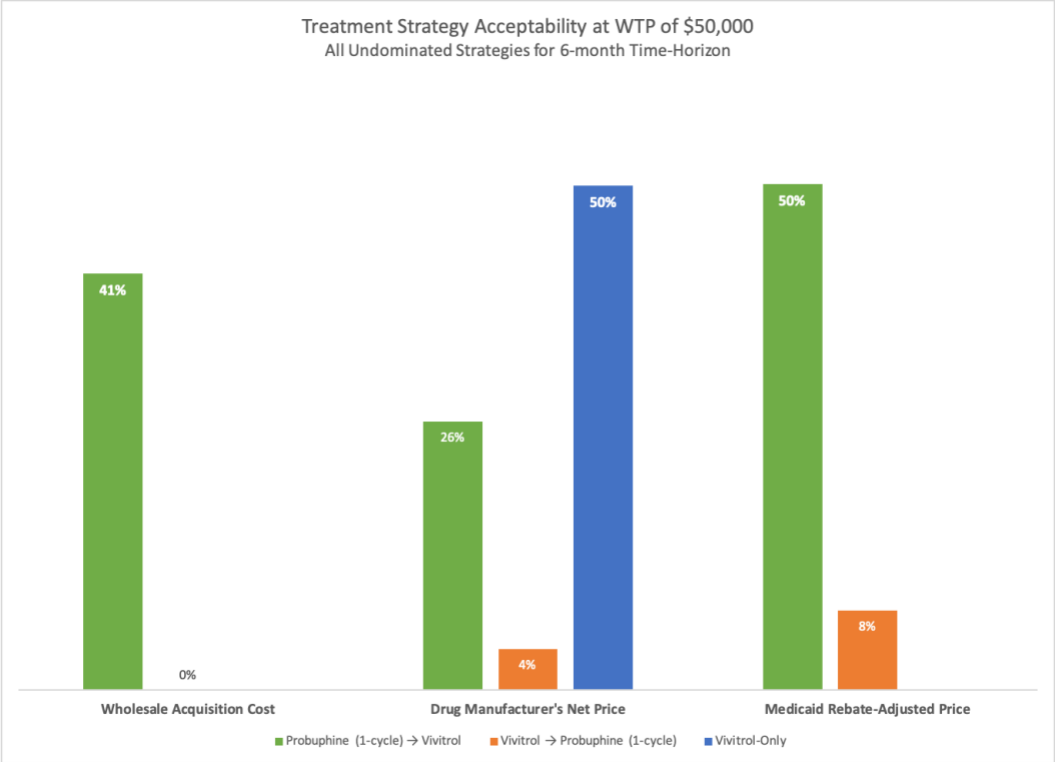
Appendix B.3.4 2-year timeframe

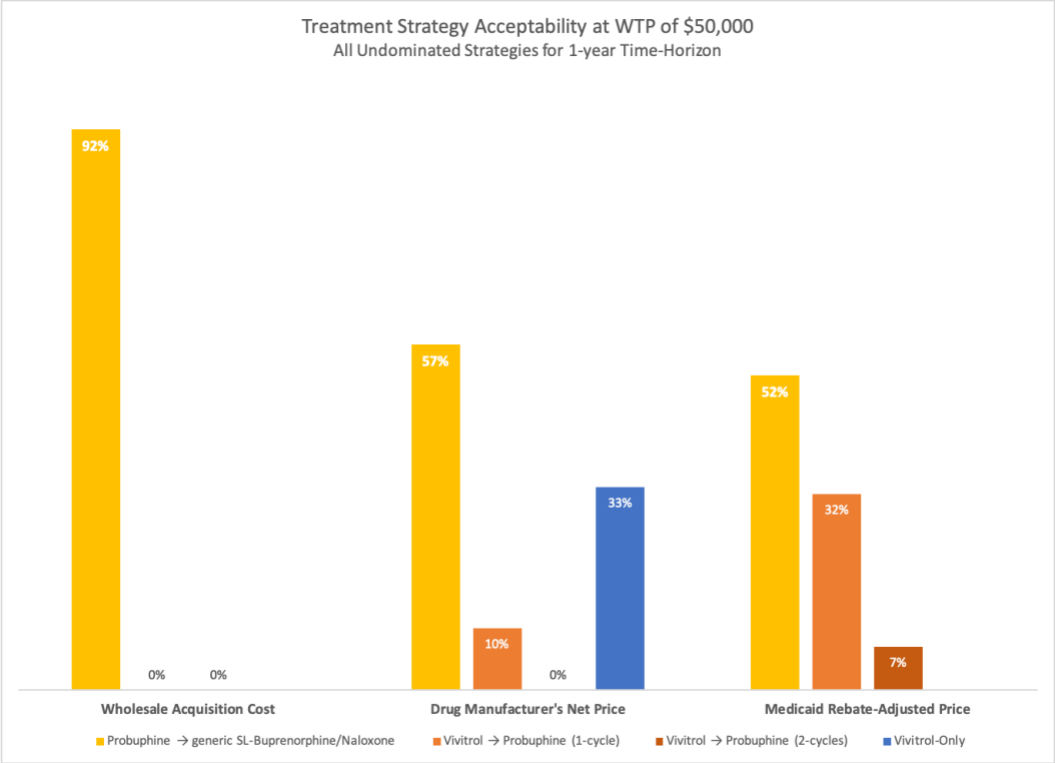


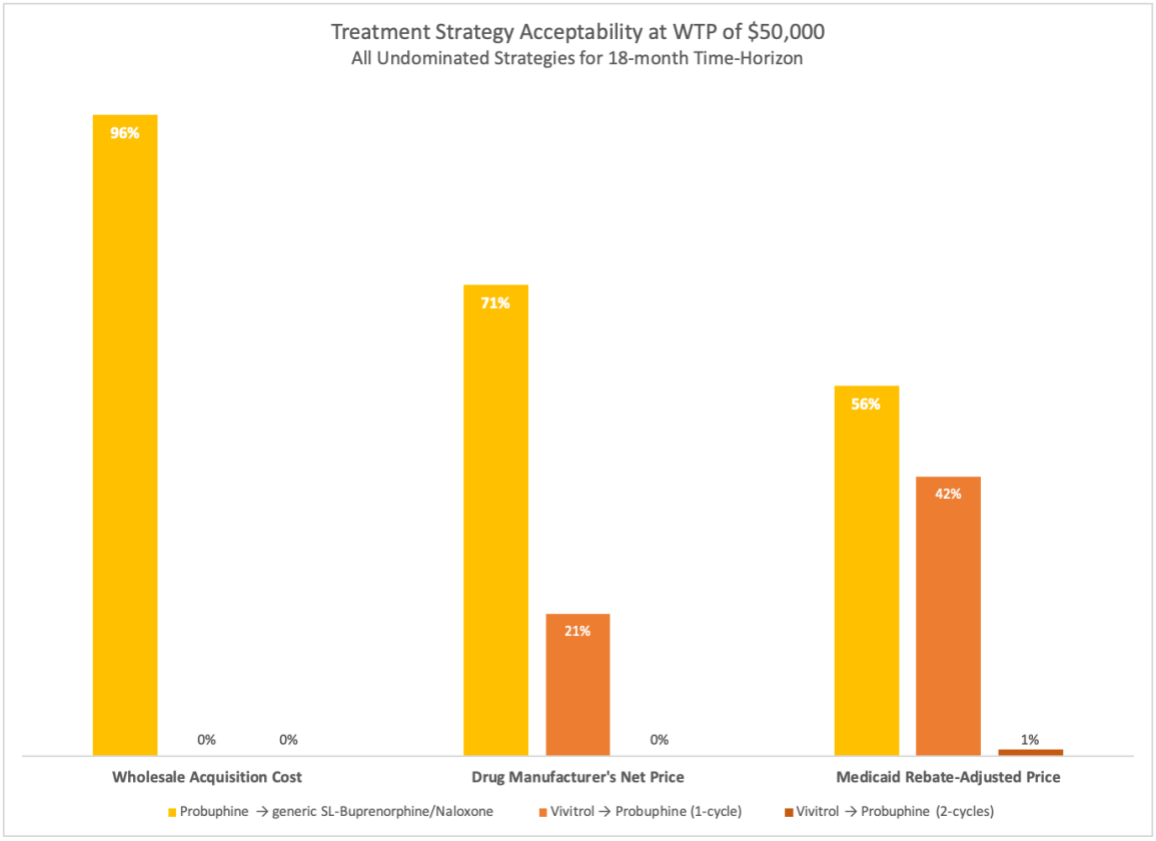


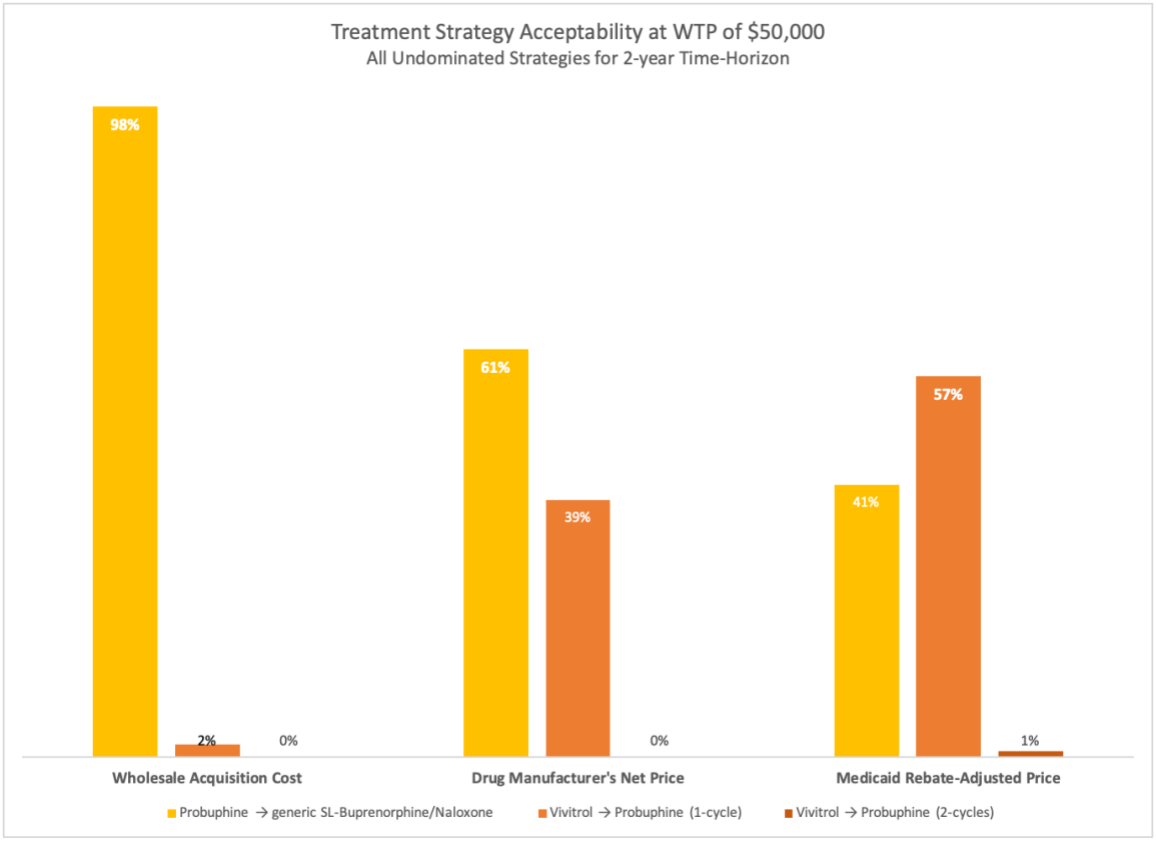


Appendix B.4 Probabilistic Analysis Strategy Selection






Treatment Strategy Acceptability at WTP of $50,000
All Undominated Strategies for 18-month Time-Horizon
96%
0%
0%
71%
21%
0%
56%
42%
1%
Wholesale Acquisition Cost
Drug Manufacturer's Net Price
Medicaid Rebate-Adjusted Price
Probuphine → generic SL-Buprenorphine/Naloxone
Vivitrol → Probuphine (1-cycle)
Vivitrol → Probuphine (2-cycles)


Treatment Strategy Acceptability at WTP of $50,000
All Undominated Strategies for 2-year Time-Horizon
98%
2%
0%
61%
39%
0%
41%
57%
1%
Wholesale Acquisition Cost
Drug Manufacturer's Net Price
Medicaid Rebate-Adjusted Price
Probuphine → generic SL-Buprenorphine/Naloxone
Vivitrol → Probuphine (1-cycle)
Vivitrol → Probuphine (2-cycles)

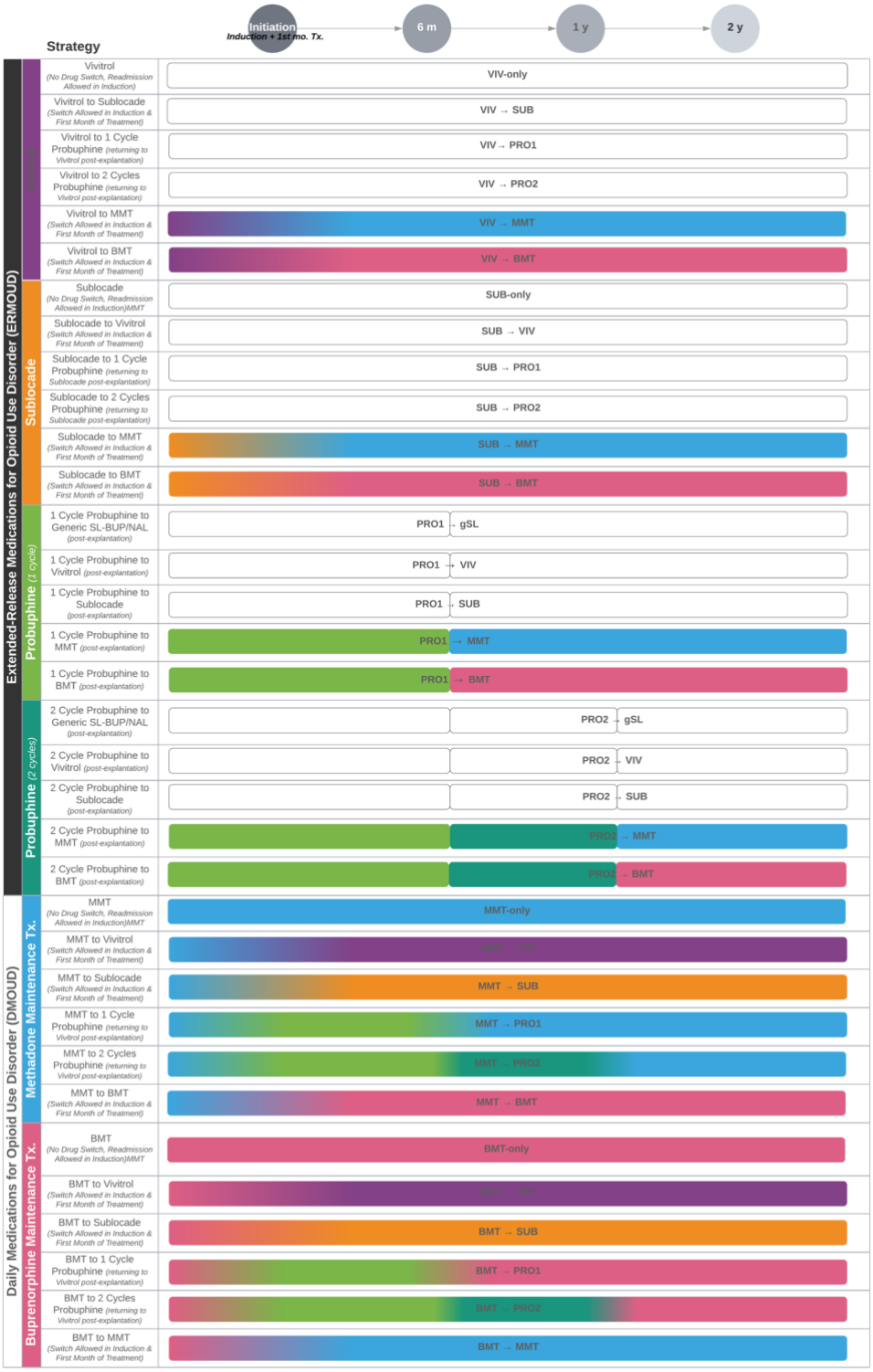
Appendix B.5 One-Way Sensitivity Analysis Tornado Diagram Variable Comparison

	6-month	1-year	18-months	2-years
MRA	Probuphine Induction Success			Probuphine Treatment Retention
	gSL-Only Induction Success	Success Transfer to gSL after Probuphine	gSL-Only Induction Success	Vivitrol Treatment Attrition
	gSL-Only Treatment Attrition	gSL-Only Induction Success	Successful Transfer to gSL after Probuphine	Vivitrol Induction Success
DMN	Vivitrol Induction Success		Probuphine Induction Success	
	gSL-Only Induction Success	Vivitrol Treatment Attrition	Successful Transfer to gSL after Probuphine	
	Vivitrol Treatment Attrition	gSL-Only Induction Success	gSL Treatment Attrition after Probuphine	gSL-Only Induction Success
WAC	gSL-Only Induction Success	Probuphine Induction Success		
	Probuphine Induction Success	gSL-Only Induction Success		Successful Transfer to gSL after Probuphine
	gSL-Only Treatment Attrition		Successful Transfer to gSL after Probuphine	gSL Treatment Attrition after Probuphine

Appendix C Additional Tables and Figures for:

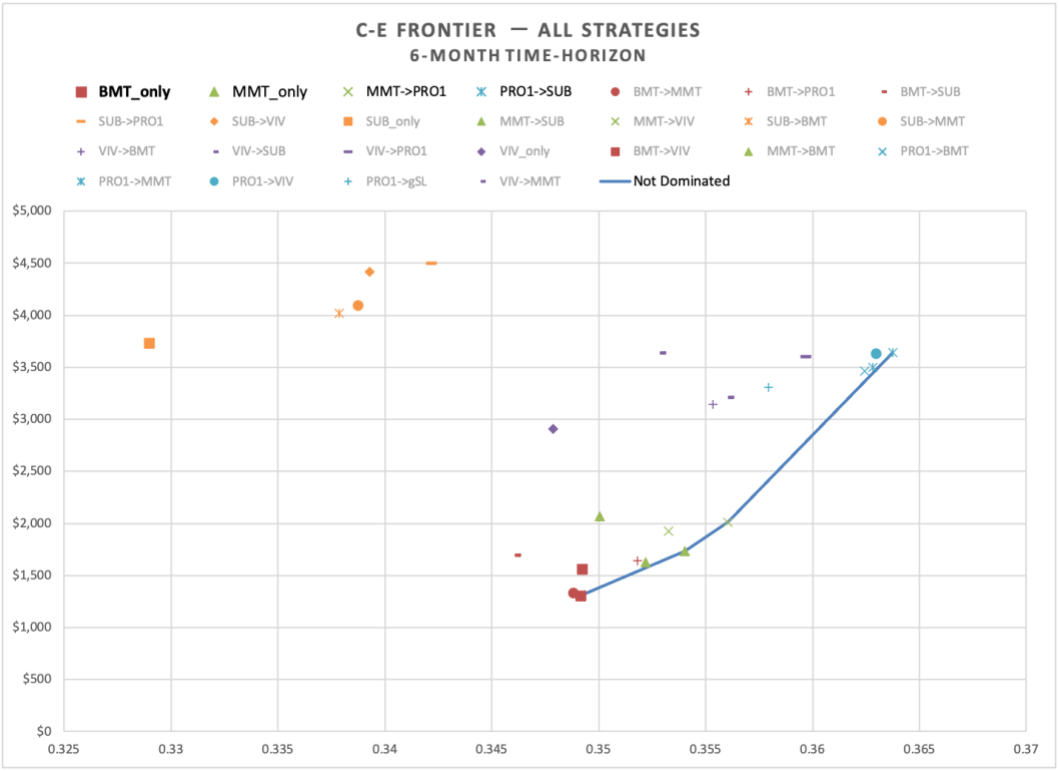
Comparing Methadone & Buprenorphine Maintenance Treatments with Extended-Release Medications for Opioid Use Disorder: Including Single-Drug and Multi-Drug-in-Sequence Treatment Strategies

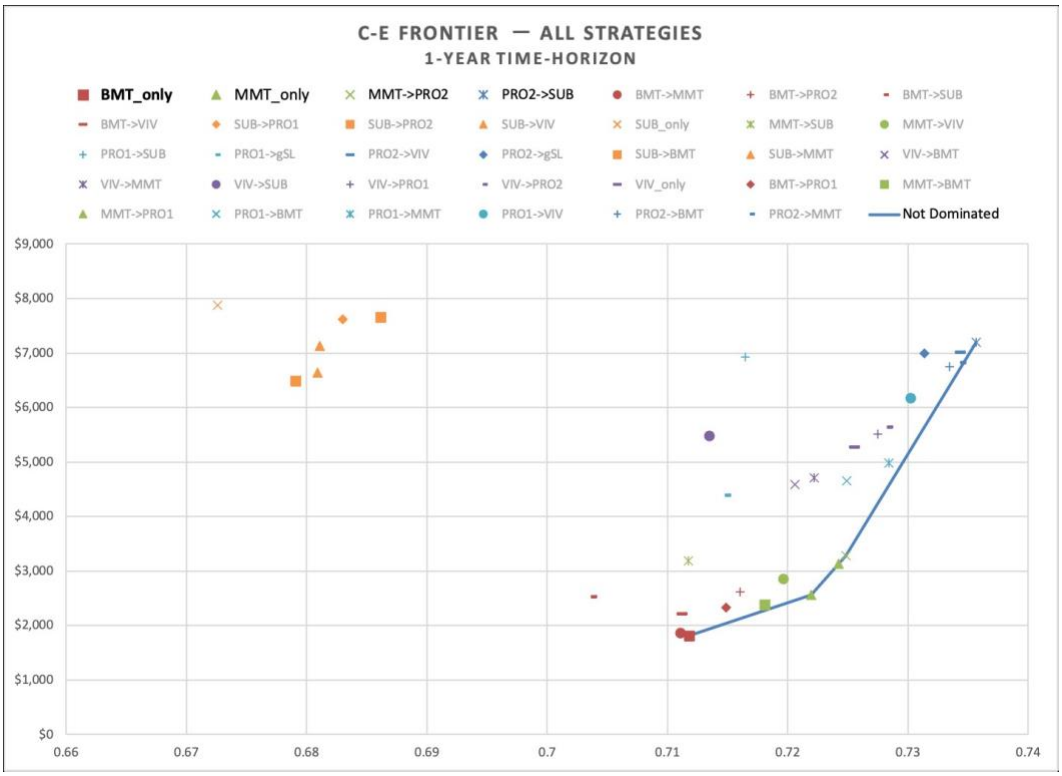
Appendix C.1 Treatment Strategies Added to Previous Study

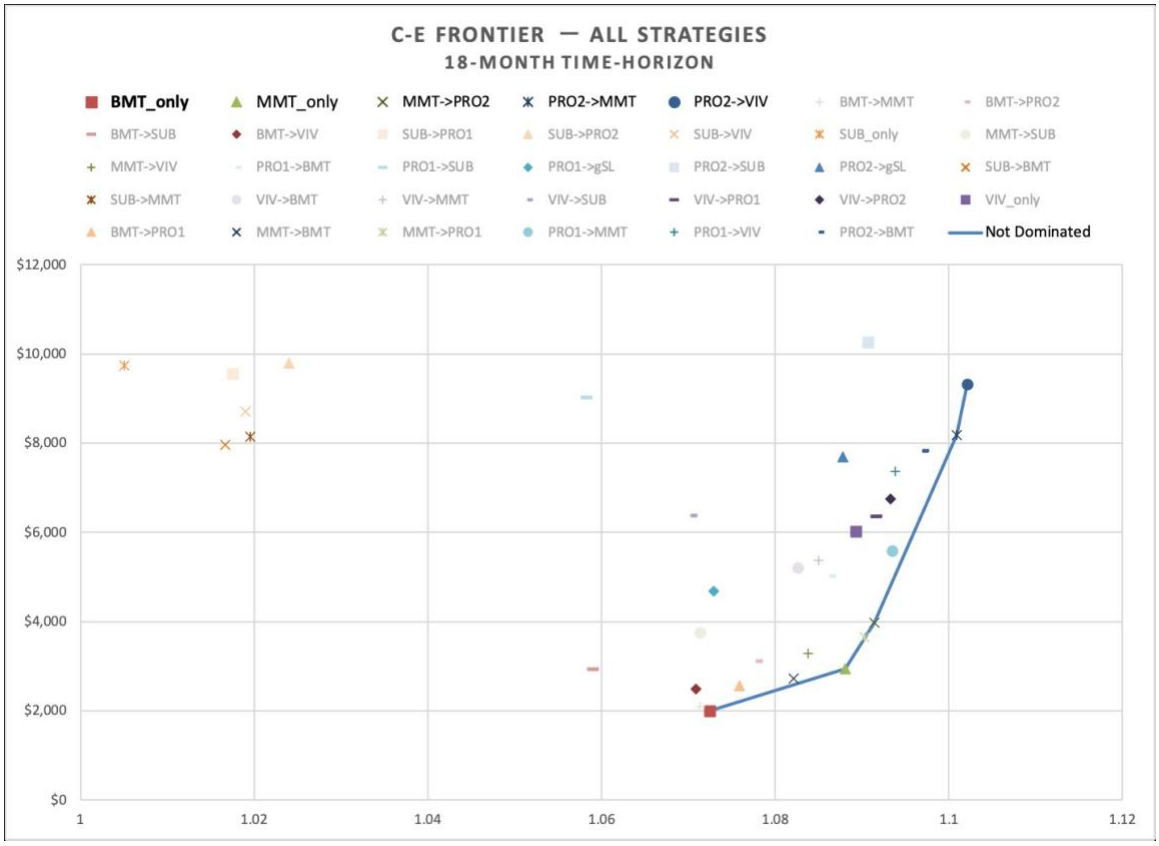


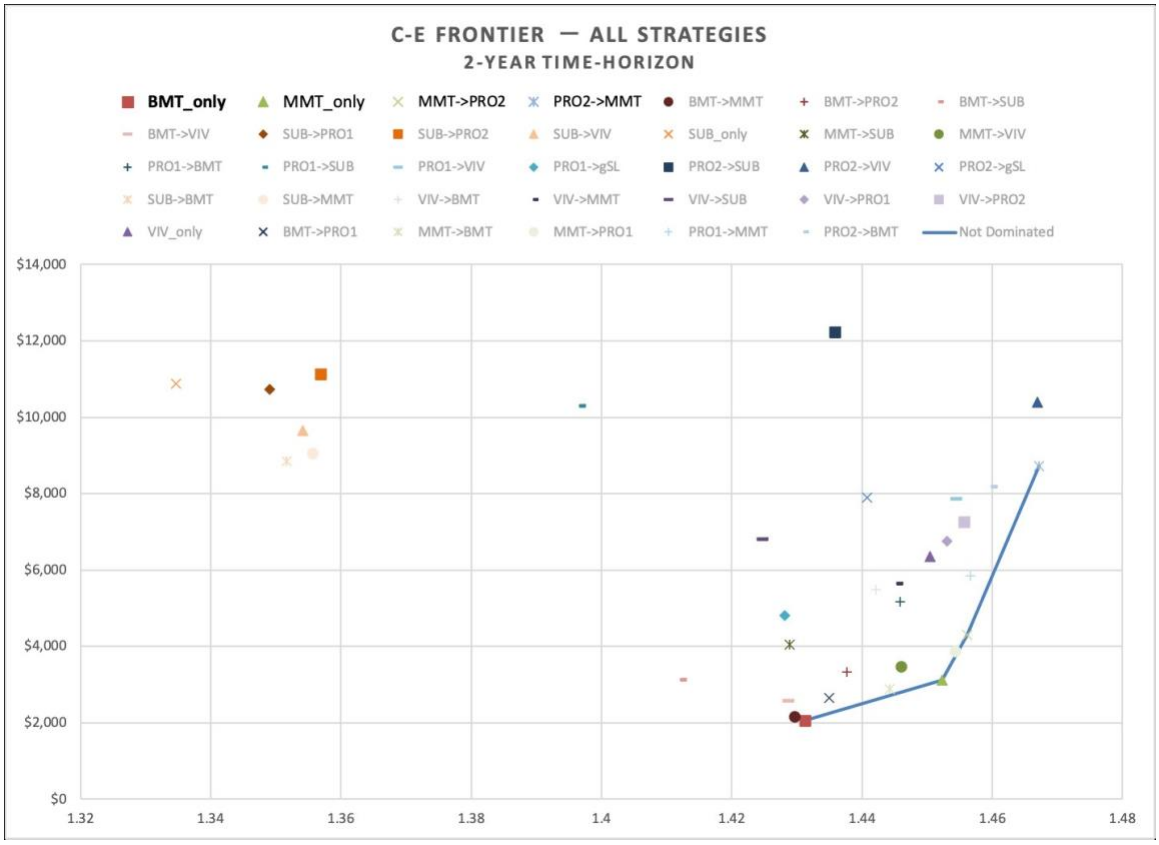
VIV: Vivitrol BUPXR: Sublocade gSL: generic Sublingual-Buprenorphine/Naloxone PRO1/PRO2: Probuphine (1-cycle/2-cycles)
MMT: Methadone Maintenance Treatment BMT: Buprenorphine Mainenance Treatment

Appendix C.2 Cost-Effectiveness Frontiers (All Strategies)

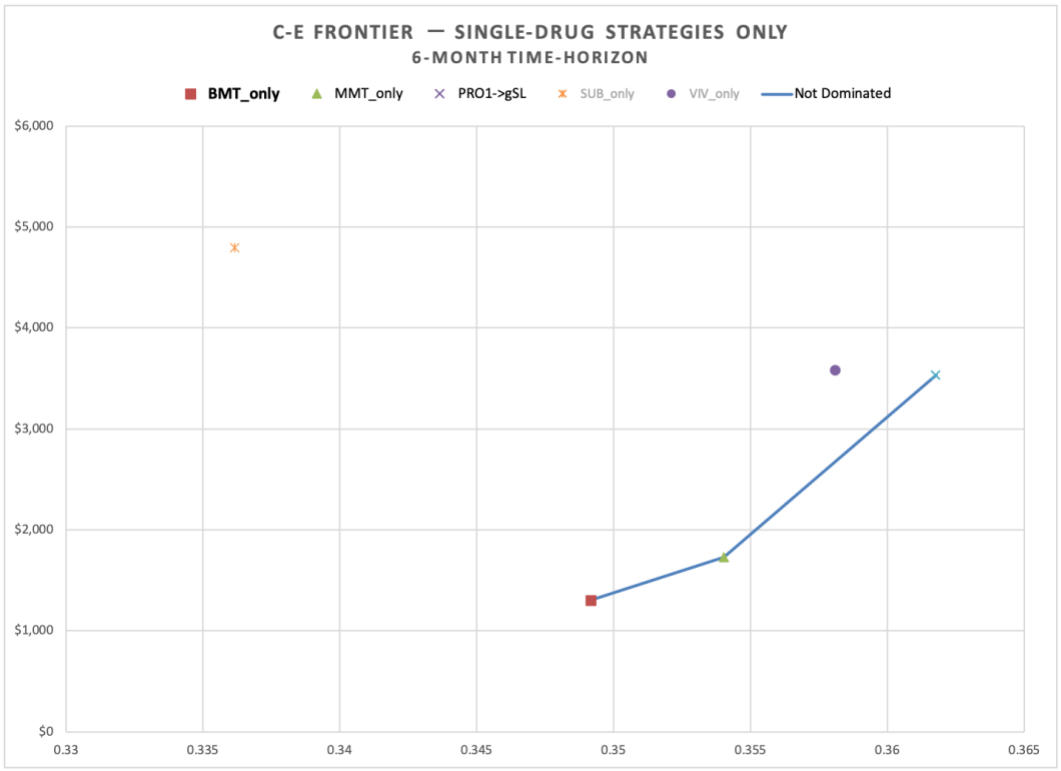


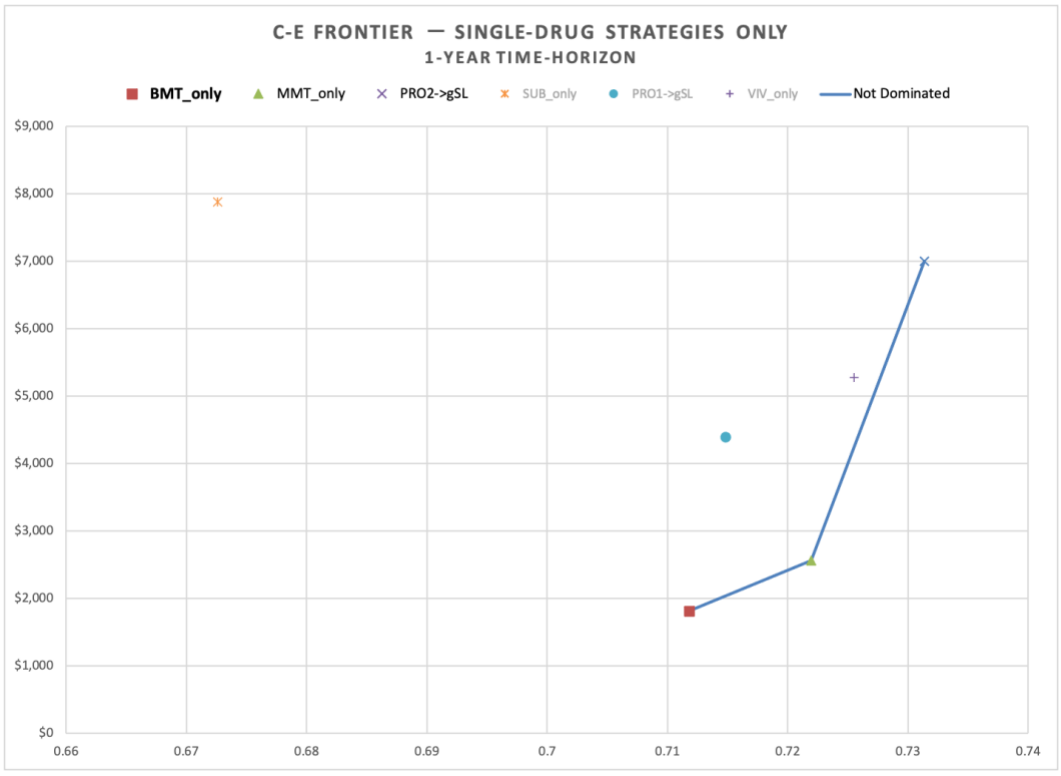


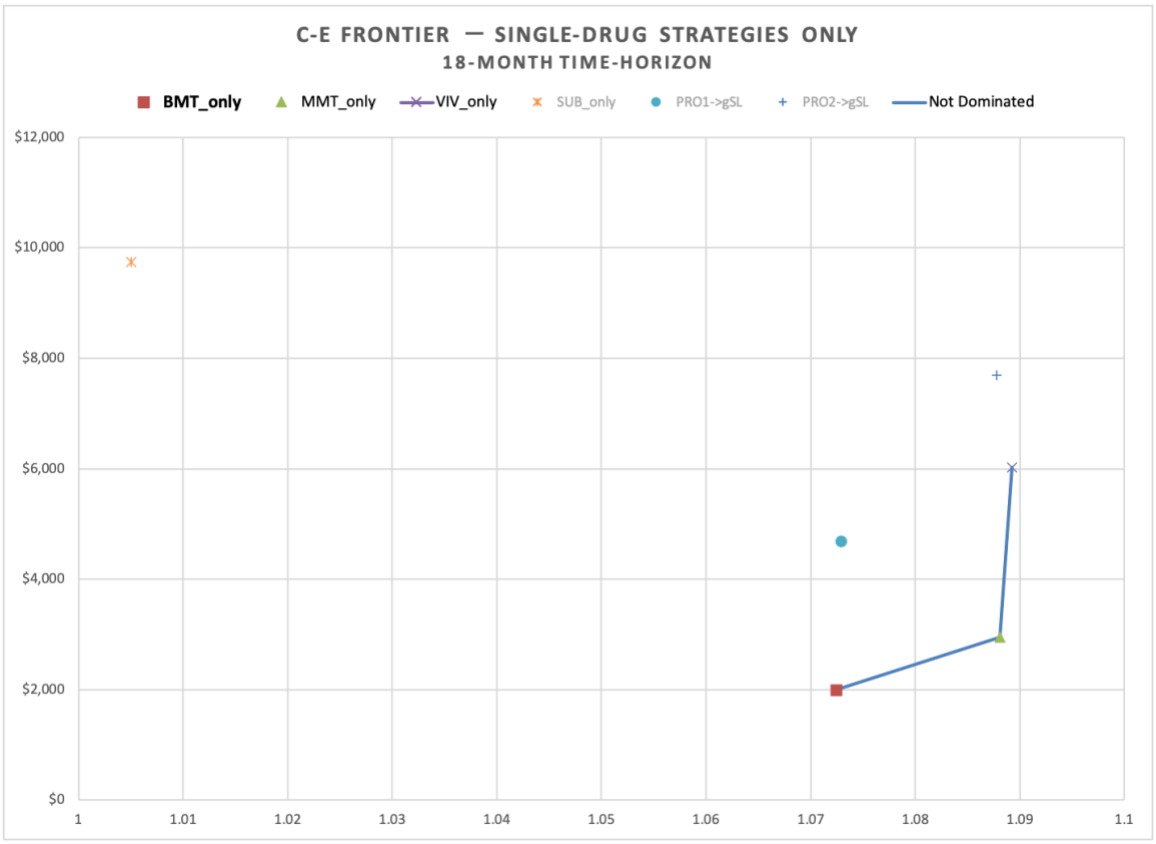

C-E FRONTIER — ALL STRATEGIES
18-MONTH TIME-HORIZON
BMT_only
MMT_only
MMT->PRO2
PRO2->MMT
PRO2->VIV
BMT->MMT
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->gSL
PRO2->SUB
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
BMT->PRO1
MMT->BMT
MMT->PRO1
PRO1->MMT
PRO1->VIV
PRO2->BMT
Not Dominated
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
1
1.02
1.04
1.06
1.08
1.1
1.12

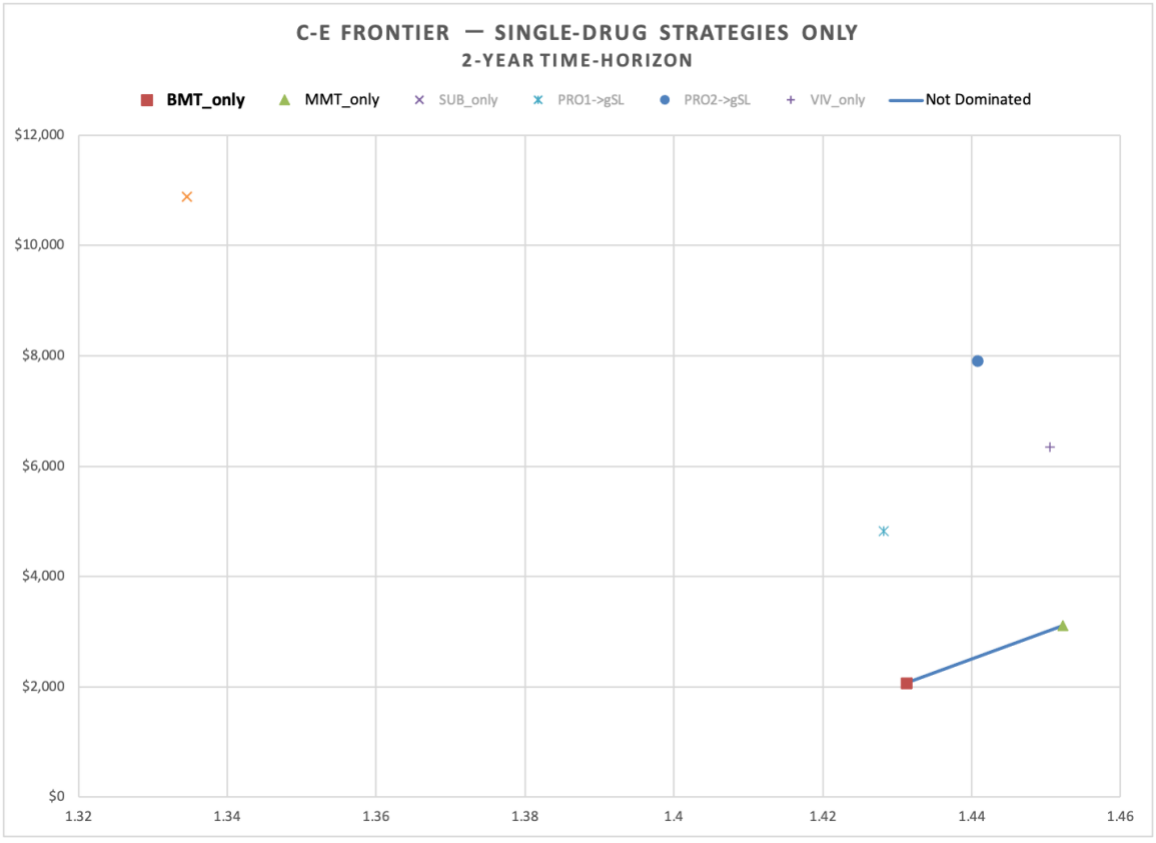

C-E FRONTIER — ALL STRATEGIES
2-YEAR TIME-HORIZON
BMT_only
MMT_only
MMT->PRO2
PRO2->MMT
BMT->MMT
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->VIV
PRO1->gSL
PRO2->SUB
PRO2->VIV
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
BMT->PRO1
MMT->BMT
MMT->PRO1
PRO1->MMT
PRO2->BMT
Not Dominated
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
1.32
1.34
1.36
1.38
1.4
1.42
1.44
1.46
1.48

Appendix C.3 Cost-Effectiveness Frontiers (Single-Drug Strategies Only)

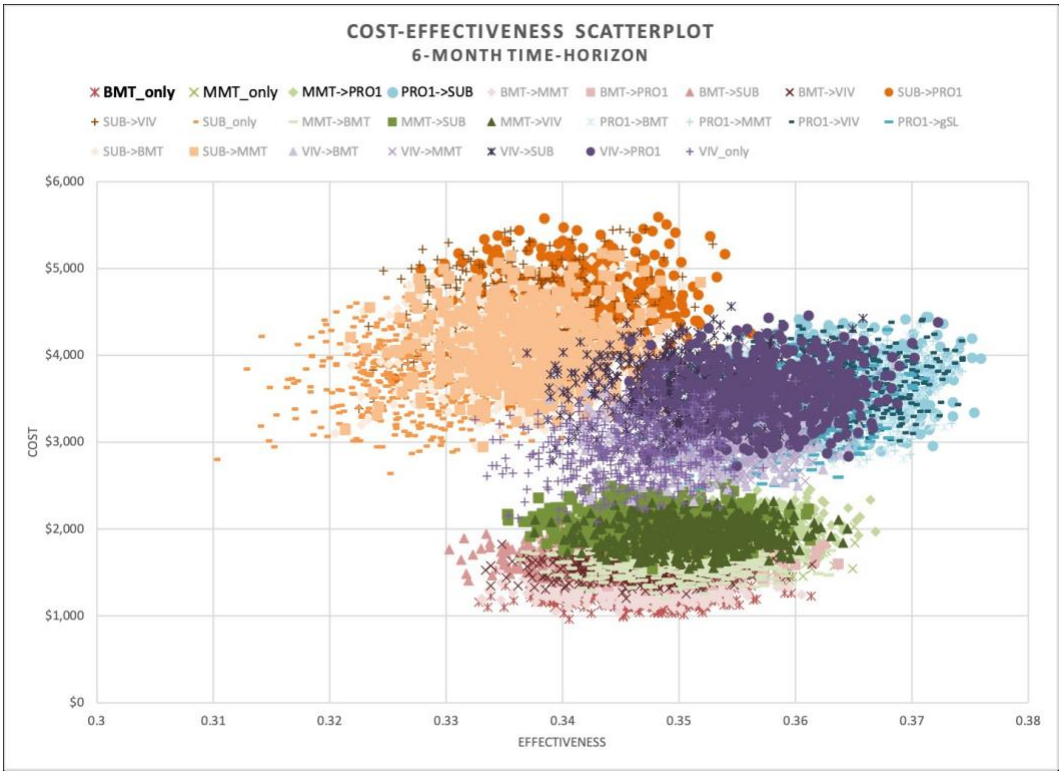


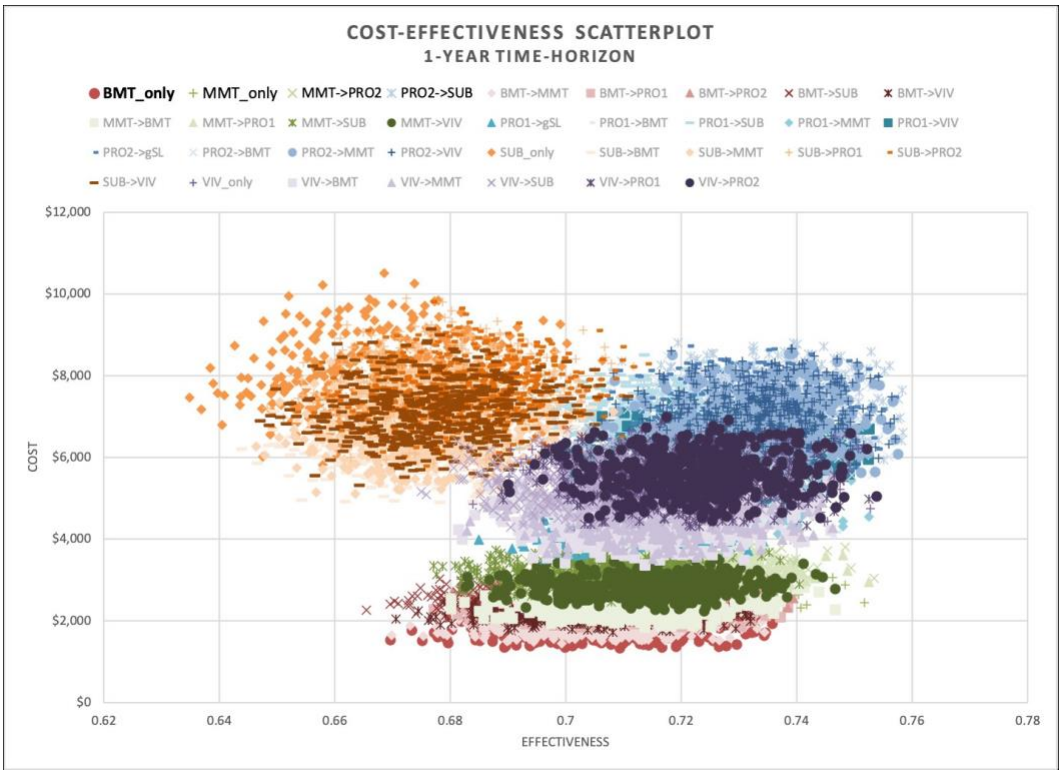


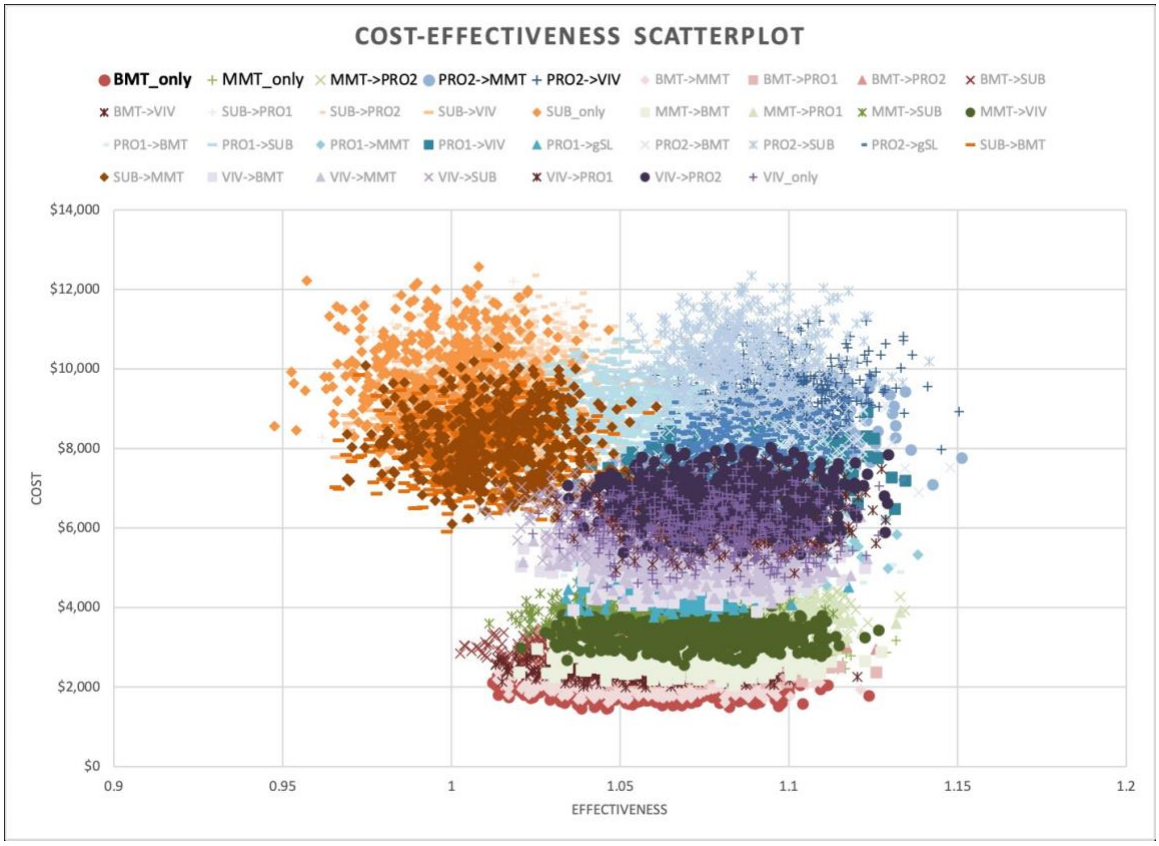

C-E FRONTIER — SINGLE-DRUG STRATEGIES ONLY
18-MONTH TIME-HORIZON
BMT_only
MMT_only
VIV_only
SUB_only
PRO1->gSL
PRO2->gSL
Not Dominated
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
1
1.01
1.02
1.03
1.04
1.05
1.06
1.07
1.08
1.09
1.1

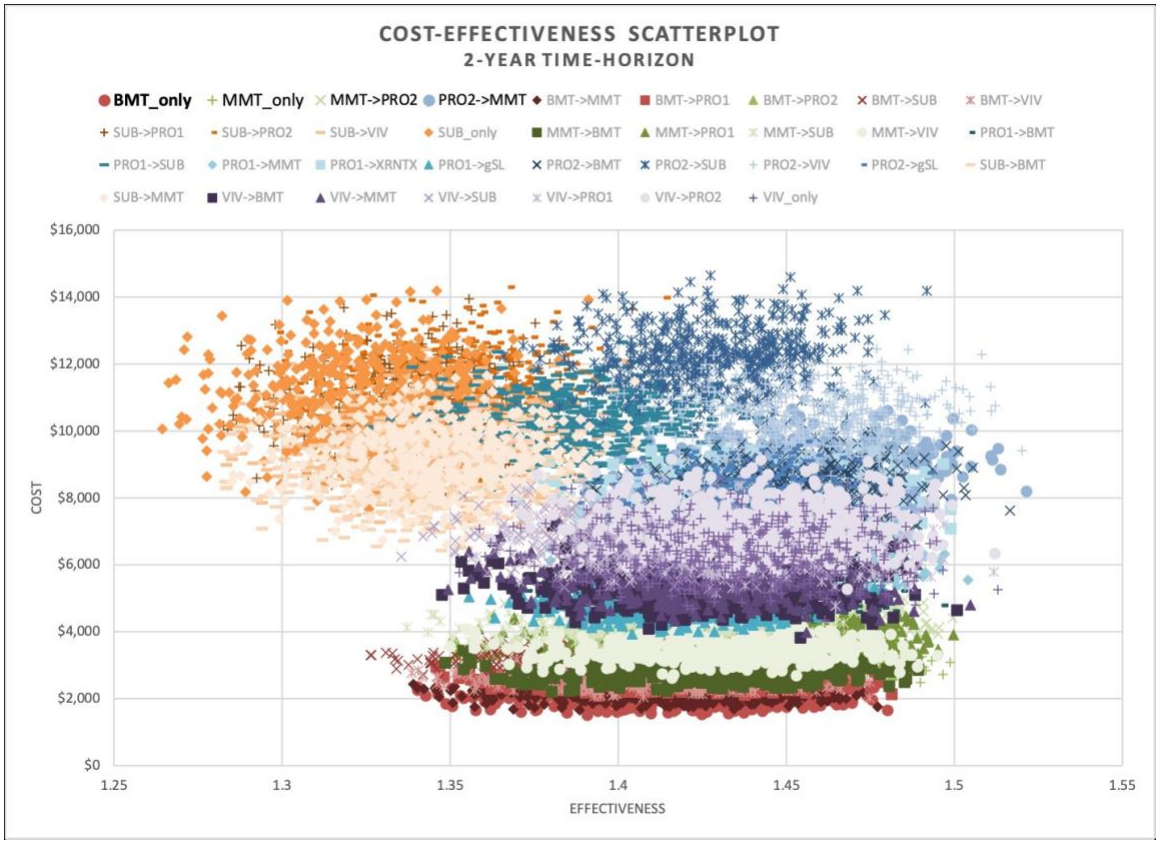

C-E FRONTIER — SINGLE-DRUG STRATEGIES ONLY
2-YEAR TIME-HORIZON
BMT_only
MMT_only
SUB_only
PRO1->gSL
PRO2->gSL
VIV_only
Not Dominated
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
1.32
1.34
1.36
1.38
1.4
1.42
1.44
1.46

Appendix C.4 Cost-Effectiveness Scatterplots (All Strategies)

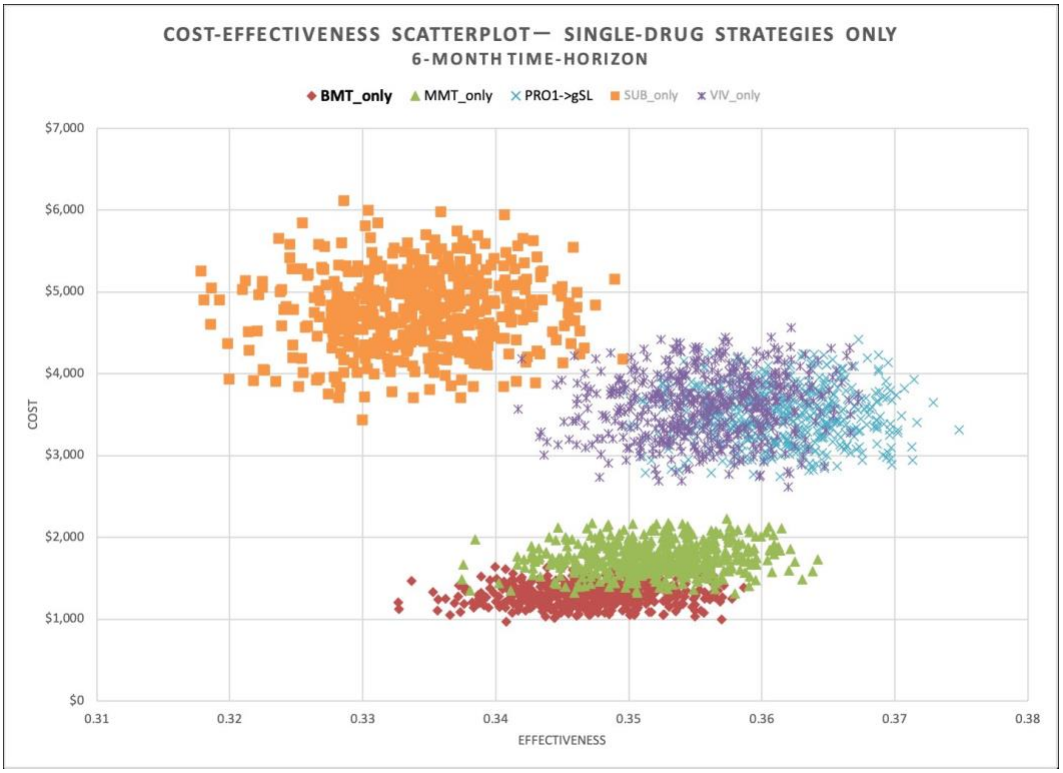


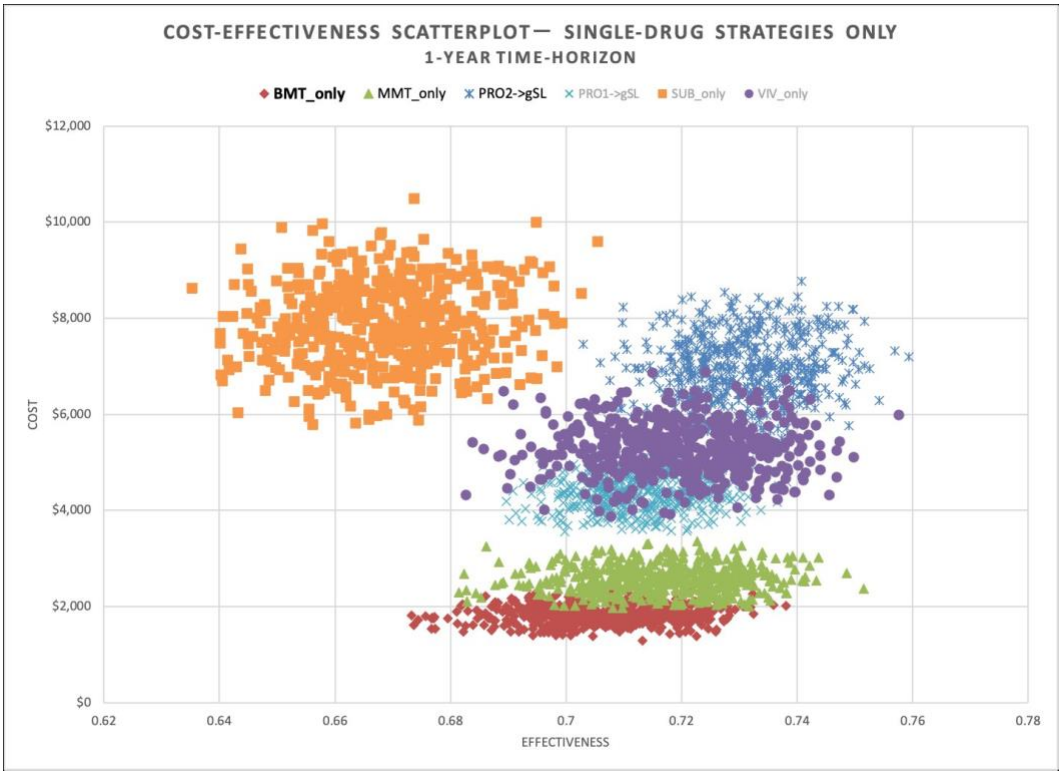


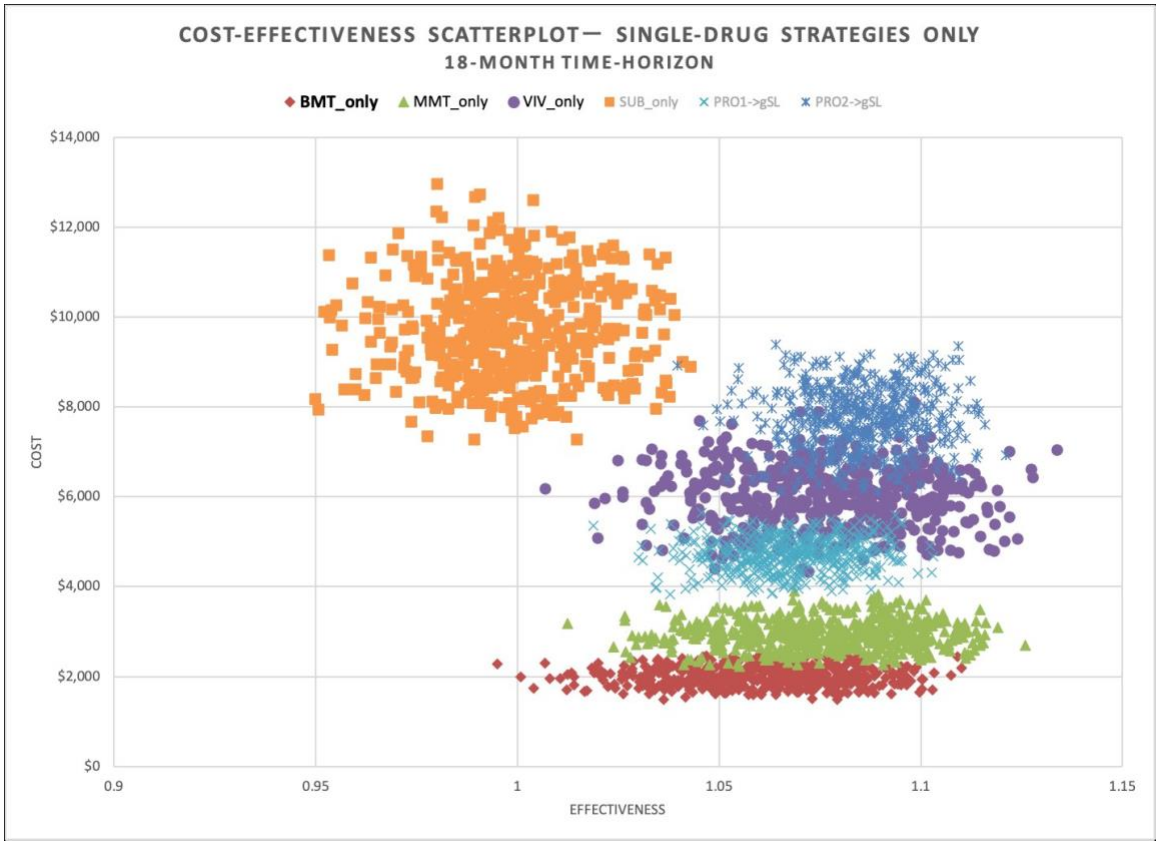

COST-EFFECTIVENESS SCATTERPLOT
BMT_only
MMT_only
MMT->PRO2
PRO2->MMT
PRO2->VIV
BMT->MMT
BMT->PRO1
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->BMT
MMT->PRO1
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->MMT
PRO1->VIV
PRO1->gSL
PRO2->BMT
PRO2->SUB
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
COST
0.9
0.95
1
1.05
1.1
1.15
1.2
EFFECTIVENESS

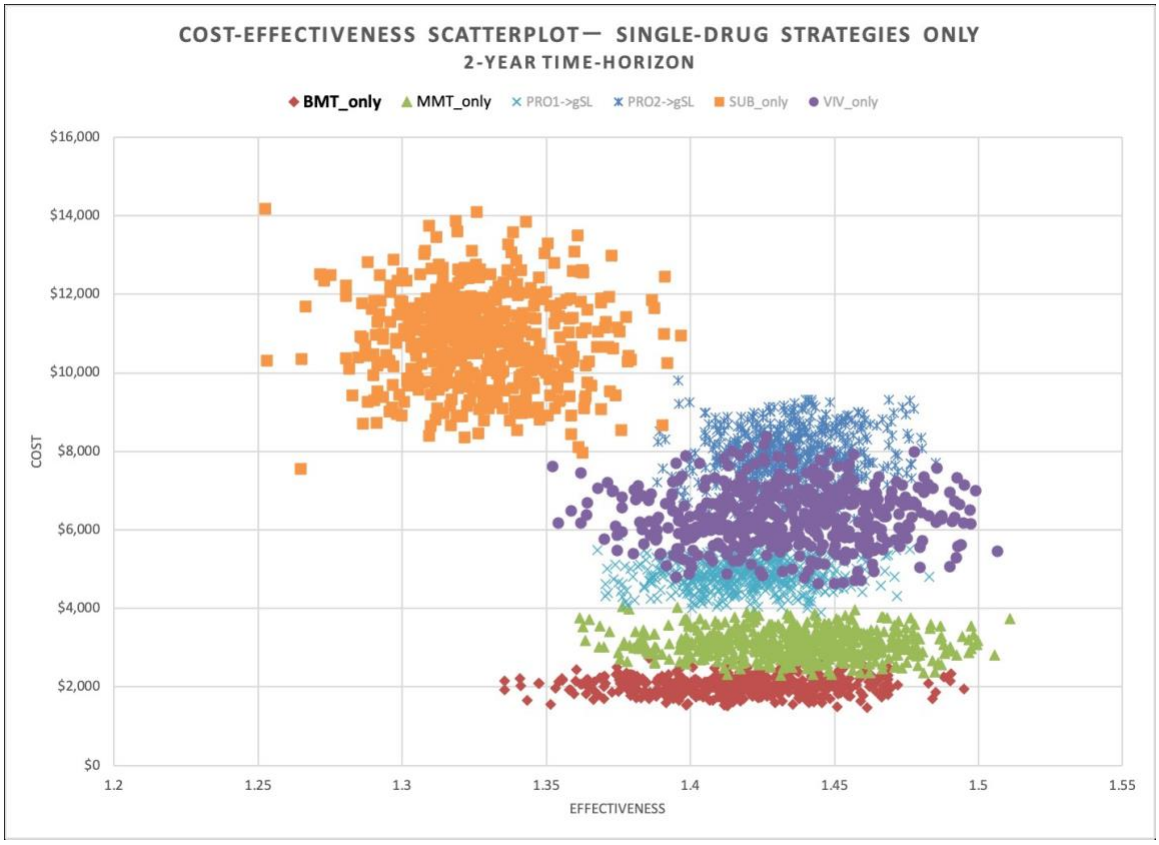

COST-EFFECTIVENESS SCATTERPLOT
2-YEAR TIME-HORIZON
BMT_only
MMT_only
MMT->PRO2
PRO2->MMT
BMT->MMT
BMT->PRO1
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->BMT
MMT->PRO1
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->MMT
PRO1->XRNTX
PRO1->gSL
PRO2->BMT
PRO2->SUB
PRO2->VIV
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
COST
1.25
1.3
1.35
1.4
1.45
1.5
1.55
EFFECTIVENESS

Appendix C.5 Cost-Effectiveness (Single-Drug Strategies Only)

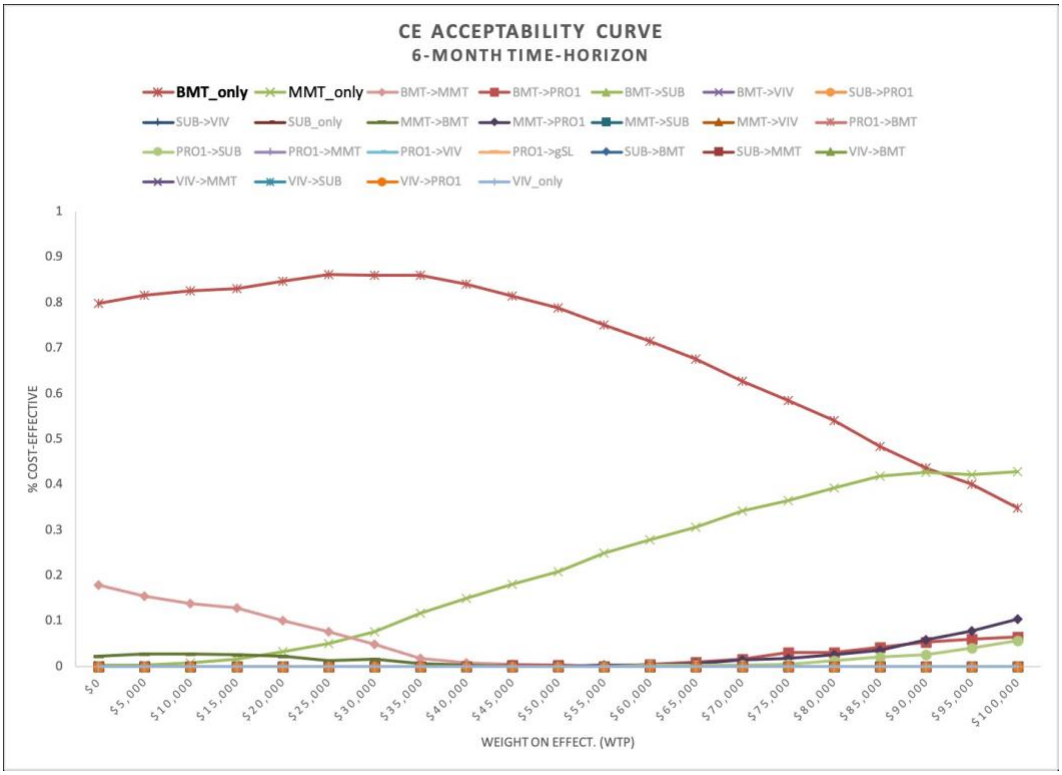


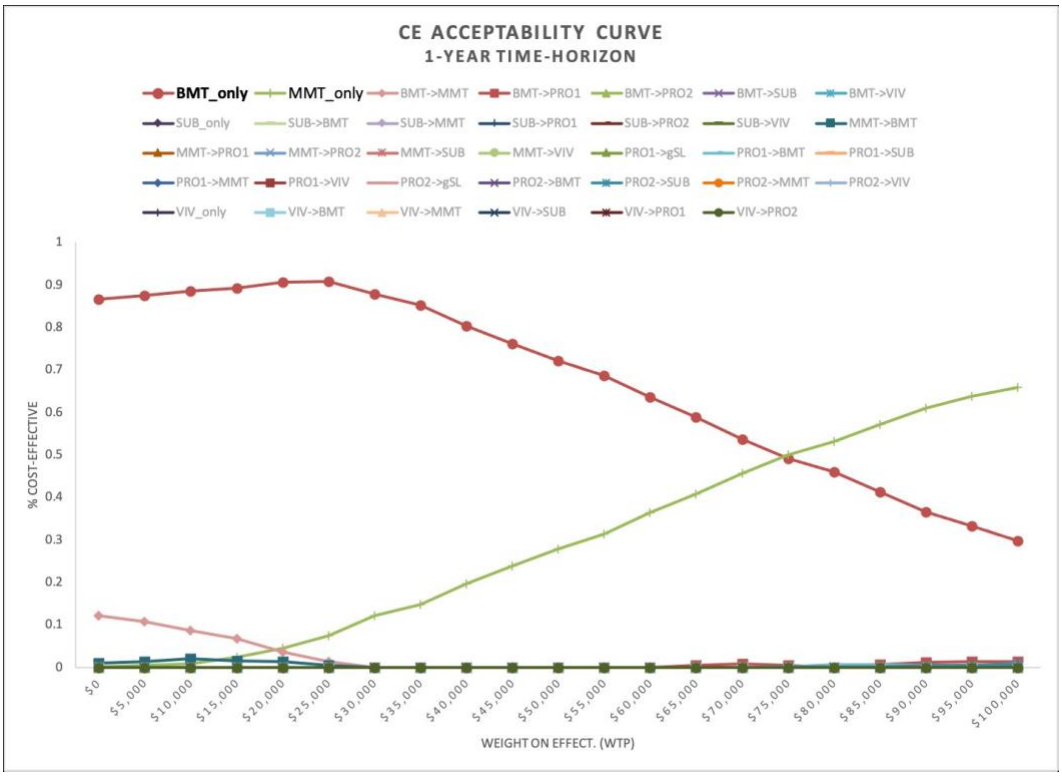


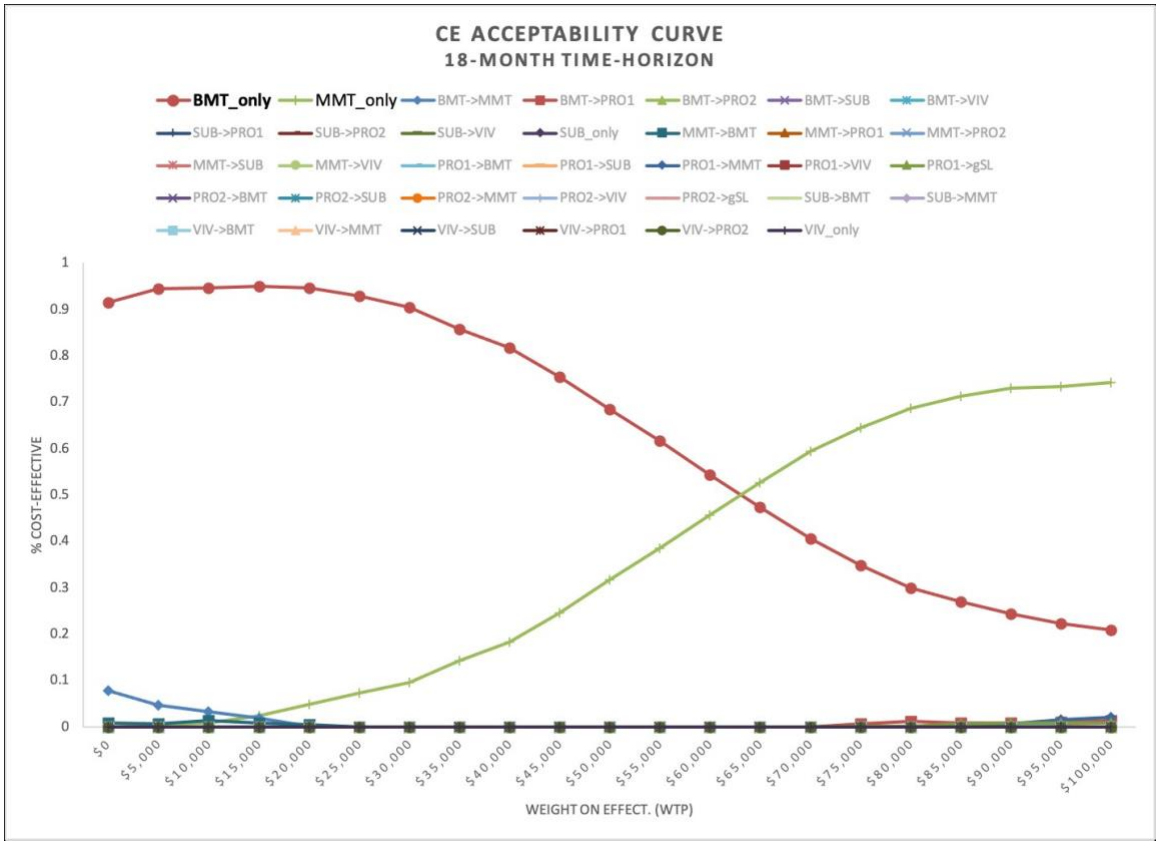

COST-EFFECTIVENESS SCATTERPLOT— SINGLE-DRUG STRATEGIES ONLY
18-MONTH TIME-HORIZON
BMT_only
MMT_only
VIV_only
SUB_only
PRO1->gSL
PRO2->gSL
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
COST
0.9
0.95
1
1.05
1.1
1.15
EFFECTIVENESS

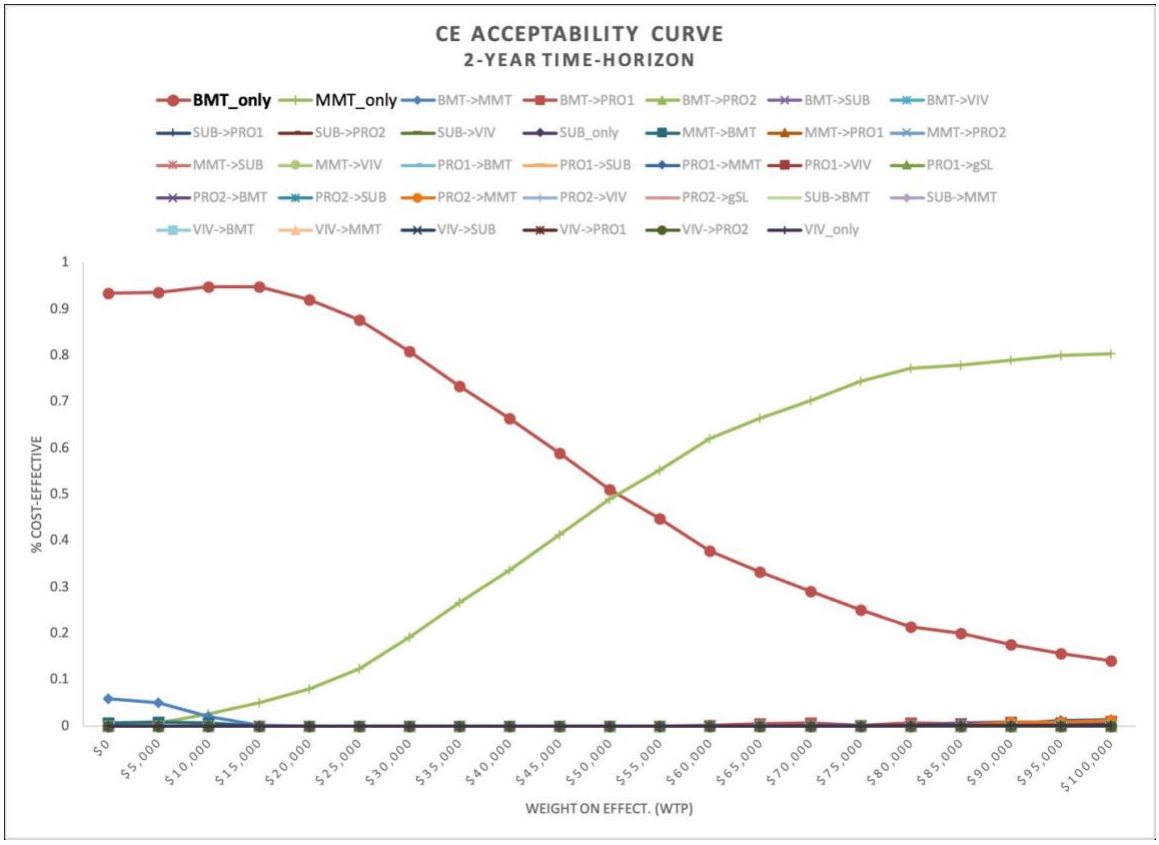

COST-EFFECTIVENESS SCATTERPLOT— SINGLE-DRUG STRATEGIES ONLY
2-YEAR TIME-HORIZON
BMT_only
MMT_only
PRO1->gSL
PRO2->gSL
SUB_only
VIV_only
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
COST
1.2
1.25
1.3
1.35
1.4
1.45
1.5
1.55
EFFECTIVENESS

Appendix C.6 Monte Carlo Acceptability Curves (All Strategies)

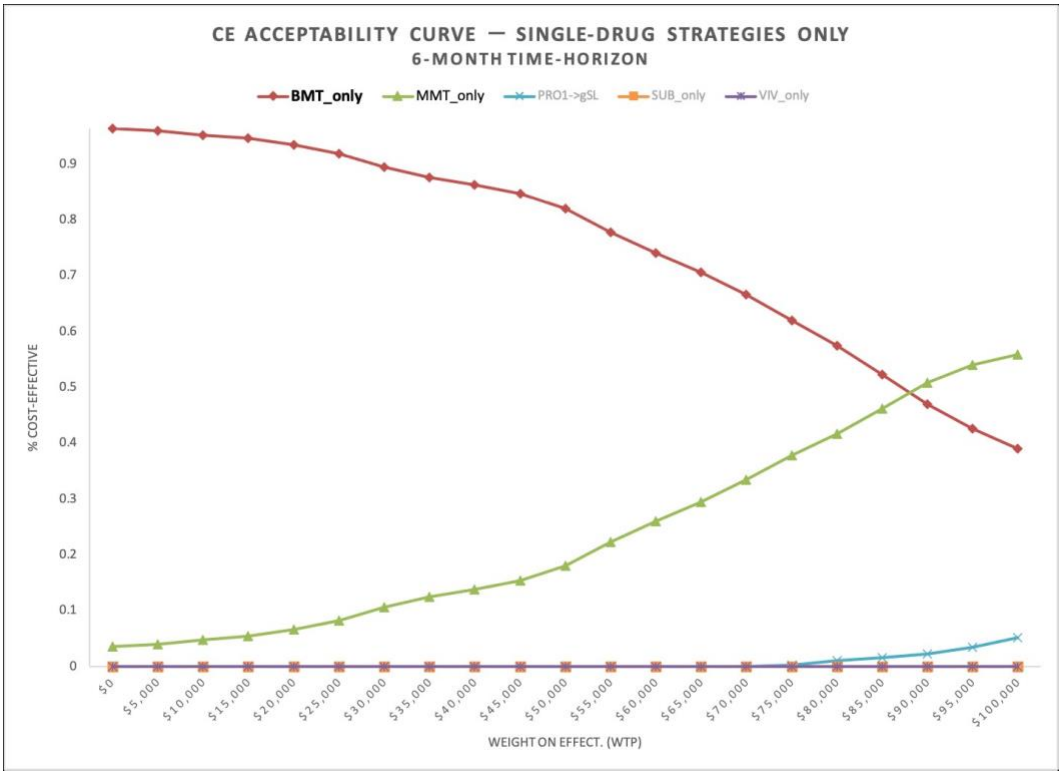


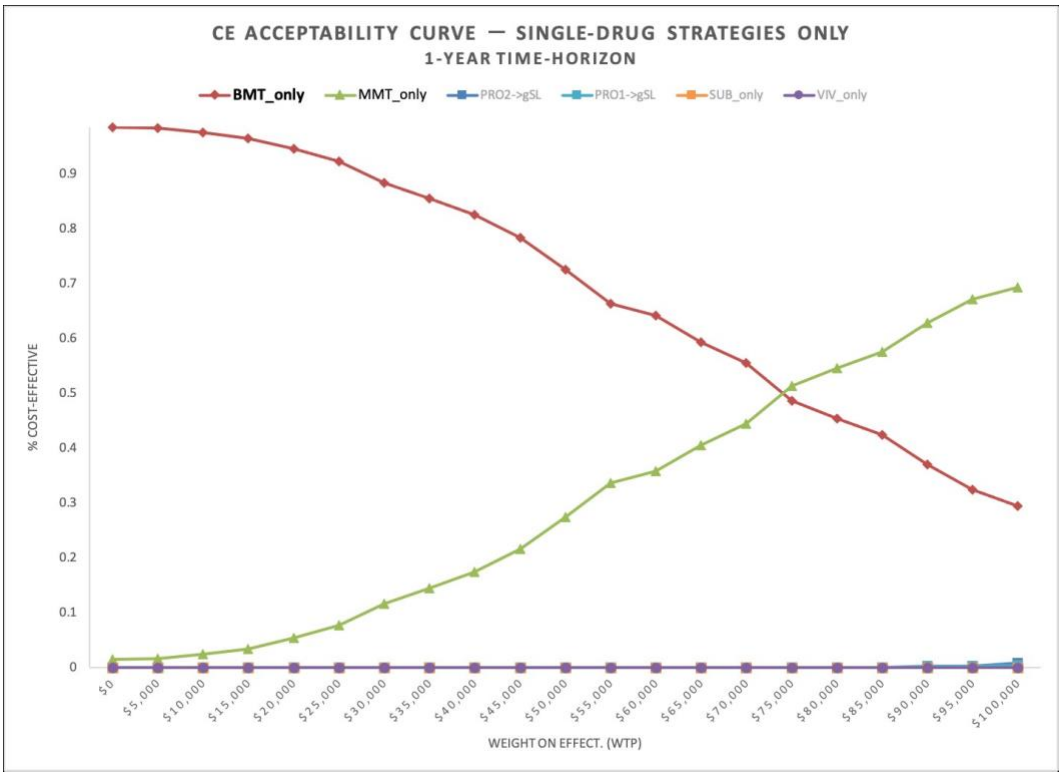


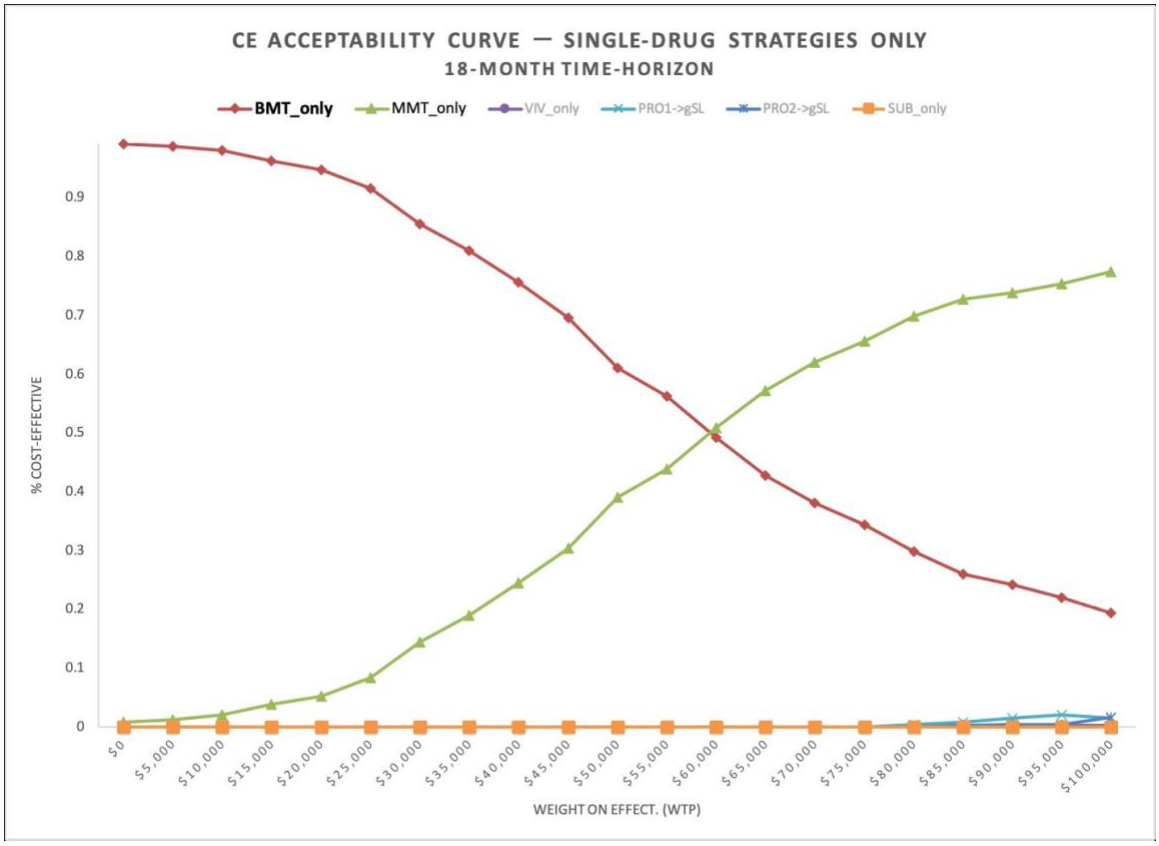

CE ACCEPTABILITY CURVE
18-MONTH TIME-HORIZON
BMT_only
MMT_only
BMT->MMT
BMT->PRO1
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->BMT
MMT->PRO1
MMT->PRO2
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->MMT
PRO1->VIV
PRO1->gSL
PRO2->BMT
PRO2->SUB
PRO2->MMT
PRO2->VIV
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
$35,000
$40,000
$45,000
$50,000
$55,000
$60,000
$65,000
$70,000
$75,000
$80,000
$85,000
$90,000
$95,000
$100,000
WEIGHT ON EFFECT. (WTP)

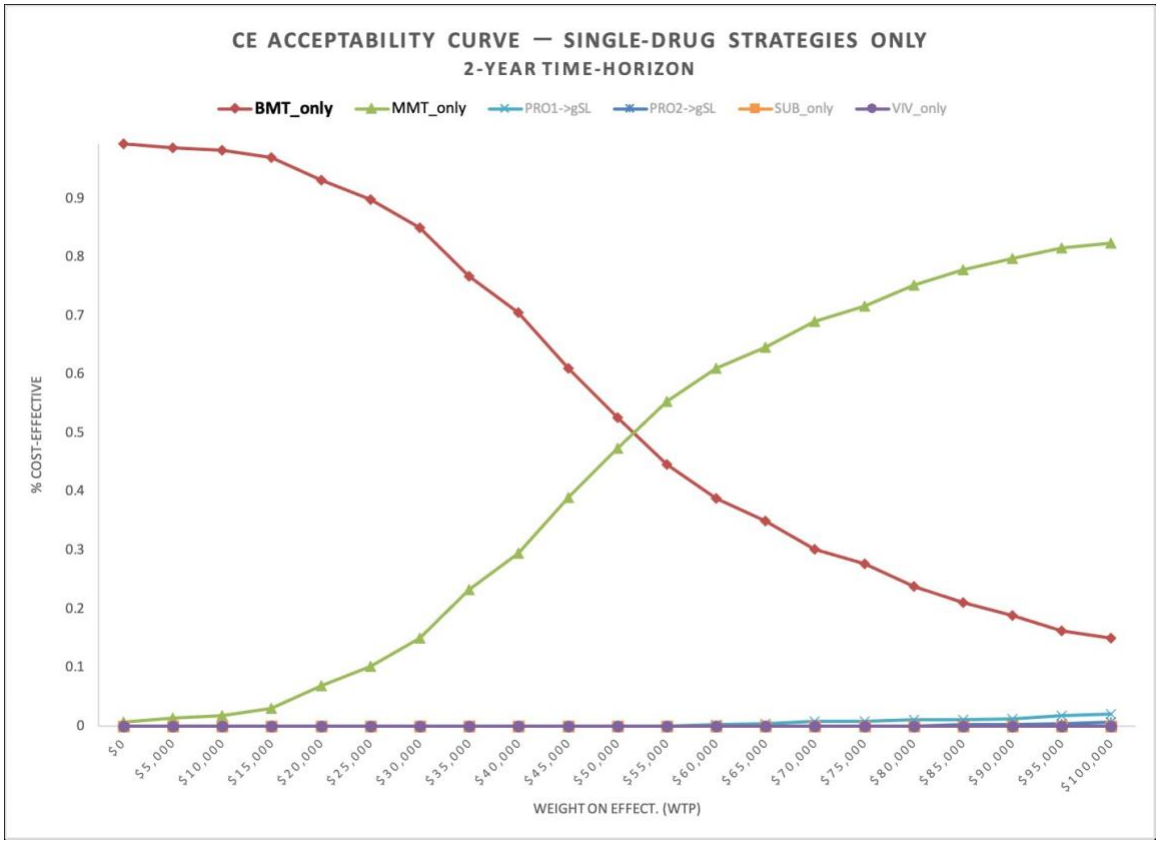

CE ACCEPTABILITY CURVE
2-YEAR TIME-HORIZON
BMT_only
MMT_only
BMT->MMT
BMT->PRO1
BMT->PRO2
BMT->SUB
BMT->VIV
SUB->PRO1
SUB->PRO2
SUB->VIV
SUB_only
MMT->BMT
MMT->PRO1
MMT->PRO2
MMT->SUB
MMT->VIV
PRO1->BMT
PRO1->SUB
PRO1->MMT
PRO1->VIV
PRO1->gSL
PRO2->BMT
PRO2->SUB
PRO2->MMT
PRO2->VIV
PRO2->gSL
SUB->BMT
SUB->MMT
VIV->BMT
VIV->MMT
VIV->SUB
VIV->PRO1
VIV->PRO2
VIV_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
$35,000
$40,000
$45,000
$50,000
$55,000
$60,000
$65,000
$70,000
$75,000
$80,000
$85,000
$90,000
$95,000
$100,000
WEIGHT ON EFFECT. (WTP)

Appendix C.7 Monte Carlo Acceptability Curves (Single-Drug Strategies Only)

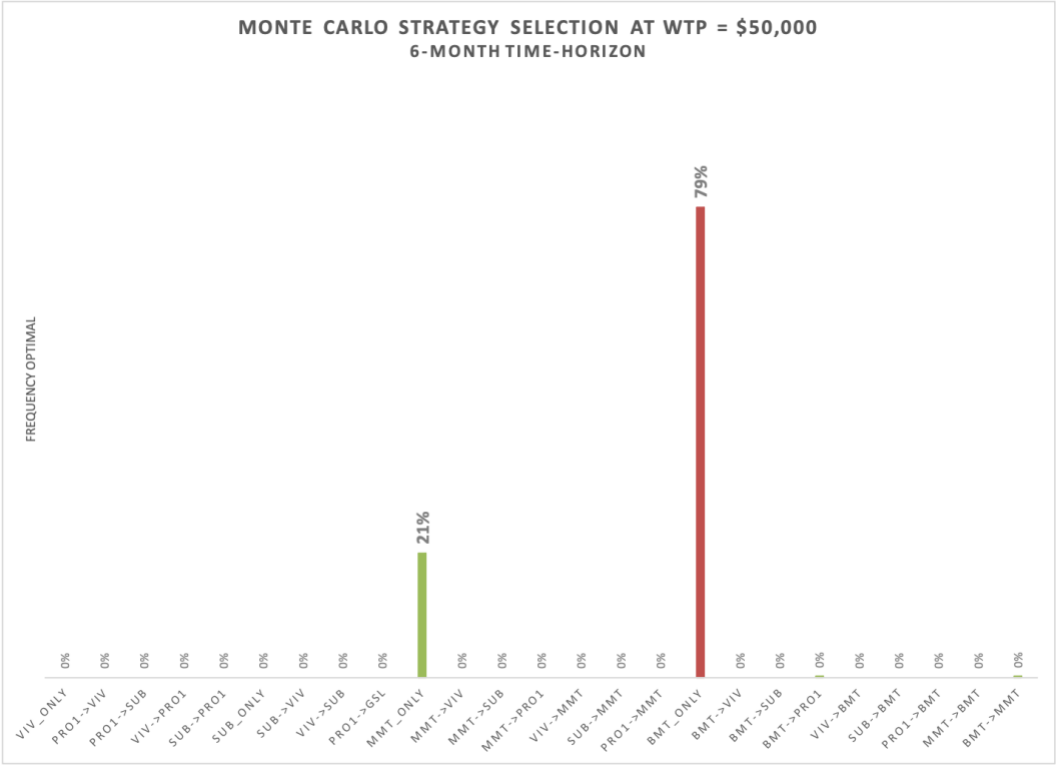


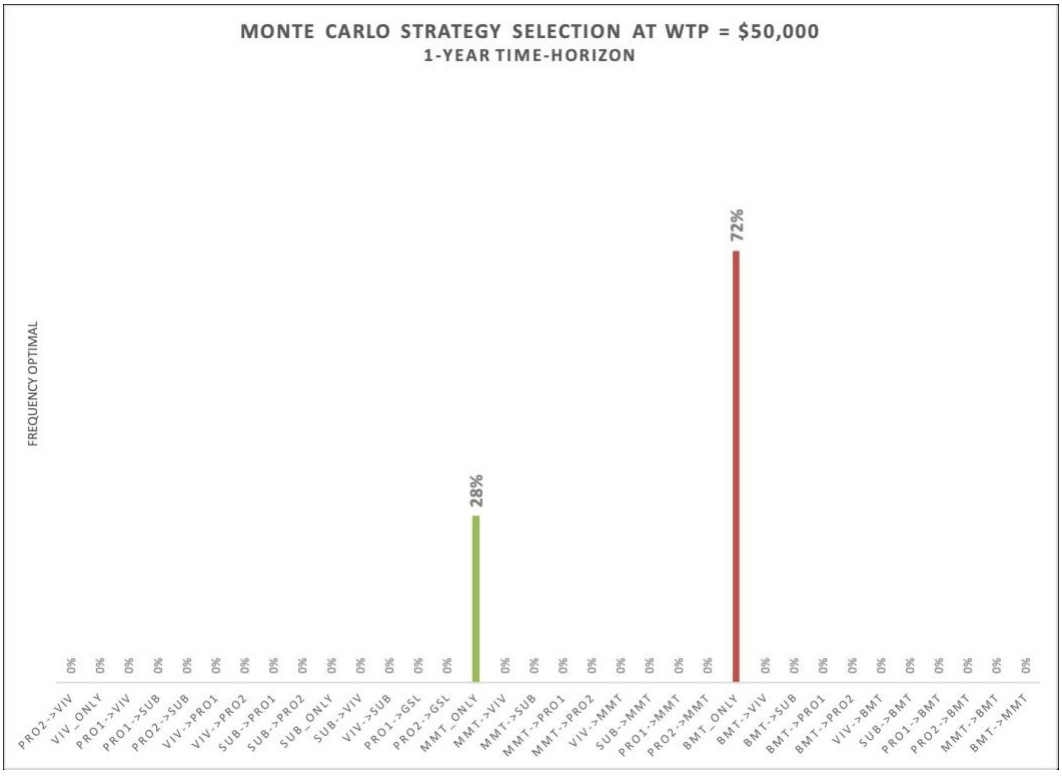


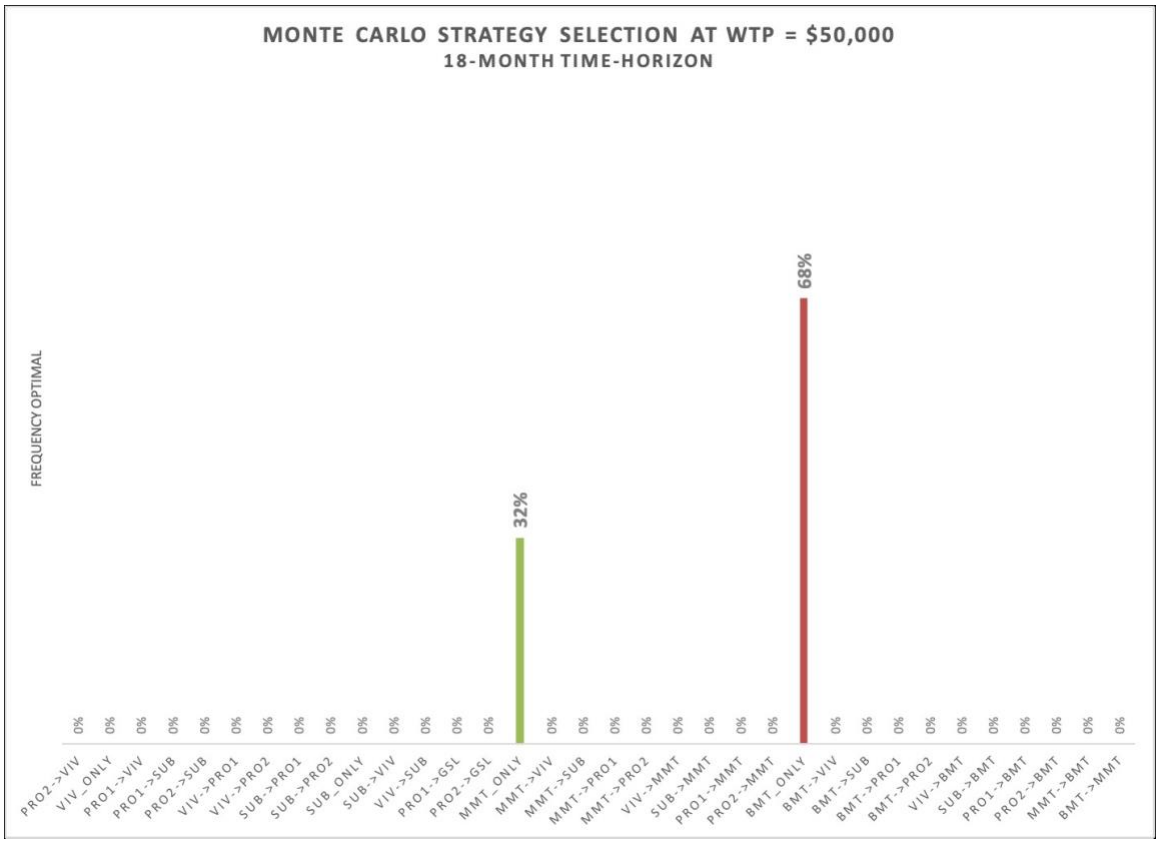

CE ACCEPTABILITY CURVE — SINGLE-DRUG STRATEGIES ONLY
18-MONTH TIME-HORIZON
BMT_only
MMT_only
VIV_only
PRO1->gSL
PRO2->gSL
SUB_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
$35,000
$40,000
$45,000
$50,000
$55,000
$60,000
$65,000
$70,000
$75,000
$80,000
$85,000
$90,000
$95,000
$100,000
WEIGHT ON EFFECT. (WTP)

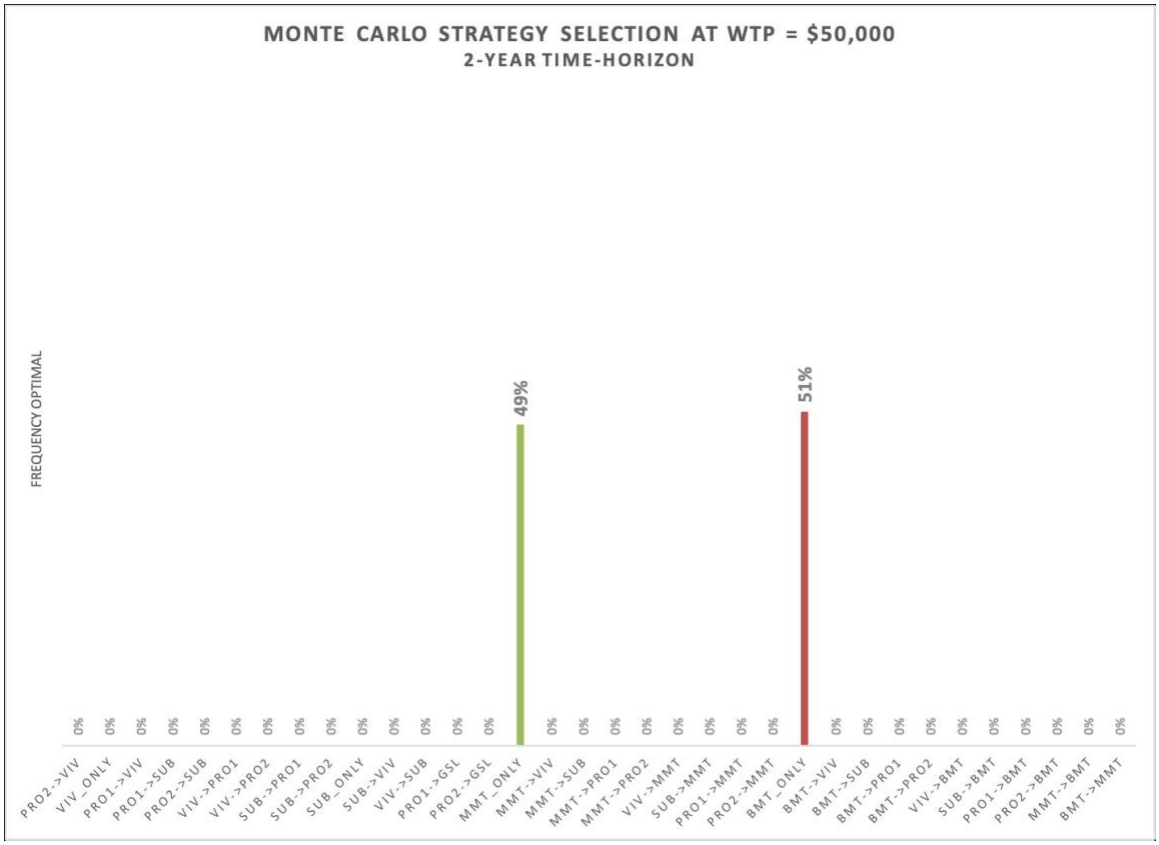

CE ACCEPTABILITY CURVE — SINGLE-DRUG STRATEGIES ONLY
2-YEAR TIME-HORIZON
BMT_only
MMT_only
PRO1->gSL
PRO2->gSL
SUB_only
VIV_only
% COST-EFFECTIVE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
$35,000
$40,000
$45,000
$50,000
$55,000
$60,000
$65,000
$70,000
$75,000
$80,000
$85,000
$90,000
$95,000
$100,000
WEIGHT ON EFFECT. (WTP)

Appendix C.8 Probabilistic Analysis Strategy Selection (All Strategies)

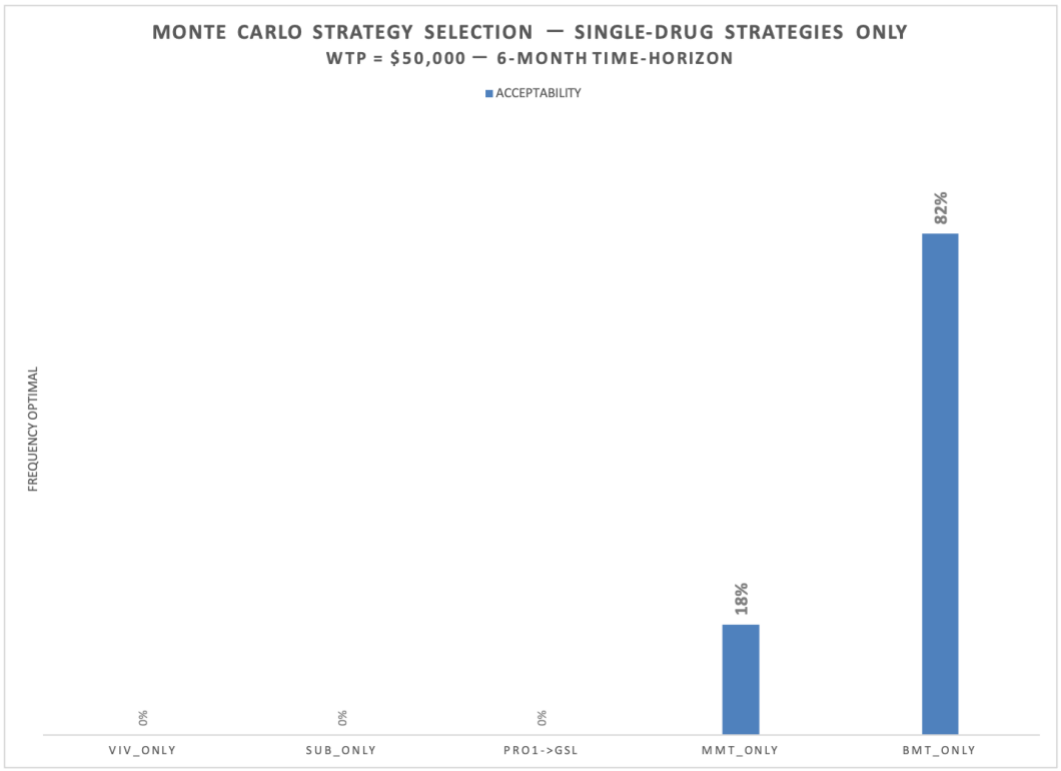


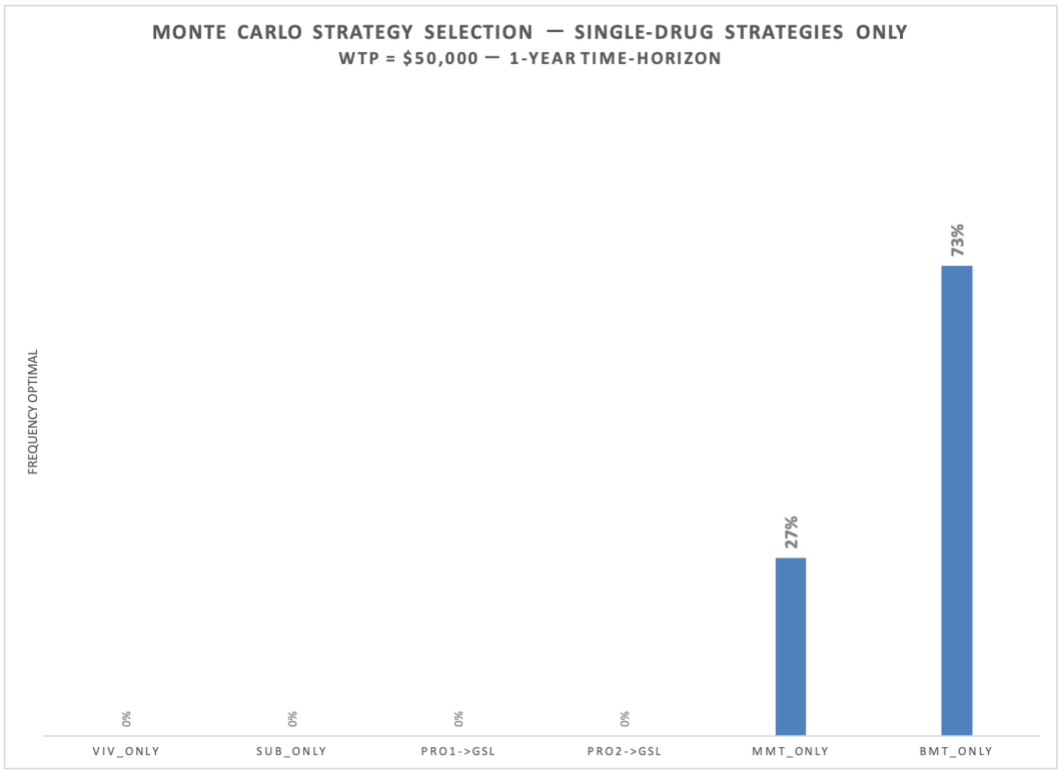


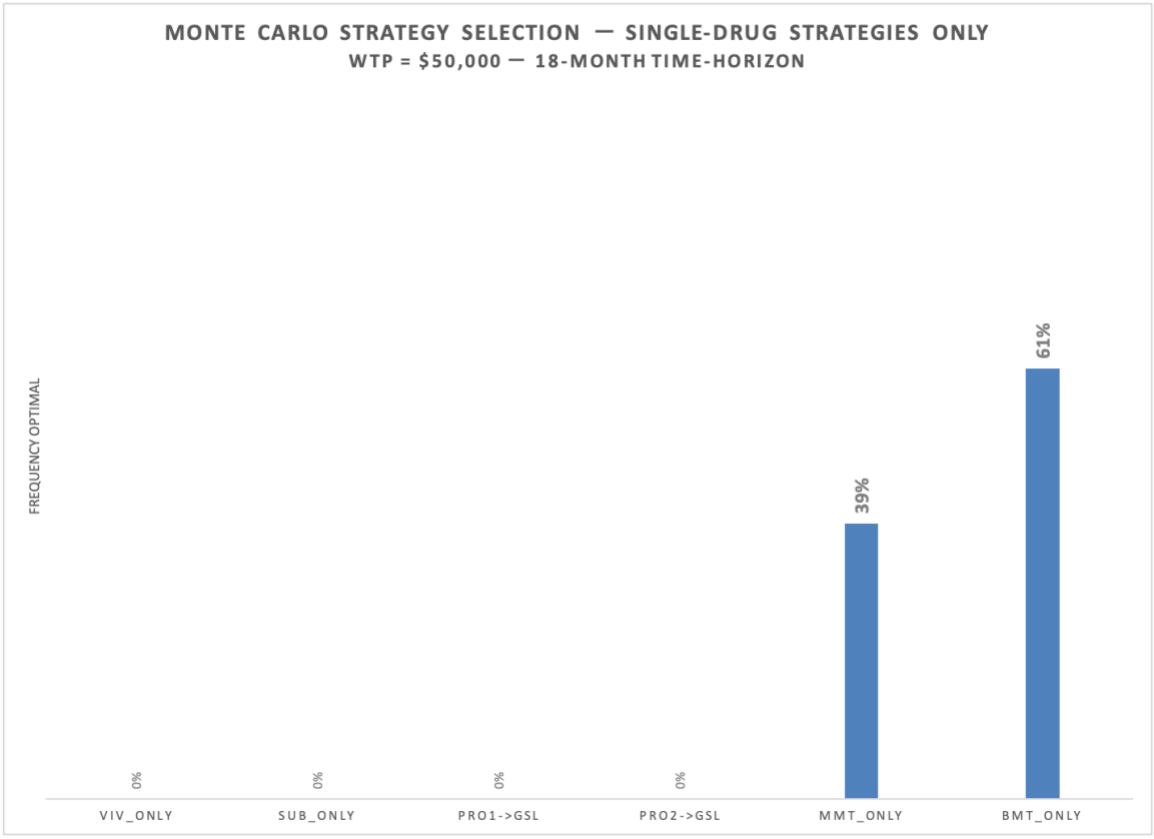

MONTE CARLO STRATEGY SELECTION AT WTP = $50,000
18-MONTH TIME-HORIZON
FREQUENCY OPTIMAL
32%
68%
0%
PRO2->VIV
VIV_ONLY
PRO1->VIV
PRO1->SUB
PRO2->SUB
VIV->PRO1
VIV->PRO2
SUB->PRO1
SUB->PRO2
SUB_ONLY
SUB->VIV
VIV->SUB
PRO1->GSL
PRO2->GSL
MMT_ONLY
MMT->VIV
MMT->SUB
MMT->PRO1
MMT->PRO2
VIV->MMT
SUB->MMT
PRO1->MMT
PRO2->MMT
BMT_ONLY
BMT->VIV
BMT->SUB
BMT->PRO1
BMT->PRO2
VIV->BMT
SUB->BMT
PRO1->BMT
PRO2->BMT
MMT->BMT
BMT->MMT

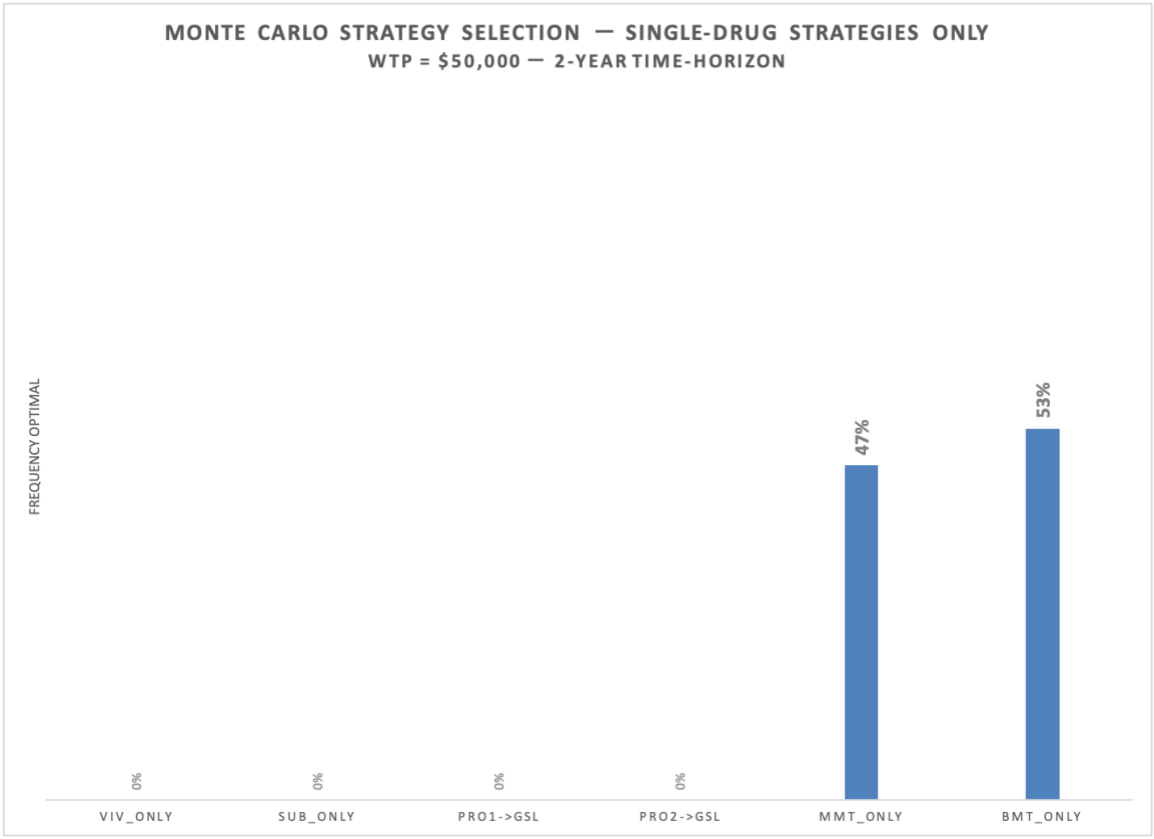

MONTE CARLO STRATEGY SELECTION AT WTP = $50,000
2-YEAR TIME-HORIZON
FREQUENCY OPTIMAL
49%
51%
0%
PRO2->VIV
VIV_ONLY
PRO1->VIV
PRO1->SUB
PRO2->SUB
VIV->PRO1
VIV->PRO2
SUB->PRO1
SUB->PRO2
SUB_ONLY
SUB->VIV
VIV->SUB
PRO1->GSL
PRO2->GSL
MMT_ONLY
MMT->VIV
MMT->SUB
MMT->PRO1
MMT->PRO2
VIV->MMT
SUB->MMT
PRO1->MMT
PRO2->MMT
BMT_ONLY
BMT->VIV
BMT->SUB
BMT->PRO1
BMT->PRO2
VIV->BMT
SUB->BMT
PRO1->BMT
PRO2->BMT
MMT->BMT
BMT->MMT

Appendix C.9 Probabilistic Analysis Strategy Selection (Single-Drug Strategies Only)



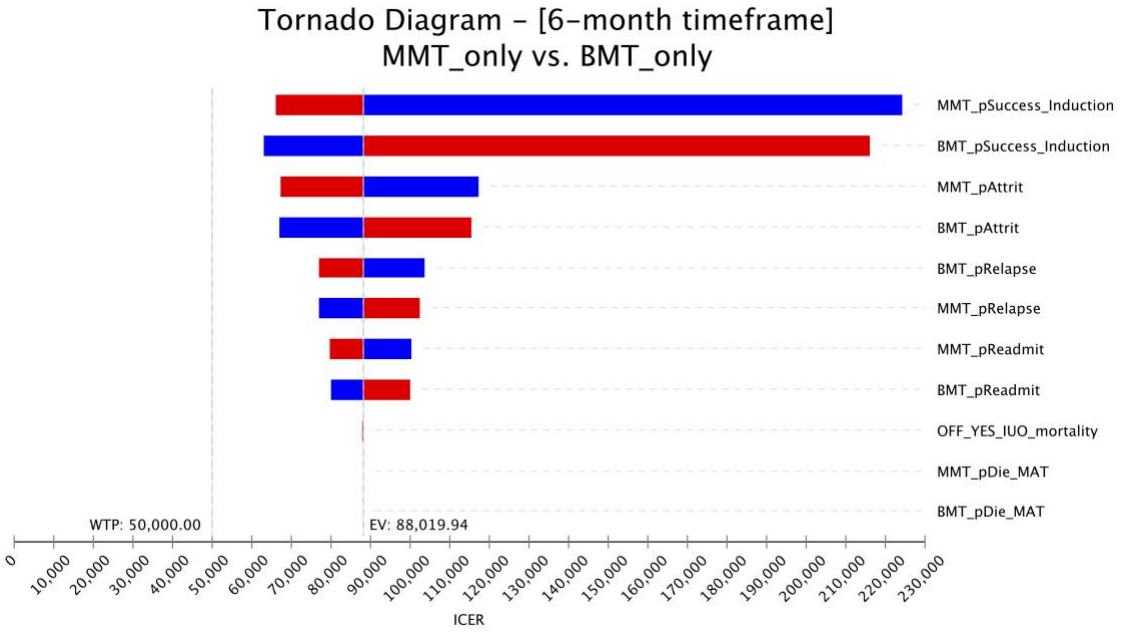


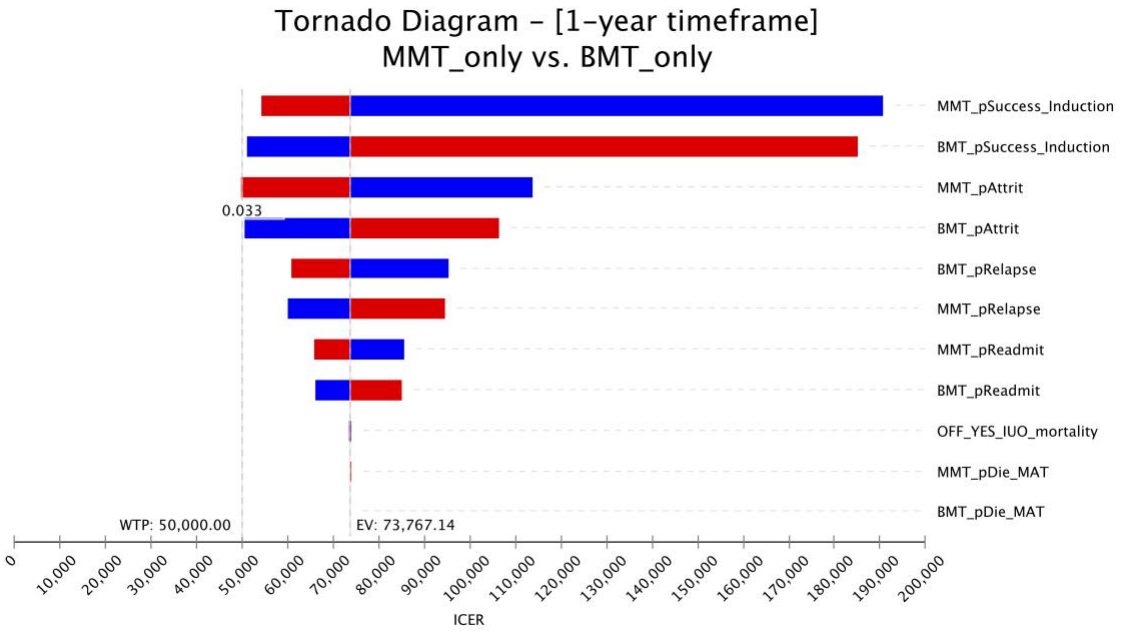

MONTE CARLO STRATEGY SELECTION — SINGLE-DRUG STRATEGIES ONLY
WTP = $50,000 — 18-MONTH TIME-HORIZON
FREQUENCY OPTIMAL
0%
0%
0%
0%
39%
61%
VIV_ONLY
SUB_ONLY
PRO1->GSL
PRO2->GSL
MMT_ONLY
BMT_ONLY

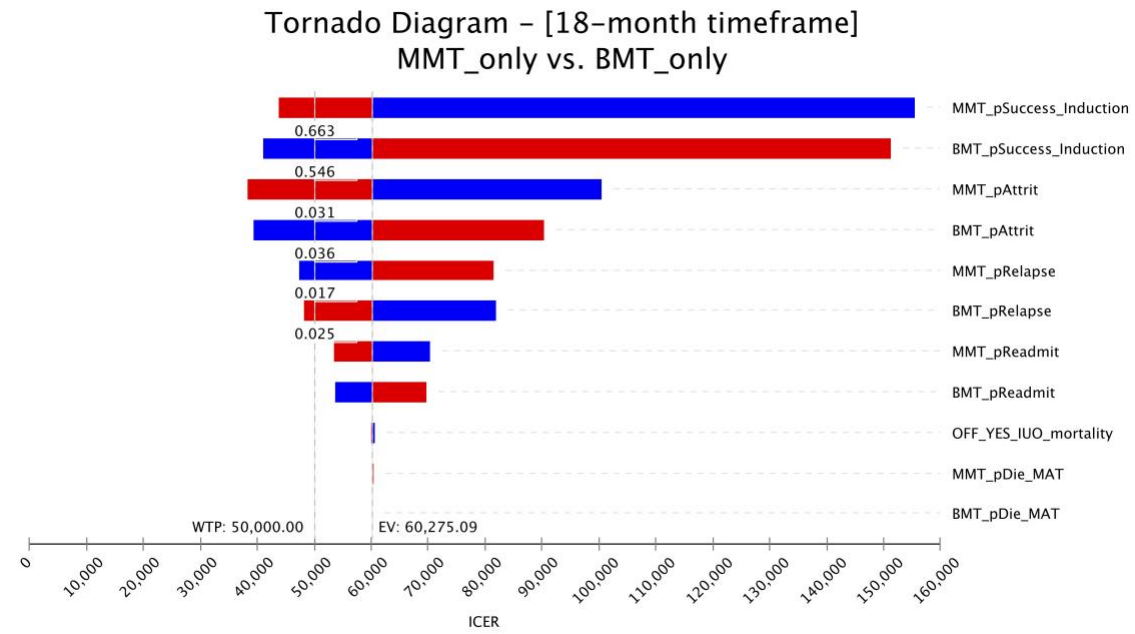

MONTE CARLO STRATEGY SELECTION — SINGLE-DRUG STRATEGIES ONLY
WTP = $50,000 — 2-YEAR TIME-HORIZON
FREQUENCY OPTIMAL
0%
0%
0%
0%
47%
53%
VIV_ONLY
SUB_ONLY
PRO1->GSL
PRO2->GSL
MMT_ONLY
BMT_ONLY

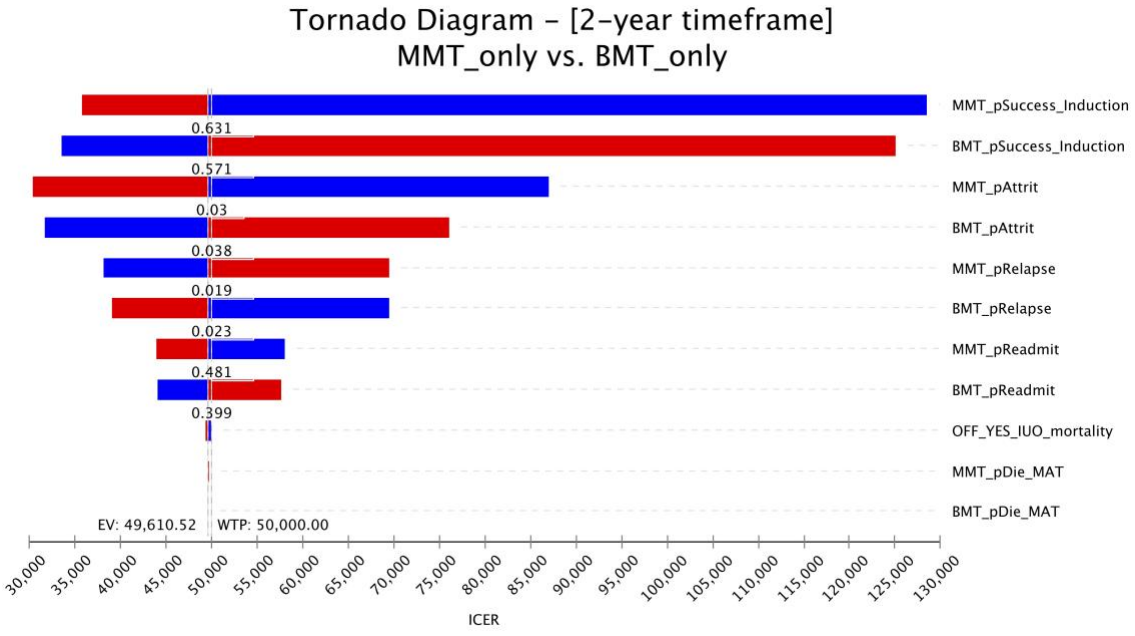
Appendix C.10 One-Way Sensitivity Analysis Tornado Diagrams

	6-month	1-year	18-months	2-years
MMT v. BMT	MMT Induction Success			
	BMT Induction Success			
	MMT Treatment Attrition			

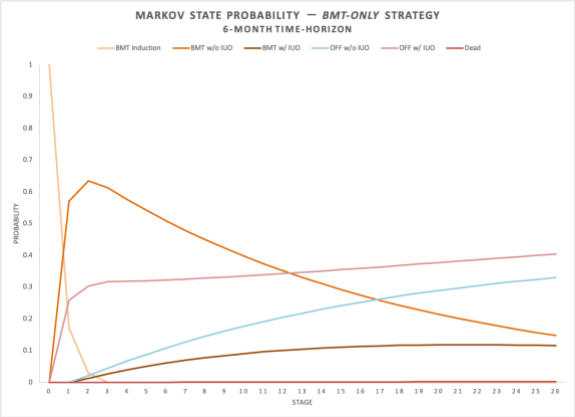


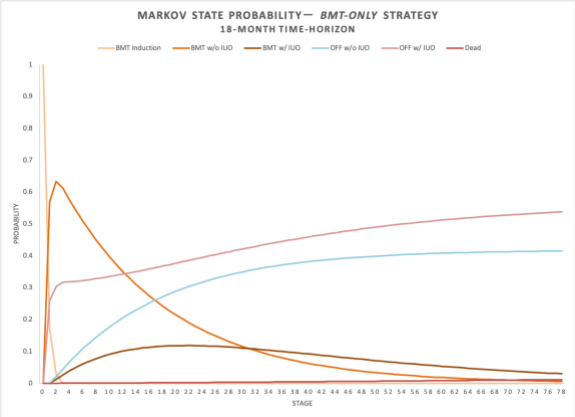


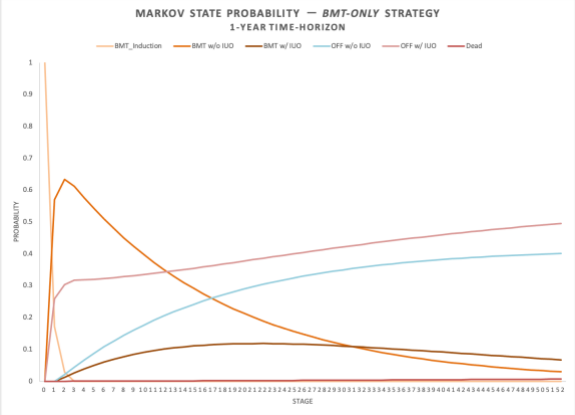

Tornado Diagram - [18-month timeframe]
MMT_only vs. BMT_only
MMT_pSuccess_Induction
0.663
BMT_pSuccess_Induction
0.546
MMT_pAttrit
0.031
BMT_pAttrit
0.036
MMT_pRelapse
0.017
BMT_pRelapse
0.025
MMT_pReadmit
BMT_pReadmit
OFF_YES_IUO_mortality
MMT_pDie_MAT
BMT_pDie_MAT
WTP: 50,000.00
EV: 60,275.09
0
10,000
20,000
30,000
40,000
50,000
60,000
70,000
80,000
90,000
100,000
110,000
120,000
130,000
140,000
150,000
160,000
ICER

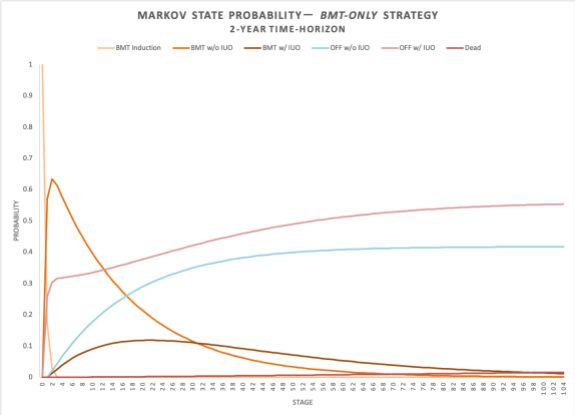

Tornado Diagram - [2-year timeframe]
MMT_only vs. BMT_only
MMT_pSuccess_Induction
0.631
BMT_pSuccess_Induction
0.571
MMT_pAttrit
0.03
BMT_pAttrit
0.038
MMT_pRelapse
0.019
BMT_pRelapse
0.023
MMT_pReadmit
0.481
BMT_pReadmit
0.399
OFF_YES_IUO_mortality
MMT_pDie_MAT
BMT_pDie_MAT
EV: 49,610.52
WTP: 50,000.00
30,000
35,000
40,000
45,000
50,000
55,000
60,000
65,000
70,000
75,000
80,000
85,000
90,000
95,000
100,000
105,000
110,000
115,000
120,000
125,000
130,000
ICER

Appendix C.11 Health State Tracings (*"BMT-Only"* Strategy)

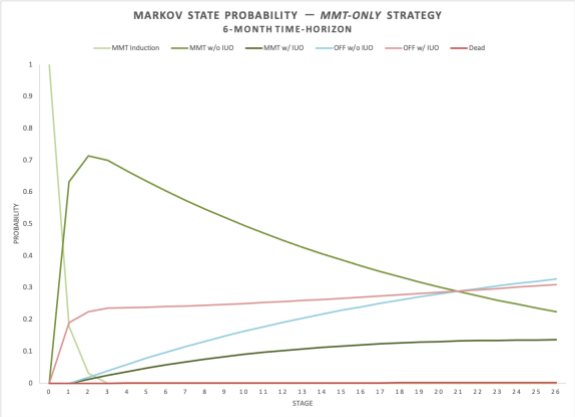


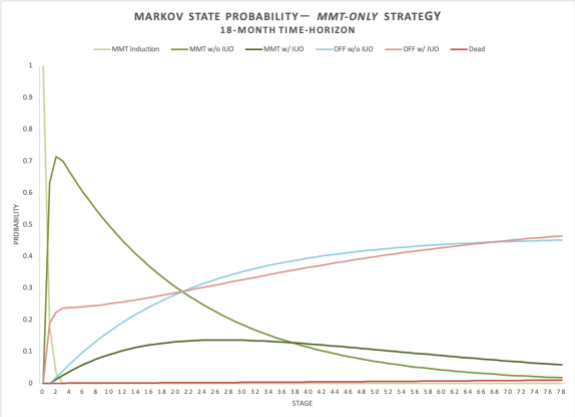


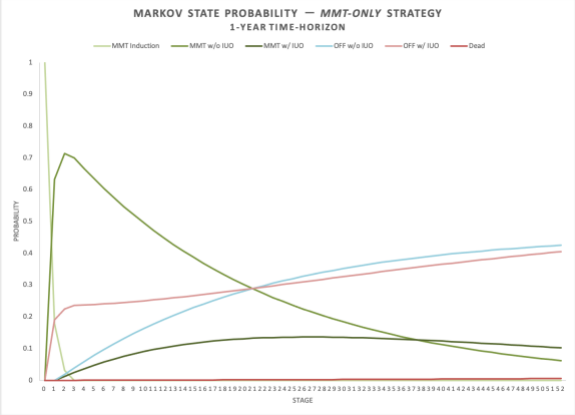


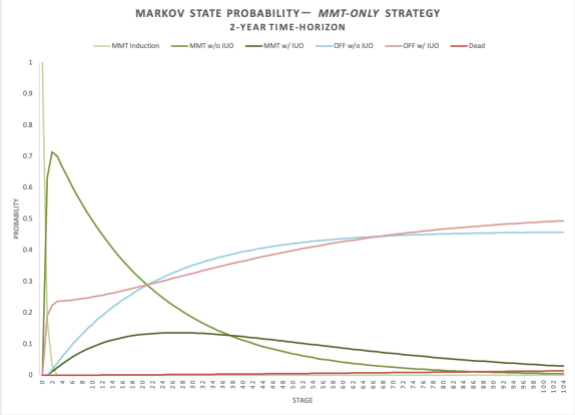


Appendix C.12 Health State Tracings (*"MMT-Only"* Strategy)

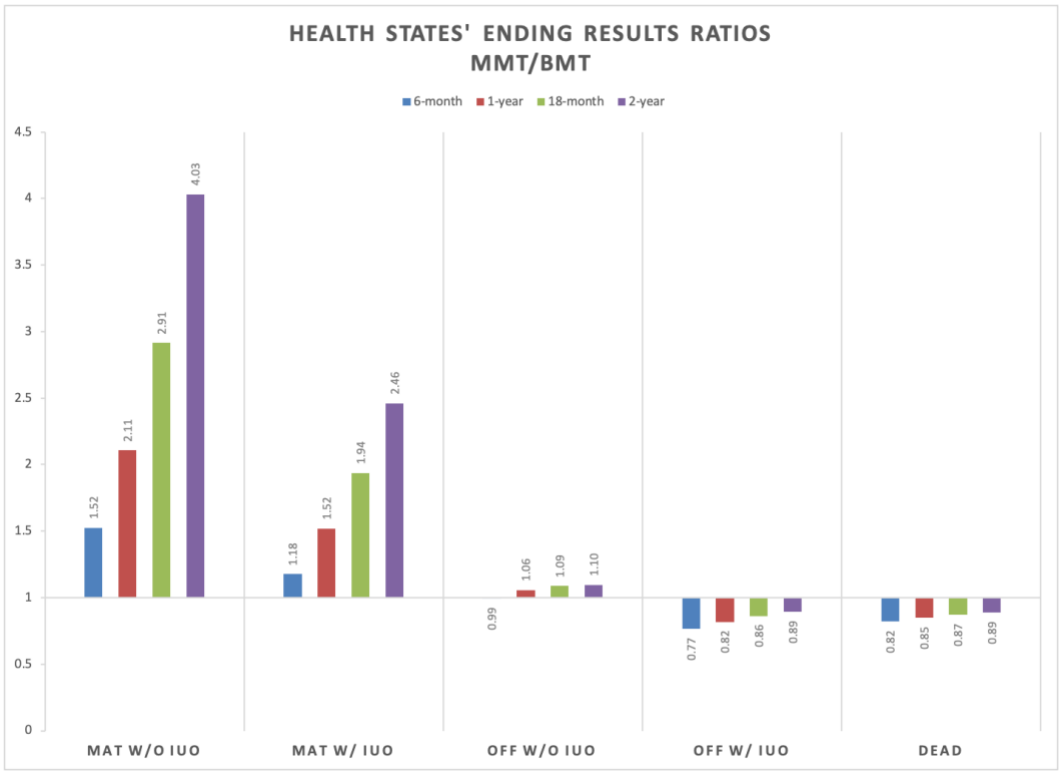


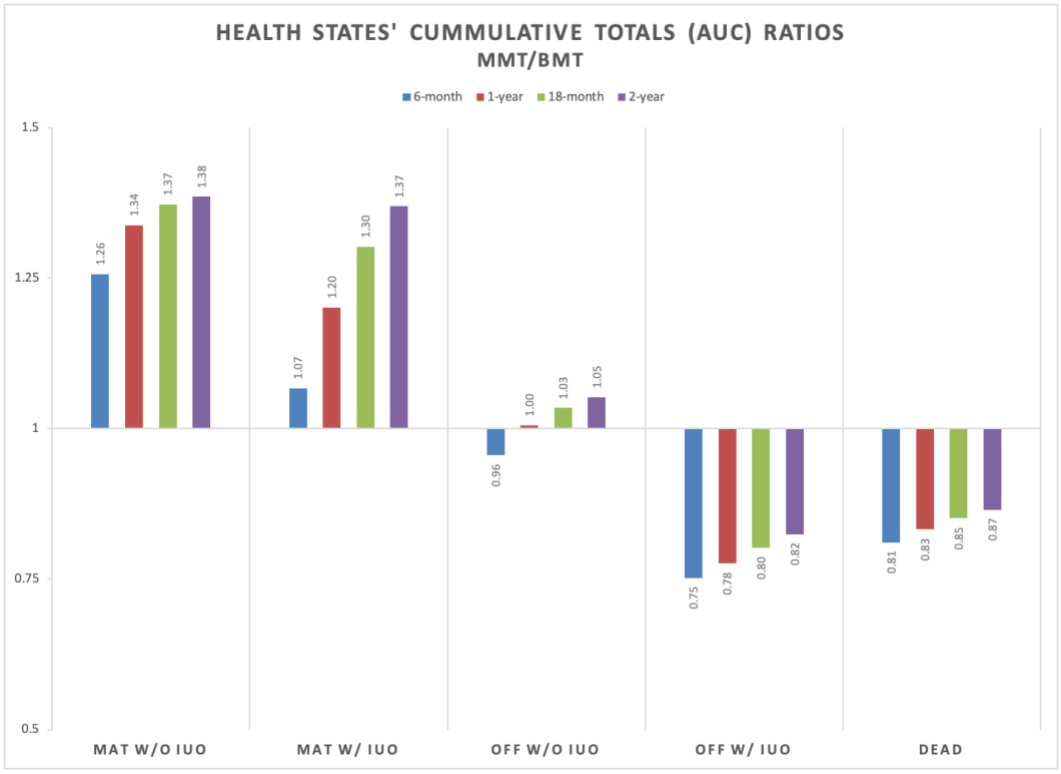




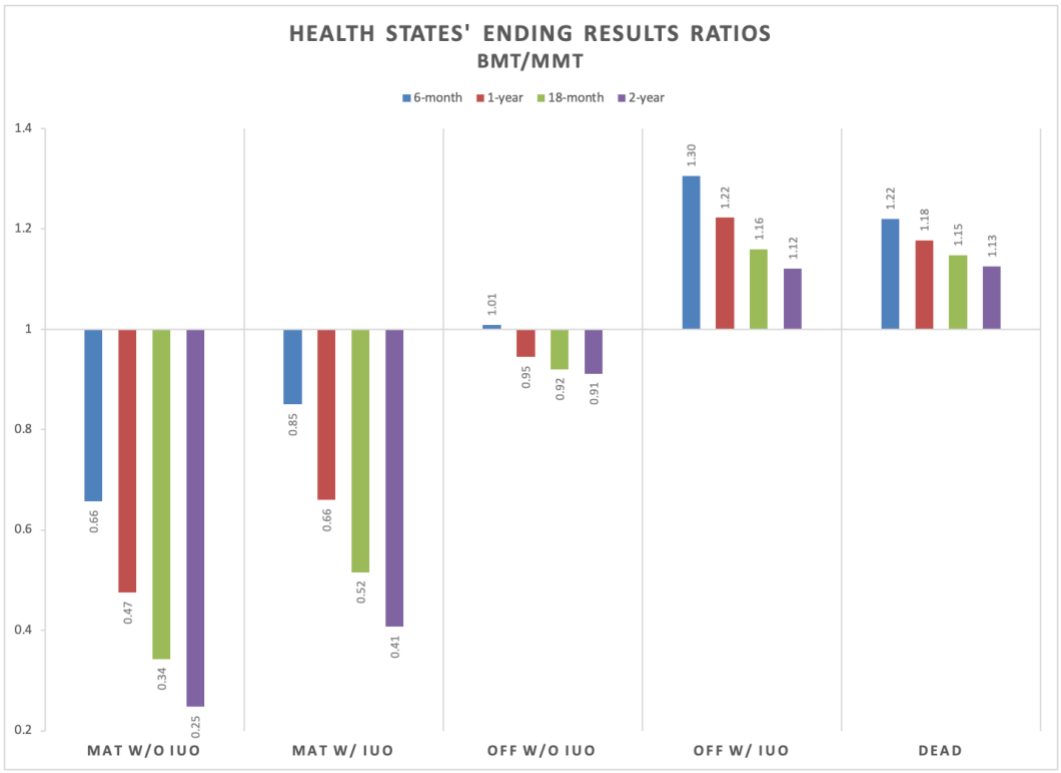


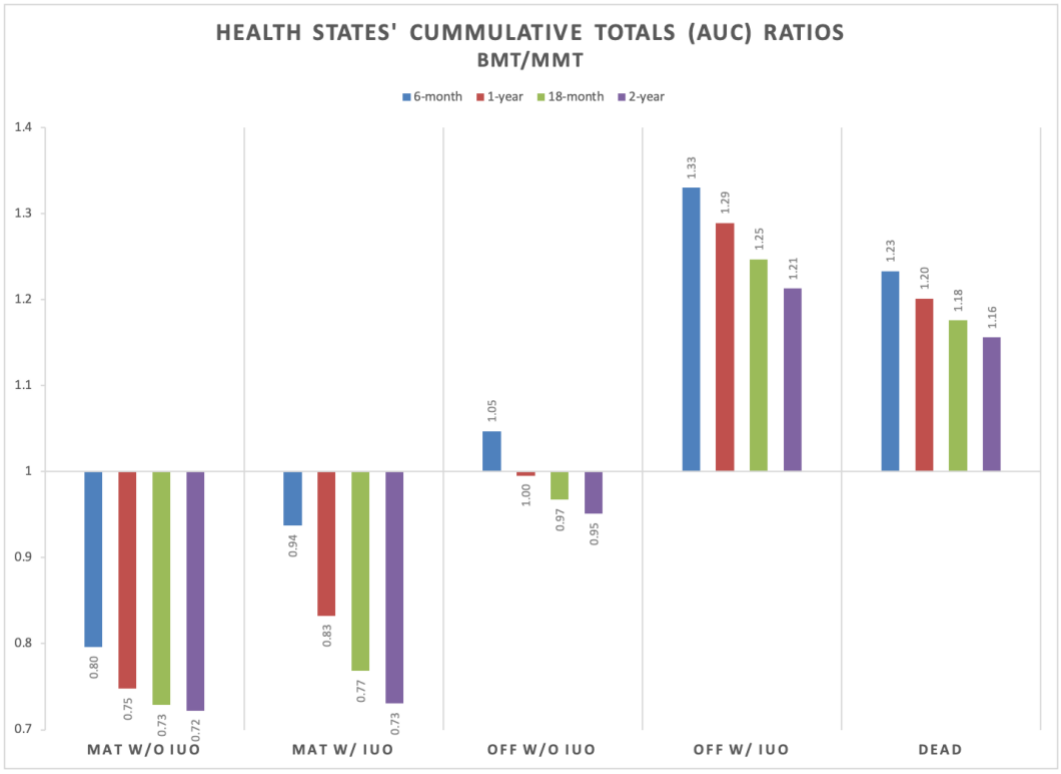
Appendix C.13 Health State Comparison Ratios (MMT/BMT)



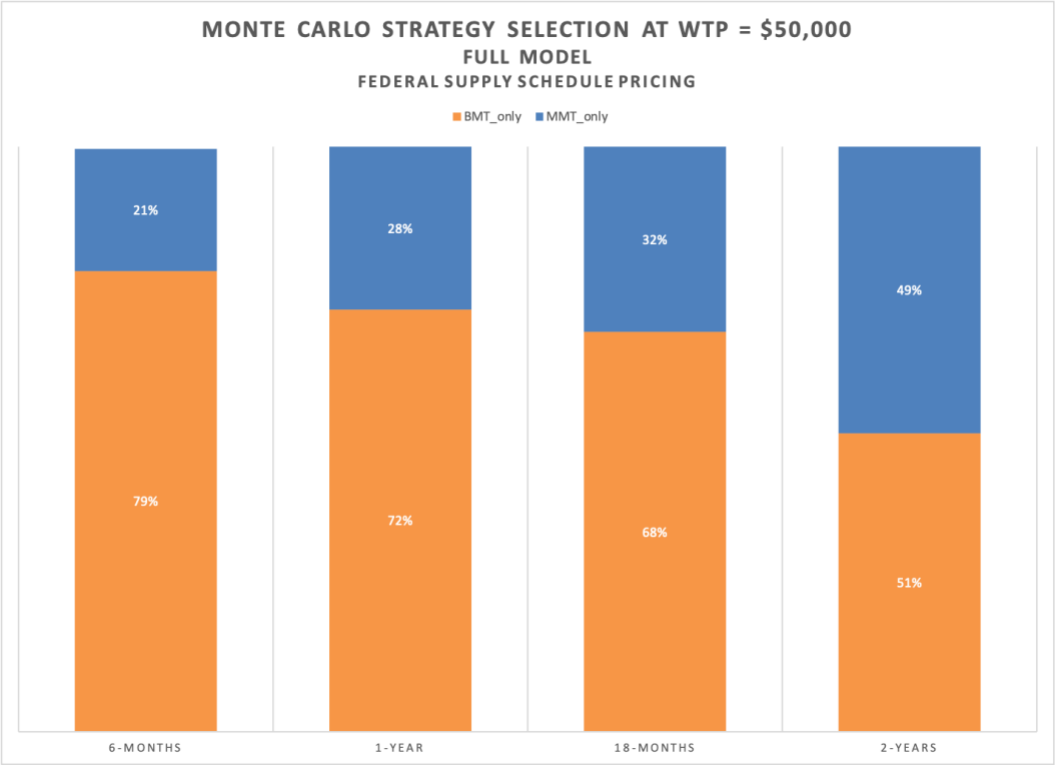


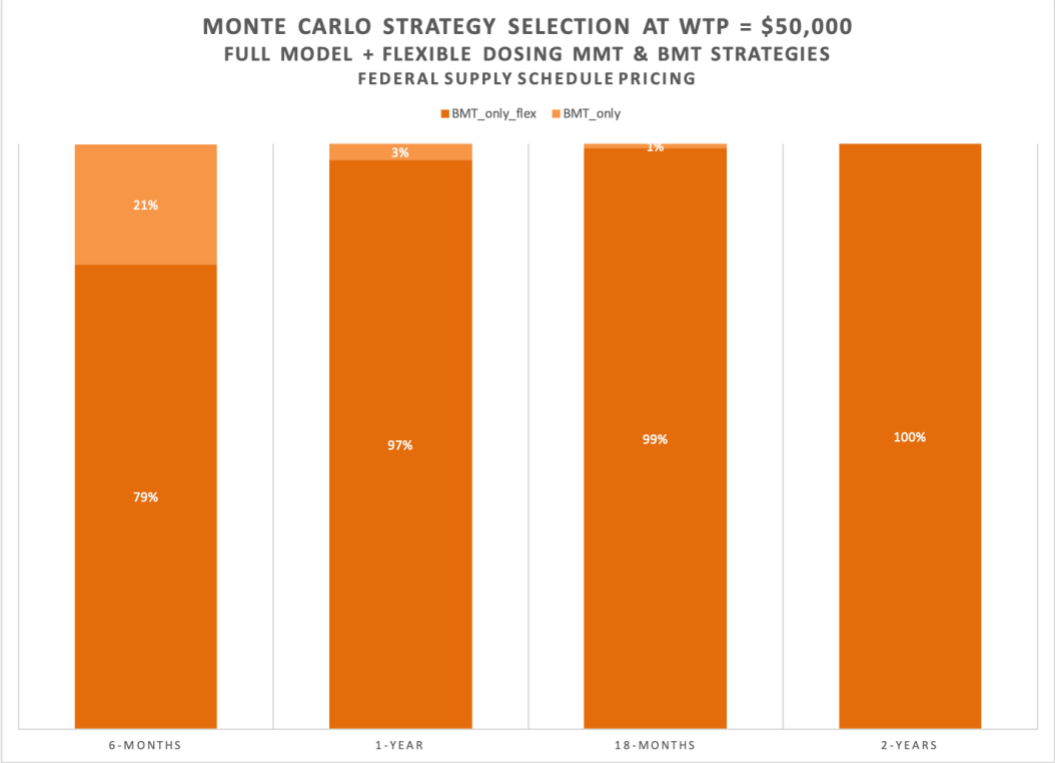
Appendix C.14 Health State Comparison Ratios (BMT/MMT)



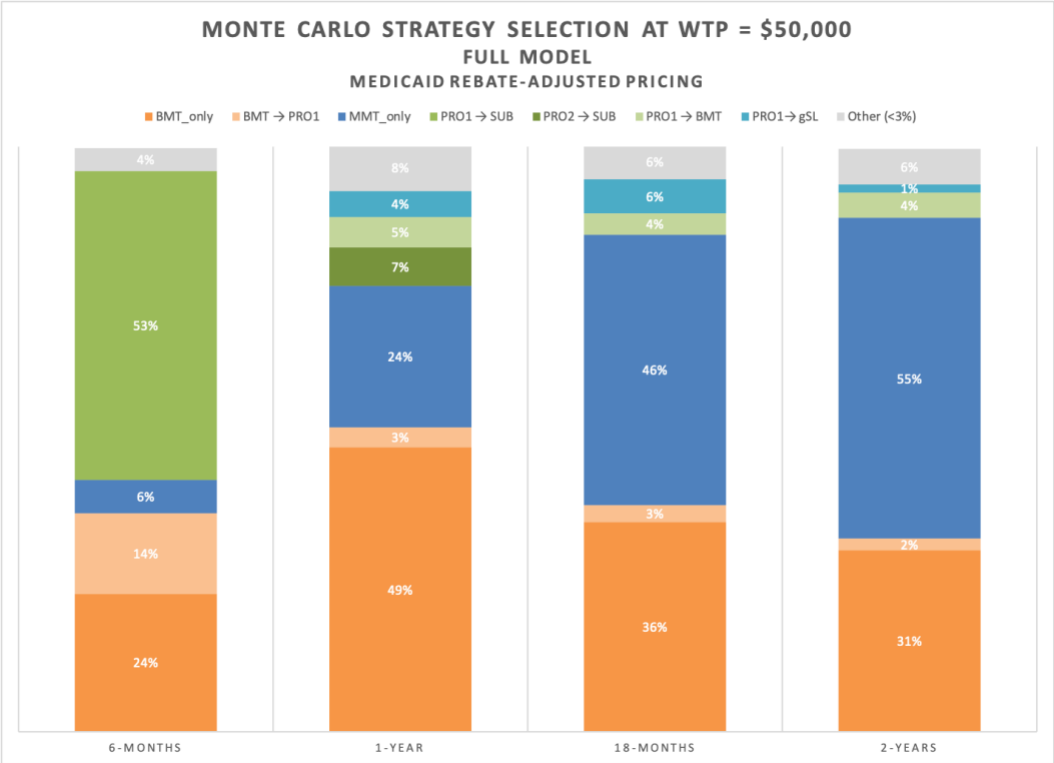


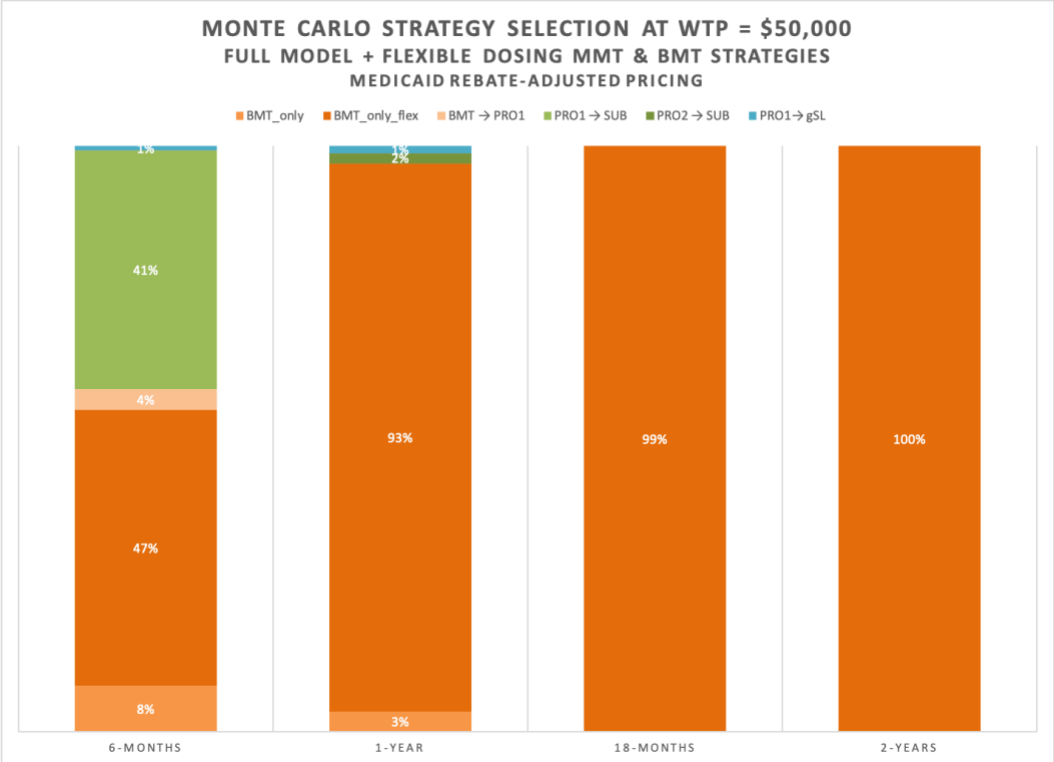
Appendix C.15 Scenario Analysis Strategy Selection Comparison (FSS Pricing)





Appendix C.16 Scenario Analysis Strategy Selection Comparison (MRA Pricing)





Bibliography

1. Hargan ED. Determination that a public health emergency exists. *Dep Heal Hum Serv*. 2017:1. https://www.hhs.gov/sites/default/files/opioid%20PHE%20Declaration-no-sig.pdf Accessed October 2, 2020.

2. Moos RH. Theory-based processes that promote the remission of substance use disorders. *Clin Psychol Rev*. 2007;27(5):537-551. doi:10.1016/j.cpr.2006.12.006

3. Chou R, Korthuis TP, Weimer M, et al. Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings. *Agency Healthc Res Qual*. 2016;(28). doi:10.1021/acs.jafc.8b03125

4. Bell J, Burrell T, Indig D, Gilmour S. Cycling in and out of treatment; Participation in methadone treatment in NSW, 1990-2002. *Drug Alcohol Depend*. 2006;81(1):55-61. doi:10.1016/j.drugalcdep.2005.05.010

5. Carter JA, Dammerman R, Frost M. Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *J Med Econ*. 2017;20(8):893-901. doi:10.1080/13696998.2017.1341416

6. Jackson H, Mandell K, Johnson K, Chatterjee D, Vanness DJ. Cost-effectiveness of injectable extended-release naltrexone compared with methadone maintenance and buprenorphine maintenance treatment for opioid dependence. *Subst Abus*. 2015;36(2):226-231. doi:10.1080/08897077.2015.1010031

7. ICER. Extended-Release Opioid Agonist and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder. 2018. https://34eyj51jerf417itp82ufdoe-wpengine.netdna-ssl.com/wp-content/uploads/2020/10/ICER_OUD_Final_Evidence_Report_120318.pdf Accessed January 27, 2020.

8. Otuonye IS, Banken R, Kumar VM, Pearson SD. *The Effectiveness and Value of Extended-Release Opioid Agonists and Antagonists for Addiction Treatment of Opioid Use Disorder*. Vol 25.; 2019:630-634. doi:10.18553/jmcp.2019.25.6.630

9. Academy of Managed Care Pharmacy. Drug Payment Methodologies - 2012. 2016;(February).

10. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: Health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction*. 2016;111(4):675-684. doi:10.1111/add.13219

11. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor R. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation HTA Health Technology Assessment NHS R&D HTA Programme www.hta.ac.uk Feedback. *Health Technol Assess (Rockv)*. 2007;11(9). http://www.hta.ac.uk. Accessed March 6, 2018.

12. Dolan R, Tian M. *Pricing and Payment for Medicaid Prescription Drugs*.; 2020.

13. American Medical Association. *Issue Brief: Reports of Increases in Opioid-Related Overdose during COVID Pandemic*.; 2020. https://chicago.suntimes.com/2020/5/13/21257820/dupage-opioid-overdose-death-. Accessed June 30, 2020.

14. Lavonas EJ, Banner W, Bradt P, et al. Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. *J Pediatr*. 2013;163(5):1377-1383.e3. doi:10.1016/j.jpeds.2013.06.058

15. Clemans-cope L, Epstein M, Basurto L. Medicaid Prescriptions for Extended-Release Medications to Treat Opioid Use Disorder State Trends from 2011 to 2018. *Urban Inst*. 2020;2020(April).

16. Revocation Of Orphan Drug Designation For Extended-Release Buprenorphine Injection: Implications And Next Steps | Health Affairs. https://www-healthaffairs-org.pitt.idm.oclc.org/do/10.1377/hblog20200302.846103/full/. Accessed November 2, 2020.

17. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health 2018. 2019. https://datafiles.samhsa.gov/.

18. Macpac. *Report to Congress on Medicaid and CHIP Medicaid and CHIP Payment and Access Commission*.; 2020.

19. Epstein M, Winiski E. *Lisa Clemans-Cope Federal Rebate Calculation for Medications to Treat Opioid Use Disorder in State Medicaid Programs MdPProgramsPSubtitle Here in Title Case*.; 2020.

20. Office CB. Congressional Budget Office The Prescription Drug Pricing Reduction Act (PDPRA) of 2019. 2019. https://www.finance.senate.gov/imo/media/doc/FINAL Description of the Chairman's Mark for the Prescription Drug Pricing Reduction Act of 2019.pdf. Accessed November 12, 2020.

21. MacGillis A. The Last Shot — ProPublica. https://www.propublica.org/article/vivitrol-opiate-crisis-and-criminal-justice. Accessed November 12, 2020.

22. Alkermes. *ALKERMES PUBLIC LIMITED COMPANY ANNUAL REPORT 2012 UNITED STATES SECURITIES AND EXCHANGE COMMISSION Form 10-K*.; 2012.

23. Alkermes. *Alkermes Public Limited Company Annual Report 2019 UNITED STATES SECURITIES AND EXCHANGE COMMISSION Form 10-K*.; 2019. https://investor.alkermes.com/static-files/b86158b0-8464-4828-99cb-5123017443ba Accessed November 12, 2020.

24. Lavonas EJ, Severtson SG, Martinez EM, et al. Abuse and diversion of buprenorphine sublingual tablets and film. *J Subst Abuse Treat*. 2014;47(1):27-34. doi:10.1016/j.jsat.2014.02.003

25. Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. *J Gen Intern Med*. 2012;27(6):669-676. doi:10.1007/s11606-011-1962-8

26. King JB, Sainski-Nguyen AM, Bellows BK. Office-Based Buprenorphine Versus Clinic-Based Methadone: A Cost-Effectiveness Analysis. *J Pain Palliat Care Pharmacother*. 2016;30(1):55-65. doi:10.3109/15360288.2015.1135847

27. ICER. Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value Evidence Report Prepared for. 2018.

28. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2014(2). doi:10.1002/14651858.CD002207.pub4

29. National Institute on Drug Abuse. Medications to Treat Opioid Use Disorder. *Natl Inst Drug Abus*. 2018;(June):1-47. https://www.drugabuse.gov.

30. Iitzoe ML, Guarnieri M. New developments in managing opioid addiction: Impact of a subdermal buprenorphine implant. *Drug Des Devel Ther*. 2017;11:1429-1437. doi:10.2147/DDDT.S109331

31. Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. *Pediatrics*. 2008;121(4). doi:10.1542/peds.2007-1774

32. ASAM. Advancing Access to Addiction Medications : Implications for Opioid Addiction Treatment. 2013:221. https://www.asam.org/docs/default-source/advocacy/aaam_implications-for-opioid-addiction-treatment_final. Accessed May 1, 2018.

33. Substance Abuse and Mental Health Services Administration. Opioid Treatment Program (OTP) Guidance. 2020;7:20857. www.samhsa.gov. Accessed June 30, 2020.

34. DEA. U.S. Department of Justice, Drug Enforcement Administration. COVID_19 Information Page: Telemedicine. *Letter*. 2020;823(2):2-4. https://www.dea.gov/press-releases/2020/03/20/deas-response-covid-19. Accessed December 17, 2020.

35. Bliley T. H.R.2634 - 106th Congress (1999-2000): Drug Addiction Treatment Act of 2000. 2000. https://www.congress.gov/bill/106th-congress/house-bill/2634. Accessed May 9, 2018.

36. Jones CM, Campopiano M, Baldwin G, Mccance-Katz E. National and State Treatment Need and Capacity for Opioid Agonist Medication-Assisted Treatment. *Am J Public Health*. 2015;105(8). doi:10.2105/AJPH

37. Thomas CP, Doyle E, Kreiner PW, et al. Prescribing patterns of buprenorphine waivered physicians. *Drug Alcohol Depend*. 2017;181(September):213-218. doi:10.1016/j.drugalcdep.2017.10.002

38. US Department of Health and Human Services. Announcement of Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder. *Fed Regist*. 2021. https://www.hhs.gov/sites/default/files/mat-physician-practice-guidelines.pdf.

39. Center for Disease Control and Prevention. Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Published 2020. Accessed March 1, 2021.

40. US Department of Health and Human Services. Statement Regarding X-Waiver. 2021:1. https://www.samhsa.gov/sites/default/files/statement-regarding-xwaiver.pdf.

41. Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349(10):949-958. doi:10.1056/NEJMoa022164