

# Design and implementation of a Type-2 hybrid, prospective randomized trial of opioid agonist therapies integration into primary care clinics in Ukraine

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## ARTICLE INFO

### Keywords:

Opioid agonist therapies (OAT)  
People who inject drugs (PWID)  
Opioids  
Integrated care  
Implementation science  
Ukraine

## ABSTRACT

**Introduction:** Ukraine has high HIV prevalence, concentrated among people who inject drugs (PWID), mostly of opioids. Maintenance on opioid agonist therapies (OAT) is the most effective evidence-based treatment for opioid use disorder. As PWID experience high morbidity and mortality from preventable and treatable non-communicable diseases, international agencies recommend integrating OAT into primary care centers (PCC).

**Methods:** A randomized, type-2 hybrid implementation trial was carried out to compare outcomes of OAT integration in PCC to OAT delivery at specialty treatment centers (STC) – standard-of-care. Tele-education supporting PCC providers in managing OAT, HIV, tuberculosis and non-communicable diseases along with pay-for-performance incentives were used to facilitate implementation. Consenting patients underwent 1:2 randomization to either STC or PCC. Quality health indicators (QHIs), a composite percentage of recommended primary and specialty services accessed by patients (blood/urine tests, cancer screenings, etc.), were defined as efficacy outcomes and were assessed by participant self-report at baseline and every 6 months over 24 months and electronic chart reviews after the completion of the follow-up. The primary outcome is defined as the difference in composite QHI scores at 24 months, in which a repeated measures likelihood-based mixed model with missing at random assumptions will be used. Providers at PCC completed surveys at baseline, 12 and 24 months to assess implementation outcomes including changes in stigma and attitudes towards OAT and PWID.

**Preliminary results:** Among the 1459 participants allocated to STC ( $N = 509$ ) or PCC ( $N = 950$ ), there were no differences in clinical and demographic characteristics. Self-reported prevalences were available for HIV (42 %), HCV (57 %), and prior tuberculosis (17 %). Study retention at 6, 12, 18, and 24 months was as 91 %, 85 %, 80 %, and 74 %, respectively.

**Abbreviations:** EECA, Eastern Europe and Central Asia; ECHO-IC, Extension for community healthcare outcomes for integrated care; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; i-PARIHS, Integrated promoting action on research implementation in health services; ICD-10, 10th revision of International Statistical Classification of Diseases; IRB, Institutional review board; OAT, Opioid agonist therapies; OUD, Opioid use disorder; P4P, Pay for performance; PCC, Primary care center; PWID, People who inject drugs; QI, Quality improvement; STC, Specialty treatment center; SUD, Substance use disorders.

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<https://doi.org/10.1016/j.cct.2024.107690>

Received 22 May 2024; Received in revised form 28 August 2024; Accepted 9 September 2024

Available online 14 September 2024

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**Conclusion:** PWID have a high prevalence of medical comorbidities and integrating OAT into primary care settings has the potential to improve the health of PWID. Findings from this study can help guide implementation of integrated care in Ukraine and throughout similar low-resource, high-burden countries in the Eastern European and Central Asian region.

## 1. Introduction

Despite reductions in HIV globally, HIV incidence and mortality are increasing in the Eastern Europe and Central Asian (EECA) region. Like other EECA countries, Ukraine's HIV epidemic is concentrated among people who inject drugs (PWID). The majority of PWID in Ukraine use illicit opioids and meet the diagnostic criteria of opioid use disorder [1]. PWID experience poor health outcomes, including HIV, HCV, and tuberculosis comorbidities, overdose, hospitalizations [2–4], and increased morbidity and mortality, mostly from diseases that can be screened for and managed in primary care settings [5,6].

Maintenance with opioid agonist therapies (OAT) using methadone or buprenorphine is the most effective evidence-based practice for managing opioid use disorder [7,8]. Maintenance with OAT has been shown to be the most cost-effective HIV prevention strategy in a setting where HIV is mostly concentrated among PWID [9,10]. Along with improving HIV outcomes, OAT decreases HCV transmission risk, illicit drug use, overdose risk, and improves other health and social outcomes [11–13]. Despite the recent gains, the national OAT coverage in Ukraine remains low [14]. Mathematical modeling suggests that OAT cannot be reasonably scaled up in specialty clinics alone, where it is currently being provided as standard of care [15,16]. To achieve the World Health Organization's recommended OAT treatment coverage level of over 40 % for individuals with OUD [17], a simultaneous scale-up in integrated primary care settings is required.

Integration of OAT into primary care settings is recommended by national and international agencies [18,19]. Primary care settings offer a valuable opportunity for individuals like PWID who have several comorbid diseases to access comprehensive and continuous healthcare services delivered by a multi-disciplinary care team as part of integrated care [20]. The Ukrainian health system used to prioritize secondary and tertiary care in hospital-based settings, with low reliance on primary care for specialty conditions [21]. However, introduction of integrated care for PWID was facilitated by the legislative changes in 2016 that prioritized the strengthening of the primary care system and permitted OAT delivery in those settings. Cross-sectional and retrospective cohort studies conducted following the legislature change confirmed improved health outcomes for those receiving healthcare services in integrated care clinics [22–25].

Receiving buprenorphine in primary care settings has been shown to have similar OAT retention to specialty care settings in the United States [26], and other health benefits of integrated OAT have been documented in cohort or observational studies [27,28]. The majority of the studies exploring integrated OAT care, though, have been assessed in high-income settings and specifically examined OUD-related outcomes rather than more the comprehensive health metrics for PWID. To address this knowledge gap, we conducted Integrating Methadone into Primary Care & Treatment (IMPACT), a type-2 hybrid implementation trial [29] using a randomized design to examine both effectiveness and implementation outcomes of integration of OAT services into primary care settings in a high-burden, middle-income country, Ukraine.

## 2. Methods

### 2.1. Local context

OAT was first introduced in Ukraine in 2004 with buprenorphine, followed by methadone in 2008 [30]. When IMPACT began in early 2018, there were ~ 350,000 PWID in Ukraine. OAT coverage ranged

from 1.1 % to 6.9 % in the oblasts (regions) participating in the trial [14], far below the levels recommended by the World Health Organization (Table 1) [17]. OAT scale-up had been hindered by structural, provider- and patient-level factors [31–35]. Following the legislative changes in 2016 which allowed for OAT to be delivered in primary care settings for the first time, a 6-month pilot study integrating methadone into PCC in Ukraine demonstrated feasibility with high levels of retention on methadone. Patients reported higher levels of satisfaction with treatment and self-perceived wellbeing, while providers reported improved attitudes towards patients with OUD [15].

Before the legislative changes in 2016, Ukraine had the highly siloed healthcare system where OAT was prescribed by specialists (called narcologists) mostly in specialty treatment clinics which offered only OUD services to their clients. Providers were often underpaid (~\$250 USD per month) [36,37], and held negative attitudes about OAT and would prescribe OAT for HIV prevention, rather than to treat OUD, which they perceived to be ineffective [38]. Primary care providers, on the other hand, had not been tasked with providing OAT and other specialty care services before (those for HIV and tuberculosis) and lacked confidence and expertise in providing care for PWID in primary care settings.

### 2.2. Implementation framework

We employed the integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) [39,40] framework to guide our implementation efforts. I-PARIHS was chosen because it integrates diffusion of innovation theory and implementation research and provides a comprehensive approach to implementing evidence-based practices in healthcare settings. The i-PARIHS framework's four key constructs are innovation, context, recipients, and facilitation, which make it particularly well-suited for real-world implementation.

In the case of IMPACT, innovation was implementing OAT in primary care settings. The *contextual* factors in Ukraine included overlapping epidemics of HIV, tuberculosis, and opioid use disorder (OUD); a siloed healthcare system; primary care providers' lack of expertise in managing specialty conditions; and the low remuneration of healthcare workers. *Facilitation*, another core construct of i-PARIHS, played a critical role in overcoming contextual barriers through implementation strategies like expert coaching via tele-education and financial incentives [41,42]. The *recipient*-centered nature of i-PARIHS was helpful in engaging both patients and OAT providers, as active participation of and acceptance from these stakeholders is crucial for the successful implementation. Therefore, the i-PARIHS framework provided a structured and flexible approach essential for the effective and sustainable implementation of OAT in the Ukrainian primary care context.

### 2.3. Study design

The type-2 hybrid design was chosen to test both the effectiveness of the intervention and examine the implementation process. Although OAT is an evidence-based practice, we chose to test its effectiveness as it was being introduced in primary care setting in Ukraine for the first time. The study was carried out in 12 cities (Dnipro, Zhytomyr, Kryvyi Rih, Mykolaiv, Cherkasy, Kropyvnytskyi, Kramatorsk, Kyiv, Mariupol, Rivne, Sloviansk, and Odesa) using a stratified, phase-in, controlled design (Fig. 1, Fig. 2). Cities were selected from regions of Ukraine with the highest burden of HIV. The two study arms included OAT delivered in STC (control arm), and OAT delivered within PCC (intervention arm).

Within each city, one STC and two PCC participated in the trial. Providers at one PCC in each city received pay-for-performance (P4P) financial incentives, while providers at the other PCC received no financial incentives. The phase-in order for the cities was based on the site readiness to start OAT at both PCC sites. In October 2022, Lviv was added following the disruptions and site closure in Mariupol after Russia invaded Ukraine. The first participant was enrolled on 01/20/2018 and enrollment was completed on 12/31/2023, with follow-up activities completed on 06/31/2024. The maximum follow-up period of each participant was 2 years following the enrollment date.

#### 2.4. Participant recruitment and randomization

Participants were recruited continuously from the natural flow of individuals presenting to STC to initiate OAT. Eligibility criteria included: 1) 18 years or older; 2) diagnosed with OUD using the 10th revision of International Statistical Classification of Diseases (ICD-10) criteria; and 3) residing within the legal catchment area of study sites. Participants were excluded if: (1) they were under police investigation; (2) were planning to move to another city; and (3) were not able to provide informed consent. Originally, the study intended to randomize participants to three arms: STC, PCC with P4P, and PCC without P4P. However, after consultations with local stakeholders, we decided to retain only two arms, STC and PCC and allow participants randomized to PCC arm to choose between the two participating PCC within each city based on geographical convenience. Participants were blinded to the P4P allocation of PCC. Subsequently, following the informed consent procedures, participants were randomized 2:1 to PCC:STC using permuted block randomization with variable block sizes. Participants were stratified equally by OAT status: those stable on methadone (>3 months) and those newly enrolling. The rationale for including newly enrolling (i.e., naïve) OAT patients was to assess how well PCC staff managed the early treatment process as dropout is highest in the first 3 months of OAT initiation [15,23,43].

#### 2.5. Study outcomes and data sources

Effectiveness outcomes were measured using standardized Quality Health Indicator (QHI) scores (Table 2) [27]. QHIs were developed in collaboration with Ukrainian experts using the Delphi method [44]. They encompassed 9 primary and 8 specialty care services and screenings recommended nationally. Primary QHIs included physical examination, general blood count, urine analysis, and screenings for cervical, breast, prostate, and other cancers. Specialty QHIs included services and screenings related to HIV, tuberculosis, and OAT.

QHI scores were calculated as a percentage of all recommended services and screenings accessed by an individual. Some screenings were specific to sex (e.g., cervical, breast, or prostate cancer screenings) or age categories (e.g., electrocardiography). Others were recommended

only for people with HIV (e.g., viral load and CD4 count, receipt of antiretroviral therapy). Consequently, the number of recommended QHIs varied for each participant.

Information about QHIs was collected from two distinct data sources: self-reported surveys and electronic medical records (EMR) from participants. Surveys were conducted at baseline and every 6 months for 24 months and participants were asked to confirm the receipt of each QHI component during the past 6 months. QHIs recommended annually or less frequently were counted towards two or more time points (e.g., if an individual reported accessing electrocardiography at the 6-month interview, it was counted as completed for the 12-month interview as well). QHI scores were calculated as primary, specialty, and composite QHI scores.

EMR were used as an additional data source to assess the receipt of QHIs by participants. OAT providers at each participating clinic manually entered information about the receipt of QHIs by participants upon verification through medical charts, visit summaries, prescriptions, and other visit documentation. For the EMR QHI scores, we calculated the final percentage of all recommended QHIs accessed by an individual over 24 months, with varying denominators for each participant based on their sex, age, or comorbidities (HIV, HCV, tuberculosis).

The difference between the two arms in the self-reported composite QHI scores at 24 months was defined as the primary outcome. Differences between the two arms at other time points, as well as differences in primary and specialty QHI scores and differences in EMR QHI scores were defined as secondary outcomes. We also compared QHI scores between PCC with and without P4P. The reasons behind choosing QHI scores were the following: (a) QHI components cover a comprehensive list of nationally recommended health screenings and services; (b) it is straightforward to collect the QHI data and does not involve performing medical tests by trained clinical providers; (c) QHIs document an individual's interaction with the health system and are a good measure of healthcare accessibility as well as downstream health benefits for PWID; and (d) can be used to measure the quality of healthcare delivery that are concordant with guidelines. QHIs have been used before for HIV and general health outcomes [22,27,45].

Additionally, the participant surveys included sections on demographic characteristics, OUD treatment experience, a stigma scale modified for drug use [46], and structured scales: Substance Abuse and Mental Illness Symptom Screener [47], SOCRATES for treatment readiness [48], DAST-10 for addiction severity [49], AUDIT-C for alcohol use [50], CES-D for depression [51], SF-12 for health-related quality of life [52], and trust in physician [53] for further sub-analyses.

Implementation process outcomes were defined as provider-level measures, which included changes in attitudes towards newly-implemented services (OAT) as an evidence-based practice [54] and a new patient population (PWID). We also measured provider confidence in implementing and providing OAT care in their practice and provider engagement in tele-education activities. Sampling included all staff

**Table 1**  
Local Context at the Time of Site Activation.

| Site (City)   | Oblast         | Oblast population by thousands | Number of PWID in Oblast | Number of people on OAT | OAT coverage in Oblast |
|---------------|----------------|--------------------------------|--------------------------|-------------------------|------------------------|
| Dnipro        | Dnipropetrovsk | 3229                           | 58,000                   | 1686                    | 2.9 %                  |
| Kryvyi Rih    |                |                                |                          |                         |                        |
| Zhytomyr      | Zhytomyr       | 1230                           | 6500                     | 386                     | 5.9 %                  |
| Mykolaiv      | Mykolaiv       | 1140                           | 12,300                   | 848                     | 6.9 %                  |
| Cherkasy      | Cherkasy       | 1219                           | 10,900                   | 233                     | 2.1 %                  |
| Kropyvnytskyi | Kirovohrad     | 955                            | 13,200                   | 350                     | 2.7 %                  |
| Kyiv          | Kyiv City      | 2934                           | 33,700                   | 1127                    | 3.3 %                  |
| Kramatorsk    | Donetsk        | 4198                           | 31,100                   | 332                     | 1.1 %                  |
| Mariupol      |                |                                |                          |                         |                        |
| Sloviansk     |                |                                |                          |                         |                        |
| Rivne         | Rivne          | 1093                           | 6100                     | 169                     | 1.7 %                  |
| Odesa         | Odesa          | 2383                           | 11,900                   | 469                     | 3.9 %                  |
| Lviv          | Lviv           | 2528                           | 9900                     | 299                     | 3.0 %                  |

Abbreviations: PWID (people who inject drugs); OAT (opioid agonist therapies).

providing direct care to PWID as well as those not involved in OAT at each PCC site. Surveys were collected at baseline and every 6 months from clinical and administrative staff at the PCC through 24 months. These measures were selected as implementation outcomes because provider attitudes and confidence are critical for the adoption and integration of new practices and can provide useful insights into the implementation process.

## 2.6. Statistical considerations

### 2.6.1. Sample size

The original design with three arms required 405 participants per group for three allocation groups, totaling 1215 participants. This calculation was based on achieving 90 % power at  $p < 0.05$  to detect a standardized effect size of 0.10, testing the null hypothesis of no difference between the mean composite QHI scores of the three groups against the alternative of at least one difference by 24 months. Given the 24-month study follow-up, we addressed potential dropout by inflating the sample size by 10 %, resulting in a required sample size of 1350 participants for the primary effectiveness outcome. Following a study design modification to include only two arms, the initial sample size of 1350 was retained, providing more than sufficient power for the planned analysis. The sample size calculation was performed using PASS software [55].

### 2.6.2. Statistical analysis plan

A pre-planned interim analysis of self-reported QHI outcomes at 12 months and a secondary analysis of provider outcomes has been reported [56,57]. The primary and secondary efficacy, as well as implementation outcome analyses described below will be conducted following the conclusion of data gathering.

All analyses will be conducted according to the principle of intent-to-treat, i.e., analysis as randomized. A repeated measures likelihood-based mixed model with missing at random assumptions will be used for the analysis of the primary outcome to compare the two arms, adjusted for the stratification variables (current vs naïve on OAT) as well a priori selected clinical and demographic characteristics. We will also adjust for covariates that are predictive of missingness to be consistent with the MAR assumption. We will identify these covariates by performing logistic regressions to investigate the relationship between each covariate and the missing data indicator. The primary and secondary outcomes will be tested at  $p = 0.05$  (2-sided) significance level. To address multiple testing, we will use the Benjamini-Hochberg method of controlling the false discovery rate [58]. We will conduct sensitivity analyses using an appropriate missing data method, such as pattern mixture models. Implementation process outcomes, including changes in provider attitudes will be evaluated using similar methods (repeated measures likelihood-based mixed models with random intercepts) to account for the intra-site clustering and within-subject variability by including a random intercept for each subject in the model. The outcomes will be compared between providers involved in OAT provision and those that



**Fig. 1.** Geographical Distribution of Study Sites for the Project IMPACT in Ukraine.

Legend: Two primary care centers and one specialty treatment center are participating within each city. The study originally was rolled out in twelve cities: Twelve cities, Dnipro, Zhytomyr, Kryvyi Rih, Mykolaiv, Cherkasy, Kropyvnytskyi, Kramatorsk, Kyiv, Mariupol, Rivne, Sloviansk, and Lviv. Following the Russian invasion in 2022, Sloviansk, Kramatorsk, and Mariupol had to halt operation. Sloviansk and Kramatorsk resumed close-to-normal operation eventually. In October 2022, Odesa site was added.

are not. R statistical software will be used for all analyses.

2.7. Implementation strategies and tools

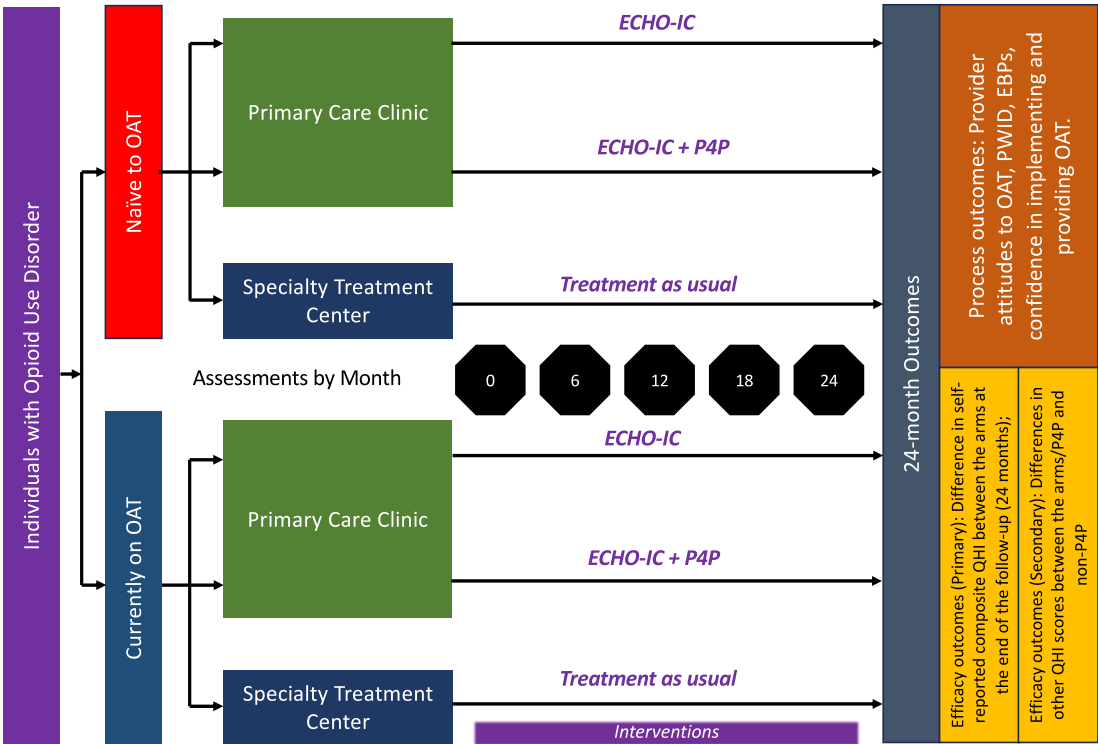
2.7.1. Project ECHO (extension for community healthcare outcomes®) modified for integrated care (ECHO-IC)

To facilitate OAT integration into PCC settings and improve provider confidence in managing OUD and related conditions like HIV and tuberculosis, providers in all PCC sites participated in a 3-day in-person training before engaging in weekly tele-education sessions of modified Extension for Community Healthcare Outcomes® for Integrated Care (ECHO-IC). ECHO-IC trainings and sessions were open for all providers from participating PCC. Providers were given a recommendation to attend ECHO-IC trainings and sessions, but were not required to do so. ECHO-IC sessions were conducted continuously and included brief didactic lectures followed by case discussions and quality improvement. ECHO, based on the educational theories of social learning and behavior change facilitated through collaborative learning with specialists, is a low-cost, high-impact facilitation strategy that creates virtual networks across considerable geographic distances and provides continuous support for PCC by experts [59,60]. ECHO-IC sessions rotated between clinical topics (OAT, HIV, tuberculosis) along with others requested by PCC participants (e.g., legislative updates, COVID-19, hepatitis, etc.) and were conducted by local and international experts in their fields. Each session started with a brief didactic session from an expert followed by a series of cases presented by PCC providers. An additional monthly session included topics and examples of quality improvement (QI) coaching to support practice transformation and help providers and organizations harness the knowledge and creativity of front-line teams in order to make lasting improvements in their care delivery systems and core processes and achieve desired outcomes [61]. Integrating QI activities within a collaborative team model is supported by a meta-analysis that QI is most effective when combined with clinical disease management, e.g., ECHO-IC [62]. Therefore, QI coaches helped providers set goals,

**Table 2**  
Patient Quality Health Indicators and Recommended Frequency of Assessment based on the Delphi Method.

|                         | QHI                         | Indication        | Recommended Frequency |
|-------------------------|-----------------------------|-------------------|-----------------------|
| Primary Care Services   | Physical examination        | Everyone          | Every year            |
|                         | Complete blood count        | Everyone          | Every year            |
|                         | Urine analysis              | Everyone          | Every year            |
|                         | Electrocardiogram           | Age ≥ 50          | Every year            |
|                         |                             | Age ≥ 50 & female | Every year            |
|                         | Mammogram                   | Female            | Every 3 years         |
|                         | Cervical cancer screening   | Age ≥ 50 & male   | Every year            |
|                         | Prostate cancer screening   | Everyone          | Every year            |
|                         | Hepatitis B virus screening | HCV negative      | Every year            |
|                         | Hepatitis C virus screening | HIV negative      | Every year            |
|                         | HIV screening               | Living with HIV   | Every 6 months        |
|                         | CD4 or viral load           | Living with HIV   | Continuous            |
| Specialty Care Services | Receipt of ART              | Everyone          | Every year            |
|                         | TB screening                | Everyone          | Continuous            |
|                         | Receipt of TB treatment     | Living with TB    | Continuous            |
|                         | Receipt of take-home OAT    | Everyone          | Continuous            |
|                         | Adequate OAT dose*          | Everyone          | Continuous            |
|                         | Retention on OAT            | Everyone          | Continuous            |

Adequate OAT dose was considered >84 mg for methadone and > 15 mg for buprenorphine based on the study by Farnum et al., 2021.  
Abbreviations: QHI quality health indicators; OAT Opioid agonist therapies; TB Tuberculosis.



**Fig. 2.** Project IMPACT Study Design.

Abbreviations: OAT opioid agonist therapies; P4P pay for performance; ECHO-IC Extension for Community Healthcare Outcomes® for Integrated Care; QHI quality health indicators; HIV human immunodeficiency virus; PWID people who inject drugs; EBPs evidence-based practices.

establish measures, design improvement tests of change, and study results to build sustainable capacity in clinics to implement continuous quality management programs and successfully guide the integration of OAT in PCC settings.

### 2.7.2. Pay-for-performance

Pay-for-performance (P4P) is an implementation strategy that financially incentivizes healthcare providers for adhering to certain pre-set guidelines, providing optimal care, and improving health outcomes in their patients [63]. P4P has been used as a cost-effective implementation strategy in substance use disorder treatment settings [64]. In Ukraine, physician salaries were low when the study was designed, and nursing staff earned substantially less [37,65]. Consequently, P4P payments were offered to OAT providers in one of the two PCC in each participating city as an additional implementation strategy. The pre-set P4P indicators for providers included retaining participants on OAT and achieving each of the QHI items, which could either be achieved directly by the PCC or through successful referrals to and patient engagement with other off-site providers to achieve the QHI. Incremental amounts were pre-defined for each indicator, reflecting the relative priority of the services from Delphi experts. P4P incentives were paid monthly, following the data collection and assessment. The maximum monthly P4P incentives per patient successfully achieving all QHI items and being retained in OAT for 12 months was 100 UAH (about \$3.60) for doctors and 60 UAH (~\$2.16) for nurses, which added up to the monthly maximum of 4000 UAH (~\$111 USD) for doctors and 2400 UAH (~\$67 USD) for nurses for the target number of 40 patients (2018 exchange rate was used for these calculations). An important factor that may have influenced the effectiveness of the P4P implementation strategy in this study is the fundamental changes in the national healthcare funding system during the study period. These changes included the introduction of a capitated payment system in primary care settings and special funding packages for treating specialty conditions like HIV and OUD, leading to increased baseline physician remuneration.

### 2.8. Institutional review and ethical considerations

This research is approved by the institutional review boards (IRB) at Yale University and the Ukrainian Institute on Public Health Policy. All individuals participating in the study provide written informed consent approved by the IRB. Participants were paid 250 UAH (~\$9 USD) for each of the five surveys completed. The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with the identifier NCT04927091.

### 2.9. Adaptation during the COVID-19 pandemic

Ukraine's Ministry of Health issued emergency interim guidance on March 16, 2020 in the response to the COVID-19 pandemic, supported continued treatment and encouraged providers to provide take-home dosing for up to 10 days to mitigate community transmission and reduce patient stress [66]. Even though OAT enrollment dropped initially throughout the country as providers responded to the early pandemic and increased patient stress levels [66], it increased steadily thereafter [67,68]. Throughout this period, all research and clinical staff strictly adhered to personal protective measures, such as wearing face masks, using hand sanitizers, and practicing physical distancing. The research team adapted to the situation by conducting telephone interviews when possible, ensuring that research activities continued without significant interruptions.

### 2.10. Adaptation during the war

The full-scale war waged by Russia in Ukraine created an unprecedented and devastating impact on physical and mental well-being of all people in Ukraine. In addition to physical insecurity (not only in

locations of active combat, but all across Ukraine), it has had a detrimental effect on all levels of healthcare [69]. The Ministry of Health, regional health departments, non-governmental organizations and health professionals at all levels have demonstrated a tremendous commitment to overcoming these challenges and sustaining key services for Ukrainians, including services for OAT patients [70,71]. Expert NIATx coaching throughout the country supported provider teams to effectively implement extended take-home dosing [72], accept new patients from private OAT clinics [73] and internally displaced persons from conflict regions [74].

By February 2022, the three participating clinics in Kramatorsk, Sloviansk, and Mariupol in the Donbas conflict area temporarily halted data collection. By June 2022, most staff and patients returned to Kramatorsk and Sloviansk sites that resumed close-to-normal operation, however all sites in Mariupol ceased to operate when Russia captured the city in June 2022 and banned all OAT.

Data collection was delayed but not fully impeded during the early invasion, with fewer than expected interviews initially, but the follow-up rate returned to expected levels by the end of the year. To maximize follow-up, the study staff maintained contact with the participants, providing assistance to find OAT services for internally displaced persons and conducting interviews even if participants were displaced to a different city.

## 3. Preliminary results

The baseline demographic and clinical characteristics of the study participants are presented in the Table 3. By December 31, 2023, 1458 participants were enrolled in STC ( $N = 509$ ) and PCC ( $N = 950$ ) arms. The clinical and demographic characteristics of the sample are similar across the arms with participants being in their late 30's (mean = 98 years), mostly male (83 %), unemployed (53 %), having above secondary education (61 %), cohabitating with either their families, friends, or partners (64 %), reporting HCV (57 %) and HIV (42 %) co-infection, and having income below the poverty level (34 %). A total of 17 % reported ever being diagnosed with tuberculosis. Individual sites differed in terms of recruitment, ranging from 11 to 65 participants receiving OAT.

Among the total sample of 1459 participants, 1333 (91 %) completed 6-month follow-up interviews, 1240 completed 12-month interviews, and 1163 (80 %) and 1075 (74 %) completed 18- and 24-month interviews, respectively (Fig. 3). The retention rates were similar across the study arms [92 % vs 91 % at 6 months, 86 % vs 84 % at 12 months, 82 % vs 79 % at 18 months, and 74 % vs 73 % at 24 months for STC and PCC, respectively].

## 4. Discussion

Despite recommendations by international agencies to integrate care for PWID [19], there have been few empirical implementation studies that rigorously evaluate the benefits of integrated care on health outcomes in PWID. Even though there have been efforts to integrate HIV and mental health services within STC [75], this type-2 hybrid implementation trial is the first to examine the comprehensive health benefits of integrating OAT into primary care clinics in LMICs. The evidence generated through IMPACT will provide a heuristic for integrated care not only for Ukraine, a country that is grappling with the growing HIV epidemic during the ongoing war, but for the broader EECA region. The healthcare systems of many countries within the EECA region are facing lasting challenges due to the legacy of the Soviet Semashko system, where specialty care was provided in secondary and tertiary centers, often resulting in limited accessibility for the broader population [76]. As countries in the region transition to new healthcare models, PCC providers begin to tackle managing specialty conditions. One of the key tools to provide confidence in PCC providers is the use of ECHO-IC that provides ongoing clinical support for providers. We used P4P in a LMIC

**Table 3**

Demographic and clinical characteristics of study participants (N = 1459).

|                                                      | STC<br>N = 509 | PCC<br>N = 950 | Total<br>N = 1459 | p-<br>valu <sup>1</sup> |
|------------------------------------------------------|----------------|----------------|-------------------|-------------------------|
| <b>Age, cont. / mean (SD)</b>                        | 39 (7.8)       | 39 (7.6)       | 39 (7.7)          | 0.922                   |
| <b>Male</b>                                          | 418 (82 %)     | 793 (84 %)     | 1211 (83 %)       | 0.560                   |
| <b>Unemployed</b>                                    | 273 (54 %)     | 503 (53 %)     | 776 (53 %)        | 0.845                   |
| <b>Income below poverty<sup>2</sup></b>              | 183 (36 %)     | 309 (33 %)     | 492 (34 %)        | 0.207                   |
| <b>Married or cohabitating</b>                       | 166 (33 %)     | 331 (35 %)     | 497 (34 %)        | 0.425                   |
| <b>Housing</b>                                       |                |                |                   |                         |
| Lives in own house/apartment                         | 153 (30 %)     | 193 (37 %)     | 483 (33 %)        | 0.289                   |
| Lives with family/partner/friends                    | 336 (67 %)     | 315 (60 %)     | 929 (64 %)        |                         |
| Other <sup>3</sup>                                   | 16 (3.2 %)     | 16 (3.1 %)     | 47 (3 %)          |                         |
| <b>Above secondary education</b>                     | 319 (63 %)     | 577 (64 %)     | 896 (61 %)        | 0.505                   |
| <b>Time on OAT</b>                                   |                |                |                   |                         |
| >3 months on OAT                                     | 288 (57 %)     | 508 (53 %)     | 796 (55 %)        | 0.280                   |
| <3 months on OAT                                     | 221 (43 %)     | 442 (47 %)     | 663 (45 %)        |                         |
| <b>HIV status, self-report</b>                       |                |                |                   |                         |
| Negative                                             | 261 (51 %)     | 497 (52 %)     | 758 (52 %)        | 0.896                   |
| Positive                                             | 215 (42 %)     | 396 (42 %)     | 611 (42 %)        |                         |
| Unknown                                              | 33 (7 %)       | 57 (6 %)       | 90 (6 %)          |                         |
| <b>HCV status, self-report</b>                       |                |                |                   |                         |
| Negative                                             | 135 (27 %)     | 238 (25 %)     | 373 (26 %)        | 0.771                   |
| Positive                                             | 284 (56 %)     | 548 (58 %)     | 832 (57 %)        |                         |
| Unknown                                              | 90 (18 %)      | 164 (17 %)     | 254 (17 %)        |                         |
| <b>Ever diagnosed with tuberculosis, self-report</b> | 83 (16 %)      | 158 (17 %)     | 241 (17 %)        | 0.925                   |
| <b>City</b>                                          |                |                |                   |                         |
| Cherkasy                                             | 37 (7 %)       | 76 (8 %)       | 113 (8 %)         | 0.991                   |
| Dnipro                                               | 39 (8 %)       | 83 (9 %)       | 122 (8 %)         |                         |
| Kramatorsk                                           | 53 (10 %)      | 103 (11 %)     | 156 (11 %)        |                         |
| Kropyvnytskyi                                        | 38 (8 %)       | 76 (8 %)       | 114 (8 %)         |                         |
| Kyiv                                                 | 65 (13 %)      | 95 (10 %)      | 160 (11 %)        |                         |
| Lviv                                                 | 11 (2 %)       | 22 (2 %)       | 33 (2 %)          |                         |
| Mariupol                                             | 30 (6 %)       | 55 (6 %)       | 85 (6 %)          |                         |
| Mykolaiv                                             | 36 (7 %)       | 69 (7 %)       | 105 (7 %)         |                         |
| Odesa                                                | 50 (10 %)      | 89 (9 %)       | 139 (10 %)        |                         |
| Rivne                                                | 37 (7 %)       | 65 (7 %)       | 102 (7 %)         |                         |
| Sloviansk                                            | 41 (8 %)       | 77 (8 %)       | 118 (8 %)         |                         |
| Zhytomyr                                             | 30 (6 %)       | 59 (6 %)       | 89 (6 %)          |                         |
|                                                      | 42 (8 %)       | 81 (9 %)       | 123 (8 %)         |                         |

Abbreviations: STC Specialty treatment center; PCC Primary care center; P4P Pay for performance; OAT Opioid agonist therapies; HIV Human immunodeficiency virus; HCV Hepatitis C virus, IQR Interquartile range.

<sup>1</sup> Pearson's Chi-squared test for categorical variables, Student's *t*-test for continuous variables;

<sup>2</sup> <1630 UAH (~\$45)/month;

<sup>3</sup> category other includes dormitory, hotel, temporary housing, and homeless;

as a context-specific implementation tool. P4P efforts, however, may not prove as beneficial in the final analyses as Ukraine implemented a National Health System as the trial was underway, providing increased salaries and support for PCC staff.

This study differs markedly from the only other prospective study of integrated care for PWID in a LMIC where PWID were surveyed in community rather than clinical settings, no implementation outcomes were reported and the primary outcome was uptake of HIV testing, not

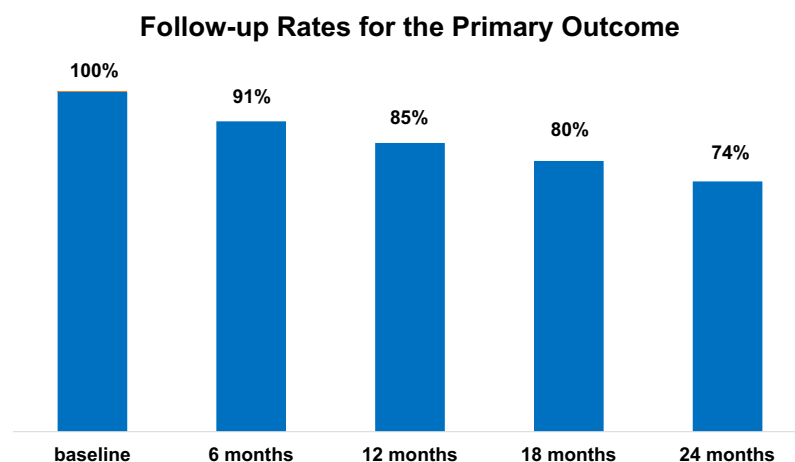
direct delivery of care outcomes [77]. The type-2 design in IMPACT ensures patient-level effectiveness is measured while implementation outcomes are included to guide opportunities for improvement in the processes that will be required for optimized implementation.

This study was continued despite observed disruptions that threatened to limit the study activities and undermine the OAT scale-up progress in Ukraine [66]. The reality, however, was that all stakeholders, including the Ministry of Health, healthcare workers, nongovernmental organizations, and other organizations working in the country addressed these challenges in a way that not only ensured OAT continuation, but influenced a sustained scale-up of OAT with the enrollment for new patients [78,79]. The rapid response from the Ministry of Health in facilitating the take-home OAT dispersion strategy, along with the efforts from the clinical staff and other stakeholders to increase scale-up in regions where internally displaced PWID had to move, was crucial for the continuation of OAT dispersion both within our trial and throughout the country [67,68,70–72]. Subsequently, the experience from IMPACT can be used to address some of the challenges introduced by considerable disruptions in other settings where conflict and war are threatening to undermine healthcare delivery.

The self-reported prevalence of comorbidities among PWID was high, as evidenced by the study population characteristics. Prevalence of HIV was reported to be 42 %, while more than half of the sample said they had been diagnosed with HCV sometime in the past. Almost a fifth of the sample said that they had ever been diagnosed with tuberculosis. These numbers are alarmingly high compared to the general population in Ukraine, where HIV is estimated to be between 0.9 % and 1.0 %, and HCV up to 3.1 % [80,81], underscoring the need for comprehensive screening and management for these and other comorbidities for PWID. Primary care settings provide an optimal environment for accessible screening, management, and in some cases, referral to relevant services to ensure that the complex health needs of this population are met. The interim analysis examining patient-level outcomes for the first 12 months confirmed that patients receiving OAT in the integrated settings achieved higher QHI scores, i.e., were screened and managed clinically for more health conditions, including for both primary and specialty conditions [56]. Determining whether outcomes are sustained over a longer period, however, will require a final analysis of the data gathered over 24 months of follow-up. Study findings will also generate evidence on how novel tele-education strategies like ECHO-IC can support non-specialists and facilitate better screening and management processes.

The study should provide insights into how integrated care impacts both healthcare providers and patients. For example, does implementation of integrated care impact how providers view patients, especially PWID who experience extraordinary stigma from healthcare providers generally? Or, how do patients perceive stigma as they either transfer from STC or start OAT anew in such settings relative to STC? Strong evidence exists that increasing intergroup contact decreases stigma and discrimination, and improves attitudes not only among those who provide direct medical care to the marginalized group, but among the wider population employed at clinics where care may be provided [82]. When assessed, such findings may guide further implementation, including behavioral design intervention strategies that re-engineer how healthcare is delivered using techniques like framing, nudging, and choice architecture to guide healthcare delivery to make values-based choices to change clinical behaviors [83]. In the case of integrating care for PWID, re-engineering where patients receive care and how it is delivered has great potential to influence health outcomes and potentially reduce stigma. Consequently, the IMPACT trial may influence health disparities experienced by the PWID on multiple levels.

One of the key elements that may be challenging to test is the sustainability of integrated care. Integrated OAT has been shown to be cost-effective within the United States [84], but further studies are needed to test the cost-effectiveness of the intervention in Ukraine and similar settings. IMPACT showed that the scale-up of the OAT services within primary care in Ukraine is feasible [15,85], and the 12-month interim



**Fig. 3.** Retention rates for the primary outcome of the IMPACT study at each follow-up time-point.

Legend: At baseline a total of 1459 participants were enrolled. Retention was 1333 (91 %) for 6 months, 1240 (85 %) for 12 months, 1163 (80 %) for 18 months, and 1075 (74 %) for 24 months.

analysis confirmed the comprehensive health benefits for PWID receiving OAT within primary care settings [56]. Sustainability of integrated services can be achieved through the collaborative effort of the stakeholders, including primary care providers and the Ministry of Health, to ensure that the provision of OAT in primary care settings is not only legal, but also convenient and financially rewarding for clinical providers as well as the health system. Since 2020, there are additional funding packages available to primary care providers for the provision of specialty services like those for HIV and OUD. A challenge for the OAT implementation in primary care settings, however, is the lack of awareness of primary care providers of the availability of these funding packages (unpublished material). Efforts are needed to increase awareness of primary care providers and assist them in applying for these packages. Finally, the ongoing war in Ukraine may influence the direction of integration, with little flexibility to shift the paradigm in the setting of multiple competing priorities. In this light, ensuring access to potentially life-saving care for the most vulnerable populations remains an important challenge.

We would like to note limitations of the study. First, there were significant challenges for participant recruitment and follow-up during the COVID-19 pandemic and the 2022 Russian invasion. Our team, however, responded in a timely manner and ensured all the study activities were carried out as planned by adapting in various ways and ensuring participant safety. Second, the level of significance of QHI scores may be challenging to ascertain as all QHI components are given equal weight in the final score calculation. Certain QHI components may have relatively varying degrees of importance for an individual's health, and further studies are warranted to ascertain how to meaningfully weigh QHI components for individual patients. QHI scores, however, document patients' engagement in the healthcare system and access to evidence-based services which are expected to translate into downstream benefits. Third, as the trial follow-up period is 24 months, there was a considerable risk of loss to follow-up. We tried to mitigate this limitation by inflating the sample size. In the analysis phase, we are planning to carry out the sensitivity analysis to test for potential attrition bias. Fourth, the self-reported QHI outcomes are suspect to recall and social desirability bias. However, since both the control and intervention arms are equally susceptible to these biases, we expect that the main outcome would not be significantly affected. Finally, providers at PCC had a better opportunity to verify and document primary care services and screenings, as some of these services were performed on-site. In contrast, providers at STC had less opportunity to do so, as their clinics did not offer primary care services. Thus, EMR data may be prone to bias due to underreporting or incomplete documentation of services

provided at STC. To address this limitation, we are planning to use EMR data for the secondary outcome as an additional data source to complement self-reported QHI data.

Despite these limitations, we believe that the large sample size, multiple data sources, long observational period, and participation of 39 diverse clinics across Ukraine contribute to the robustness of our study. Together, these strengths lend sufficient validity and reliability to the conclusions to be drawn after the analysis phase and provide valuable contributions to the understanding and improvement of healthcare systems in Ukraine and similar settings.

## 5. Conclusion

IMPACT aims to provide a roadmap for the successful implementation of OAT within primary care settings, particularly in low-resource, high-burden settings like the EECA region. The findings from the study will contribute to shaping effective healthcare strategies to address the comprehensive needs of PWID while also providing necessary implementation strategies to overcome contextual challenges and disruptions.

## Funding

The trial was funded by the National Institutes on Drug Abuse (R01 DA043125).

The study is registered at [www.clinicaltrials.gov](https://www.clinicaltrials.gov) with the identifier NCT04927091.

## CRediT authorship contribution statement

**Eteri Machavariani:** Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. **Kostyantyn Dumchev:** Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Iryna Pykalo:** Project administration, Investigation, Data curation, Writing – review & editing. **Myroslava Filippovych:** Resources, Project administration, Investigation, Data curation, Writing – review & editing. **Roman Ivasiy:** Visualization, Validation, Resources, Investigation, Formal analysis, Writing – review & editing. **Denise Esserman:** Supervision, Investigation, Funding acquisition, Conceptualization, Writing – review & editing. **Lynn M. Madden:** Project administration, Investigation, Conceptualization, Writing – review & editing. **Daniel J. Bromberg:** Methodology,

Data curation, Conceptualization, Writing – review & editing. **Marwan Haddad:** Methodology, Conceptualization, Writing – review & editing. **Olga Morozova:** Methodology, Conceptualization, Writing – review & editing. **Bachar Ahmad:** Visualization, Conceptualization, Writing – review & editing. **David Oliveros Gómez:** Resources, Investigation, Writing – review & editing. **Scott O. Farnum:** Conceptualization, Writing – review & editing. **Sergii Dvoriak:** Supervision, Resources, Project administration, Methodology, Conceptualization, Writing – review & editing. **Frederick L. Altice:** Supervision, Methodology, Investigation, Funding acquisition, Conceptualization, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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