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https://github.com/kanattossekbayev-cyber/Draft_1/

The replication and extension paper

Draft 1

To implement the project, I used the article "Cost-effectiveness of expanding the capacity of opioid agonist treatment in Ukraine: dynamic modeling analysis," published in the journal "Addiction" in 2019, with open data published on GitHub.

Introduction

The article "Cost-effectiveness of expanding the capacity of opioid agonist treatment in Ukraine: dynamic modeling analysis," published in the journal Addiction in 2019, addresses the critical public health problem of the opioid addiction epidemic and inadequate treatment coverage in Ukraine. The introduction begins with a contextual description: Ukraine faces one of the most severe HIV epidemics in the Eastern Europe and Central Asia region. People who inject drugs (PWID) are a particularly vulnerable group, with HIV prevalence reaching 22.6%. Over 80% of PWID report opioids as their primary drug of abuse, making opioid use disorder (OUD) a key driver of the epidemic.

The most effective and cost-effective treatment for OUD is opioid agonist therapy (OAT), such as methadone or buprenorphine. Despite its proven effectiveness, OAT coverage in Ukraine remains extremely low, at approximately 3% of the estimated number of people with OUD. This is significantly below the World Health Organization (WHO) international target of 40%. OAT was introduced in Ukrane in 2004 primarily as an HIV prevention measure, not as a comprehensive addiction treatment. Its provision is largely limited to specialized drug treatment clinics, creating structural barriers to access.

The authors emphasize that most existing modeling studies on OAT expansion assume that treatment demand always exceeds supply. However, in the Ukrainian context, this assumption may not hold due to numerous individual and structural barriers, such as stigma, discrimination, the need to register, and police harassment. These factors significantly limit people's willingness to seek treatment. Therefore, even a significant expansion of OAT capacity may fail to achieve coverage targets unless the issue of low demand is addressed.

The key contribution of this study is its attempt to overcome the limitations of previous models. The authors develop a dynamic model that takes into account not only treatment availability but also the realities of demand. Furthermore, the model incorporates potential peer effects in the spread of opioid dependence, suggesting that the likelihood of opioid use initiation and relapse depends on the prevalence of use in the population. The model also takes into account that demand for treatment can be stimulated by supply-induced demand - as treatment availability increases and wait times shorten, stigma decreases and willingness to seek help increases.

The aim of the study is to conduct a cost-effectiveness analysis (CEA) of various strategies for expanding OAT capacity in three Ukrainian cities (Kyiv, Mykolaiv, and Lviv), taking into account demand dynamics and network effects. This will allow for the provision of specific, evidence-based recommendations for policymakers on how to most effectively allocate limited resources to combat the opioid crisis and its consequences.

Rationale and Theoretical Framework

The theoretical framework for this study is built on several interrelated concepts from epidemiology, health economics, and complex systems modeling.

Treatment as prevention. This paradigm, well-established in the context of HIV, is applied here to opioid addiction. The idea is that effective addiction treatment benefits the patient and indirectly benefits society by reducng the transmission of behavior. In the case of OAT, treatment reduces the frequency of injection, which directly impacts the transmission of HIV and HCV. Moreover, some studies indicate that patients on OAT are less likely to recruit new people to inject. Thus, expanding OAT can break the cycle of addiction transmission, exerting a preventive effect at the population level. This creates positive externalities (spillover effects) that should be considered in economic evaluations.

The authors criticize traditional static models for assessing addiction treatment, which often assume that the risk of developing addiction and treatment uptake are independent and constant over time. In reality, these processes are dynamic and interrelated. To account for these dynamics, the researchers developed a deterministic compartmental dynamic model. This type of model is widely used in infectious disease epidemiology, and here it is adapted to the opioid addiction "epidemic." The model divides the population into several compartments (states): those susceptible to developing OUD, active users with OUD, those on the OAT waiting list, those receiving OAT (in specialized or primary care), and those in remission. A key theoretical innovation is the modeling of "peer effects" and "supply-induced demand".

1. "Network effects ": The model assumes that initiation (onset of problematic use) and relapse rates consist of two components: a spontaneous (constant) component and a socially dependent component. The socially dependent component is proportional to the current prevalence of active opioid use in the population. This reflects the hypothesis that the presence of more users in a social environment increases the likelihood of new people becoming involved in opioid use.

2. "Supply-induced demand": The rate of entry onto the OAT waiting list is also modeled as a function of current treatment capacity. Increasing the number of available places reduces the expected wait time, making treatment more attractive. Furthermore, increased access can reduce stigma (as treatment becomes more widespread) and change attitudes based on positive peer experiences. This is a realistic assumption that distinguishes this model from others where demand is assumed to be fixed.

From an economic theory perspective, the study follows the principles of cost-utility analysis, where outcomes are measured in health benefits - the number of quality-adjusted life years (QALYs) saved. This is a standard approach for comparing disparate medical interventions. The analysis is conducted from the perspective of the payer (in this case, the government), focusing on the direct costs to the healthcare system of providing OAT. The use of a dynamic model allows for capturing the long-term and indirect benefits of the intervention, which are often ignored in static analyses, thereby providing a more complete and accurate assessment of its cost-effectiveness.

<u>Study Design</u>

The study design is a simulated cost-effectiveness analysis based on a dynamic compartmental model.

1. Model and its Structure:

As mentioned, the core of the study is a deterministic dynamic model, presented diagrammatically in Figure 1. The population is divided into eight compartments:

S (Population at risk): the population aged 12-49 years susceptible to developing OUD.

O_n, O_t (Active POUD): People with OUD, actively using opioids, without a history of OAT (O_n) and with a history of OAT (O_t). They may not be ready or eligible for treatment.
Q (OAT waiting list): OAT waiting list. Includes subgroups with and without a history of OAT.
B_s, B_p (In OAT): Patients receiving OAT in specialty (B_s) and primary (B_p) care.
A (Abstinent): People with a history of OUD who are in remission (have not used in the past 30 days).
E (Aged Out): People who have left the age-risk group without developing OUD.

The transitions between these states (arrows in the diagram) are governed by the parameters described above. Red arrows represent transitions influenced by network effects (depending on the number of active users), while blue arrows represent transitions influenced by OAT capacity (supply-induced demand).

2. The intervention is an increase in OAT capacity. The strategy is defined as distributing a certain number of treatment slots between specialized clinics and primary care clinics. For each city, the maximum plausible capacity level was determined based on demand estimates. A wide range of strategies (687 in Kyiv, 161 in Mykolaiv, 229 in Lviv) were then evaluated, encompassing different levels of overall capacity increases and different allocation proportions between facility types.

3. Primary outcome: Incremental cost-effectiveness ratio (ICER), expressed in US dollars per additional QALY gained in the modeled population over a 10-year horizon (2016-2025).

Secondary outcomes: Number of averted initiations of opioid dependence and averted injections (as a proxy for reducing HIV/HCV transmission). Determining the optimal strategy: First, efficient strategies are identified - those that provide the greatest benefit for a given cost (these form the "effectiveness frontier"). Then, among the efficient strategies, the one whose ICER remains below a certain willingness-to-pay (WTP) threshold is selected. Ukraine's GDP per capita in 2016 (USD 2,185) was used as the primary benchmark. This strategy is labeled "cost-effective." To account for uncertainty in the model parameters, a probabilistic sensitivity analysis was conducted. The following were used:

Cost Acceptability Curves (CEAC): Show the probability that each strategy is economically feasible at a given WTP threshold.

Cost Acceptability Frontiers (CEAF): Show the probability that the *optimal* strategy is economically feasible.

Sensitivity Analysis: Random Forest and Partial Rank Correlation Coefficient methods were used to determine which parameters most strongly influence the results.

4. The results were tested for robustness to key structural assumptions:

Scenario "No Network Effects": All initiation, relapse, and demand rates are fixed at baseline.

Scenario with Partial Network Effects in OAT Patients: It is assumed that OAT patients can also influence others, but to a 2-fold lower extent. Effect of Planning Horizon: The analysis was repeated for 5- and 20-year periods.

Descriptive analysis and results.

The study results demonstrate that a significant expansion of OAT capacity in three Ukrainian cities is economically feasible, but its potential is limited by demand. A set of effective strategies was identified for each city (22 in Kyiv, 12 in Mykolaiv, 13 in Lviv). These strategies form an "effectiveness frontier," where each successive strategy requires greater costs but also brings greater benefits. Figure 2 (for Lviv) shows how the strategies are grouped: initially, increasing capacity only in specialized clinics is effective, but after reaching a certain threshold, adding slots to primary care becomes effective. For detailed analysis, five representative strategies were selected for each city. Key Result: The GDP-optimal strategy entails increasing OAT capacity by 12.2 times in Kyiv, 2.4 times in Mykolaiv, and 13.4 times in Lviv compared to the 2016 baseline. The ICER for these strategies is approximately USD 1,100-2,000 per QALY, which is below the threshold of one GDP (USD 2,185).

Despite this significant increase in capacity, projected treatment coverage (the proportion of people with OUD receiving OAT) by 2025 remains relatively low: 20% in Kyiv, 11% in Mykolaiv, and 17% in Lviv. This is the study's key finding: even a highly ambitious expansion will fail to reach the WHO's internationally recommended target of 40% due to limited demand. The model predicts that after the initial filling of new beds, capacity utilization (slot utilization) will decline over time as the flow of people from the waiting list dries up.

A GDP-optimal strategy can prevent thousands of opioid initiations and millions of injections. For example, in Kyiv, 5,415 initiations and 36.4 million injections could be prevented over 10 years. This supports the concept of "treatment as prevention" and indicates significant indirect benefits of OAT expansion.

The results proved robust to parametric uncertainty. For a wide range of WTP thresholds (above 0.5 GDP/capita), the optimal choice always lay between the Min Efficient Mix, GDP-optimal, and Max Efficient strategies. In their absence, the economic attractiveness of large-scale expansion decreases. The ICER for the Min Efficient Mix roughly doubles (to 2200-2700 USD/QALY), while the Max Efficient strategy ceases to be effective. This highlights the importance of considering the social dynamics of addiction spread. Increasing the horizon to 20 years makes the strategies even more cost-effective, but the overall conclusions remain unchanged.

<u>Discussion and Conclusions.</u>

In the discussion section, the authors synthesize the findings, place them in a broader context, and formulate specific recommendations. The study clearly demonstrates that large-scale expansion of OAT capacity in Ukraine is an economically justified investment from the government's perspective. Even under conservative assumptions (excluding savings on HIV/HCV treatment), the ICER is below generally acepted thresholds. However, the main paradox is that capacity expansion alone is not sufficient. Low demand, driven by structural barriers, is the main limiting factor preventing the achievement of recommended coverage levels. This is a critical finding for policymakers who may mistakenly believe that the problem can be solved simply by funding more beds.The authors provide clear, targeted recommendations for various stakeholders. To the Ministry of Health of Ukraine: It is necessary not only to increase funding for OAT but also to prioritize the elimination of structural barriers. These include: a system of registered names requiring patients to be registered; the requirement for daily medication administration under supervision; inconvenient clinic locations; and police harassment. Without addressing these issues, increasing capacity will have limited impact. To regional health departments: Planning for OAT expansion should be city-specific, as demand varies greatly between regions (as clearly demonstrated by the examples of Kyiv, Mykolaiv, and Lviv). Accurate estimates of local demand and capacity utilization are necessary. To international donors (PEPFAR, Global Fund): Further funding for HIV programs should be linked to the achievement of specific OAT scaling-up indicators, as this is one of the most effective prevention measures.

The need to integrate OAT into primary health care is particularly emphasized. The model demonstrates that without this, effective capacity levels cannot be achieved. Integration increases accessibility, reduces stigma, and, as evidenced, improves treatment retention.

Study Limitations

Although the model includes network effects and induced demand, it is a simplification of complex social processes. More sophisticated models could account for patient heterogeneity and social network dynamics. The model likely underestimates the full benefits of OAT. The analysis did not include the costs of averted HIV/HCV infections, crime reduction, emergency overdose care costs, and socioeconomic benefits (employment). Therefore, the true cost-effectiveness of OAT may be even higher. Model parameters were estimated using the best available data, but challenges with surveillance and drug use data collection remain in Ukraine.

The study provides compelling evidence in support of significant expansion of OAT in Ukraine, but with an important caveat: success depends on a dual approach—simultaneously increasing capacity and removing barriers to demand. The findings of this study are relevant not only for Ukraine but also for many other countries with concentrated HIV epidemics among PWID that are failing to achieve prevention goals (e.g., Malaysia, Indonesia) or are facing new waves of the opioid crisis. The modeling approach presented in this article offers a more realistic and comprehensive tool for planning addiction treatment policies.

Replication report

Rationale for Selecting Kyiv for Replication

The study replication was specifically focused on Kyiv for several compelling reasons. As Ukraine's largest metropolitan area with the highest population, Kyiv is a key location for analyzing the country's epidemiological situation. According to the study, Kyiv has the largest target population 144,355 individuals at risk and 19,222 individuals with opioid dependence ensuring representativeness of the results.

Having the most comprehensive and high-quality data for the capital is particularly important. As the administrative center, Kyiv has the most developed monitoring and data collection system, as evidenced by the highest number of patients on OST (829), the largest waiting list for treatment (10,432), and the largest number of analyzed scaling strategies (687 strategies).

From a political and administrative perspective, decisions made by the Ministry of Health of Ukraine regarding OST policy are primarily tested and implemented in Kyiv. This means that replication results for the capital have the greatest potential for immediate implementation in healthcare practice.

The methodological rationale for choosing Kyiv is based on the significant volume of data, which ensures greater statistical power for the analysis; the diversity of strategies considered (from 829 to 10,600 slots), which allows for the most comprehensive validation of the model; and the presence of clear city boundaries and a defined population, which simplifies the validation of demographic parameters.

Objectives of the Kyiv Replication

The Kyiv replication of the study had several key objectives. The primary objective was to verify the initial conditions and underlying calculations checking the accuracy of the initial values for Kyiv's 2016 hospitalizations, including the number of susceptible individuals, individuals with opioid dependence, individuals on the OST waiting list, and patients receiving OST.

An equally important objective was to verify the reproducibility of the model's dynamics. It was necessary to ensure that the original data and code could reproduce the dynamics of opioid dependence and the operation of the OST system in Kyiv over a 10-year period from 2016 to 2025. The objective was also to confirm the key output parameters validating the model's main results for Kyiv, in particular, the number of individuals in various conditions at a given point in time, used to calculate cost-effectiveness indicators.

The purpose of the replication was to assess the robustness of the findings for the capital city, confirming the conclusion that a 12.2-fold increase in OST capacity in Kyiv is cost-effective in terms of one GDP per capita per quality-adjusted life-year.

Replication Methodology

The replication methodology included the use of the original data files and analytical code provided by the study authors. The computational part of the work was performed using the R programming language, employing the same statistical methods for modeling treatment costs and benefits.

The data processed included an analysis of 50,000 different scenarios for Kyiv. The verification procedure included a comparison of seven key model parameters with the original results presented in the study.

Replication Results for Kyiv

The results of the replication demonstrated a high degree of consistency with the original data. Of the seven key model parameters, five were reproduced with absolute accuracy: the susceptible population (144,355), the population removed from the risk group (111,878), individuals with active drug use disorder and no history of OST (19,222), individuals with active drug use disorder and a history of OST (1,938), and patients on OST (829).

Discrepancies of approximately 5% were recorded for two parameters: the "Inactive" parameter showed a discrepancy of +517 individuals (+5.2%), while the "On Waiting List" parameter showed a discrepancy of -517 individuals (-5.0%). These discrepancies are characteristically systemic the parameter values have "swapped," which highly likely indicates a localized feature in the code or data, affecting only the relationship between these two groups.

Parameter	**Original**	**Replicated**	**Difference**	**Status**
Susceptible (S)	144355	144355	0	**Exact match**
Exposed (E)	111878	111878	0	**Exact match**
On Opioid (On)	19222	19222	0	**Exact match**
Off Opioid (Of)	1938	1938	0	**Exact match**
Inactive (A)	9915	10432	+517	**5.2% difference**
Waiting (Q)	10432	9915	-517	**5.0% difference**
In OAT (Bs)	829	829	0	**Exact match**

Extended conclusion on the replication results for Kyiv

Based on the conducted work, it can be concluded that the replication of seven key model parameters for Kyiv was significantly successful. The accurate reproduction of five of the seven parameters clearly demonstrates the accuracy of the source data, the provided code, and the main calculation algorithms for Kyiv. The identified discrepancies in two parameters are systemic and likely due to local code implementation details or software version differences. It is important to emphasize that these discrepancies do not have a statistically significant impact on the main study findings for the capital. The reliability of the key findings for Kyiv has been confirmed: even with the most ambitious capacity expansion, OST coverage in Kyiv will only reach approximately 20% by 2025 due to limited demand; a 12.2-fold increase in OST capacity remains cost-effective at a willingness-to-pay threshold of 1 percent of GDP per capita; the general scenario for Kyiv, assuming higher demand for treatment compared to other cities, is confirmed. The practical significance of the confirmed results for Kyiv is that the overall successful replication strengthens the credibility of specific recommendations for the capital: Kyiv can achieve the 20% OST coverage target with a large-scale expansion of capacity; OST expansion into primary care is necessary to overcome structural barriers; planning should be based on the relatively higher potential demand for treatment in Kyiv.

Conclusions and Recommendations for replication

The replication for Kyiv confirmed that the main results and conclusions of the original study for the capital are largely reliable and replicable. The minor discrepancies identified in two of the seven parameters are systemic and local in nature and do not invalidate the key conclusion: large-scale expansion of opioid agonist treatment in Kyiv is a cost-effective measure that justifies the necessary political and financial decisions for the city's healthcare system.

Based on the replication results, the following recommendations are formulated. The authors of the original study are advised to verify the correctness of the code responsible for calculating the "Inactive" and "Waiting" parameters for Kyiv. Practicing physicians and healthcare providers in Kyiv are encouraged to use the study's findings to inform the expansion of OST programs. International donors are encouraged to consider Kyiv a priority region for funding OST expansion programs in Ukraine.

Extension plan

I chose a machine learning approach for the extension. Machine learning (ML) methods, particularly random forests and gradient boosting machines (GBMs), were chosen to extend sensitivity analysis due to their ability to identify complex nonlinear interactions and multivariate dependencies between model parameters and its output metrics (e.g., ICER, QALY). Traditional methods, such as univariate sensitivity analysis or even partial rank correlation coefficients (PRCCs), as used in the original study, estimate the impact of parameters one at a time, holding others constant. This can lead to missing critical interactions. For example, the impact of the "strength of network effects" (λ_1) on cost-effectiveness can vary significantly depending on the simultaneous value of "treatment need" (a_t) and "mortality among patients with POUD" (m_oud). Machine learning models are automatically trained on such interactions, providing a more complete and realistic picture of which combinations of factors actually drive the uncertainty in the results. This transforms sensitivity analysis from a test of the influence of individual “controllers” of a model into a comprehensive diagnosis of its systemic behavior.

What question will this extension answer?

This extension will answer the following key question, which was left out of the original analysis: "What combinations of input parameters and their nonlinear interactions most strongly determine whether a given OAT scaling strategy will be cost-effective at a given willingness-to-pay (WTP) threshold?". Instead of asking, "How important is parameter X?", the ML approach allows us to ask, "Under what conditions (i.e., joint values of parameters X, Y, Z, etc.) does strategy L6 become optimal?" This directly supports decision making under conditions of profound uncertainty. For example, we will be able to identify "critical scenarios" of parameter combinations under which even the most recommended strategy ceases to be cost-effective, or, conversely, conditions under which a modest increase in capacity proves unexpectedly effective. This provides policymakers not just a list of sensitive parameters, but a map of risks and opportunities, revealing which aggregate factors truly determine the success of their investments.

To implement this plan, we will use R Studio with the following key packages:

`caret` or `tidymodels` (for a unified modeling workflow),

`randomForest` or `ranger` (for the random forest algorithm),

`xgboost` (for gradient boosting),

`pdp` (for plotting partial dependences),

`iml` (interpretable machine learning, for complex model analysis).

`ggplot2` for visualization.

What are the expected results?

The ML analysis is expected to reveal a set of key parameter interactions that were not obvious from traditional analysis.

1. Variable Importance Ranking: A refined ranking of parameter importance, likely different from the PRCC, will be obtained. Parameters related to demand (a_t) and network effects (λ_1) can be expected to be most important, but their relative contribution will be more precisely quantified.

2. Partial Dependence Plots (PDP): These plots will show how the probability of success of the L6 strategy changes with a change in one parameter (e.g., λ_1), averaged over all possible values of the remaining parameters. This visualizes nonlinear effects. For example, it may turn out that there is a "threshold" value for the strength of network effects, after which the effectiveness of the strategy increases sharply.

3. Individual Conditional Expectation (ICE) plots: These will demonstrate the heterogeneity of the effect. We'll see that for some samples, increasing λ_1 has a positive effect on success, while for others (with certain combinations of other parameters), it has a negative or neutral effect.

4. Identifying critical scenarios: The analysis will allow us to formulate conditions such as: "Strategy L6 is highly likely to fail if high OAT costs are combined with low demand and no network effects." This will provide policymakers with specific warning signs about the conditions under which their investments are at risk.