

METHODOLOGY OF

Study of the effectiveness of the introduction of a long-acting injectable formulation of buprenorphine (Buvidal®) in Ukraine



1.0 Study purpose, objectives, methodology and components

1.1 Study purpose

To study the effectiveness of opioid substitution treatment (OST) using a long-acting injectable formulation of buprenorphine (Buvidal®) in Ukraine as an alternative treatment option.

1.2 Study objectives

1. To assess patients' satisfaction with the medication;
2. To identify the prevalence of the medication-related adverse reactions in patients.
3. To assess the advantages and disadvantages of the medication.
4. To determine how the medication affects the quality of life of the patients, retention in treatment, risk behavior, adherence to the diagnostics and treatment of concomitant diseases, mental comorbidity, use of other psychoactive substances including alcohol, social functioning.

1.3 Study methodology and components

The purpose and objectives of the study will be achieved through two components: quantitative and qualitative, with the involvement of two target groups into a survey - healthcare professionals, instructed on the introduction of the medication, and OST patients, transferred to Buvidal® (study cohort).

Qualitative component - focus group interviews among healthcare professionals who will be introducing Buvidal® on the basis of their health care facilities (HCFs) (OST site).

Quantitative component - survey of patients switching to or starting Buvidal® (new patients) - study cohort. A link to the questionnaire will be shared with the patients through the National Coordinator. Data will be collected through self-completion of a questionnaire by the patients in the presence of a healthcare professional.

Data collection will be carried out in three stages:

- **I stage** - at the beginning of the treatment (qualitative and quantitative components),
- **II stage** - after 6 months of taking Buvidal® (approximately - the end of Q2-beginning of Q3 of 2023) - quantitative component,
- **III stage** - after 12 months of taking Buvidal® (end of Q4 of 2023) - qualitative and quantitative components.

The same patients enrolled into the study cohort at the 1st stage and the same healthcare professionals from the OST sites will be involved at **all stages of data collection**.

1.4 Study sites and sampling

The Table below contains the list of regions involved into the study (total number - 10), the list of HCFs in which the medication will be introduced in the treatment of patients and on the basis of which data collection will be carried out (total number - 11 sites), the number of patients to be enrolled into the study cohort and its recommended distribution, in particular, per each site, as well as the number of healthcare professionals with whom focus group interviews are planned to be carried out.

The total sample for the quantitative component is 500 patients, and for the qualitative component - 22 healthcare professionals, 2 from each study site, introducing Buvidal®.

The sample for the quantitative component of the study was distributed proportionally to the number of medication units provided by the international partners to Ukraine and according to a previously

conducted survey at each site regarding the potential number of patients willing to switch to a new treatment option.

The qualitative component of the study will involve all healthcare professionals introducing a new medication.

Table 1. Study sites and target sample size

Study region (oblast)	Study HCF	HCF code	No. of patients for survey			No. of healthcare professionals for 2 focus groups	
			I stage	II stage	III stage	I stage	II stage
Vinnyska	Municipal non-profit enterprise "Addiction Treatment Center "Psychotherapy" of Vinnytsia Regional Council"	01	20	20	20	2	2
Volynska	Municipal enterprise "Volyn Addiction Treatment Medical Center"	02	20	20	20	2	2
Dnipropetrovska	Municipal enterprise "Kryvyi Rih Multidisciplinary Hospital for Psychiatric Care of Dnipropetrovsk Regional Council"	03	110	110	110	2	2
	Municipal non-profit enterprise of Kamianske City Council "City Hospital No.1"	04	45	45	45	2	2
Zakarpatska	Municipal non-profit enterprise "Zakarpattia Regional Medical Center for Mental Health and Addiction Medicine" of Zakarpattia Regional Council	05	10	10	10	2	2
Zaporizka	Municipal non-profit enterprise "Regional Clinical Facility of Psychiatric Care" of Zaporizhzhia Regional Council	06	40	40	40	2	2
Lvivska	Municipal non-profit enterprise of Lviv Regional Council "Lviv Regional Medical Center for Addiction Prevention and Therapy"	07	90	90	90	2	2
Poltavska	Municipal enterprise "Poltava Regional Center for Addiction Therapy of Poltava Regional Council"	08	70	70	70	2	2
Ivano-Frankivska	Municipal non-profit enterprise "Prykarpattia Narcological Center of Ivano-Frankivsk Regional Council"	09	30	30	30	2	2
Rivnenska	Municipal enterprise "Rivne Regional Center for Population Mental Health" of Rivne Regional Council	10	15	15	15	2	2
Sumska	Municipal non-profit enterprise of Sumy Regional Council "Regional Clinical Medical Center of Socially Dangerous Diseases"	11	50	50	50	2	2
Total			500	500	500	22	22

** In case the rate of enrollment into the study cohort in a HCF does not correspond to the indicated distribution of the sample population, the regional coordinator responsible for the introduction of the medication in this HCF must inform thereon the principal investigator from the PHC in order to consider the redistribution of the sample population and timely transfer of the supply to another HCF or region.*

Before the introduction of a long-acting injectable formulation of buprenorphine, an instructional seminar will be held for healthcare professionals from the OST sites on the peculiarities of the medication use.

The following informational and methodological materials will be provided to healthcare professionals at the seminar:

- Booklet for patients
- Booklet for healthcare professionals
- General information about Buvidal® and reasons for its authorization in the EU
- Medication overview
- Guidance on adverse reactions
- Translation of pages from the manufacturer's website
- Summary of Buvidal® (buprenorphine) risk management plan
- Articles from the international journals on Buvidal® effectiveness evaluation.

Also, healthcare professionals will be familiarized with the study methodology, the principles of interviewer-assisted questionnaire administration (assisted questionnaire) during the self-completion of questionnaires by the patients and with the logs and reporting documentation to be completed during the study.

1.5 Criteria for inclusion into the study cohort

The target group for the medication and, accordingly, inclusion into the study, consists of the patients who have an established diagnosis according to ICD-10 F11.2 - mental and behavioral disorders due to the use of opioids with the prescribed OST.

The study may include both, new patients who have just been prescribed OST and patients who are already receiving treatment (buprenorphine, methadone).

Key inclusion criteria:

1. Patients **not planning to complete** OST within the next 12 months.
2. **Stable patients**, being in the OST program for a long time, demonstrating high adherence to treatment, without violations of the rules of participation in the program. Predominantly patients who are employed or studying or caring for children in a stable social environment.
3. **Unstable patients being on treatment for at least 6 (preferably 12) months**, but demonstrating one or more of the following signs:
 - miss doses
 - in unstable psycho-emotional state
 - use other psychoactive substances
 - consume alcohol above the average
 - visit HCF in a state of alcohol or drug intoxication
4. Patients **with a number of adverse reactions to OST they are receiving**, the level of which, subjectively, significantly affects the quality of life, leads to low adherence to treatment, which is manifested in missing doses, taking higher or lower doses, additional use of psychoactive substances and/or alcohol.
5. **New patients** - persons with the last episode of OST up to 12 months (confirmed), including patients who are at the stage of dosage selection (induction). The specified group is enrolled only if there are not enough patients enrolled from other groups.
6. Patient's informed consent to participate in the study and all its components in order to receive treatment.

Exclusion criteria

1. Patients under 18 years of age.
2. Unmotivated patients who do not plan to regularly receive treatment and follow the doctor's instructions (determined by the doctor based on his/her subjective assessment, knowledge about the patient and his/her behavior during the previous treatment episode).

3. Patients who do not agree to participate in the survey.

3.6. Enrollment of study cohort

A simple continuous sampling method is used to enroll a representative cohort of OST patients. All eligible patients will be invited to participate in the study until the required number of participants has been enrolled at all sites (Table 1).

All patients willing to switch to a long-acting injectable formulation of buprenorphine are evaluated by a **healthcare professional** at the OST site for their eligibility (intention to continue treatment in the next 12 months, stable patients, unstable patients who have been on treatment for 6 or 12 months, patients with adverse reactions to OST, willingness to participate in the study and all its stages/components, cognitive capacity to sign an informed consent to participate in the study).

After checking the eligibility, the healthcare professional, according to the inclusion criteria described above, assigns a patient to a certain group:

1. Stable group
2. Unstable group
3. Adverse reactions group
4. New group

If patients are eligible for assignment to two groups, for example, unstable patients and those with adverse reactions, the healthcare professional assigns such patients to **both groups** and specifies which.

Obtaining informed consent from the patient is an important step during inclusion in a study cohort. The healthcare professional informs the patient of the purpose and objectives of the study, explains the benefits of a long-acting injectable formulation of buprenorphine to the patient, and informs the patient of the following:

1. The patient will receive the first dose **only after** completing the questionnaire.
2. Before receiving each subsequent dose (approximately every 3-4 weeks), the healthcare professional will evaluate the adverse reactions, manifestations of drug ineffectiveness in the patient.
3. After 6 months from the moment of inclusion in the study cohort, the patient must undergo the II stage of the survey, which will be carried out by a social worker by means of an assisted questionnaire in order to carry out the second assessment of data as of the middle of the period of introduction of the medication in Ukraine.
4. After 12 months from the moment of inclusion in the study cohort, the patient must undergo the III stage of the survey, which will be carried out by a social worker by means of an assisted questionnaire in order to carry out the final assessment of data as of the end of the period of introduction of the medication in Ukraine.

After obtaining the patient's verbal and written consent (Annex 1) to participate in the study, the patient is enrolled into the study cohort, and the healthcare professional enters it into the Log for inclusion and registration of respondents in the study cohort (Annex 3). After that, s/he fills out the Patient's contact information form (Annex 6) and shares the link with the study participant to self-complete the questionnaire.

The prescription of the medication and subsequent administration of it to the participant of the study cohort will take place **only after s/he completes the questionnaire**.

Immediately before prescribing the medication, the patient receives the following list of informational materials from the healthcare professional:

- Booklet for patients
- General information about Buvidal® and reasons for its authorization in the EU
- Medication overview
- Guidance on adverse reactions
- Translation of pages from the manufacturer's website

2.0 Data collection and tools

4.1. Data collection, quantitative component

After enrolling the patient in the study cohort the healthcare professional refers them to a social worker. The social worker should accommodate the patient in their office or near the office, where they will be comfortable with the assisted questionnaire, which involves the patient's self-completion of the questionnaire, but s/he can ask for the help of a social worker to read the questions, answers and record the respondent's answer in the questionnaire, if necessary.

The patient will receive the dose only in case and after completing the questionnaire.

During the 1st stage of data collection, patients will undergo a questionnaire in order to assess the effectiveness of treatment indicators during the introduction of the medication. The following blocks will be included in the questionnaire to collect data on: demographic characteristics, experience of addiction treatment, assessment of satisfaction with treatment, medical history, presence of adverse reactions, social status, characteristics of alcohol use, determination of the level of depression, anxiety disorder and other mental disorders, assessment of quality of life, regarding risk behavior, adverse reactions, evaluations of the ineffectiveness of the medication, expectations from taking the medication, evaluation of advantages and disadvantages.

The healthcare professional must give the social worker the SYREX code, or the patient's C++ code, which consists of an alphanumeric code, for example (OΓOCOBA180991ж) and is written on the patient's card. IMPORTANT! the social worker should transcribe the code from the patient's record or get it from the healthcare professional, but in no case should create or write it down from the patient's words, as this will likely to lead to an error in the patient's code, making it difficult to track patient data.

Each participant must take part in the II (after 6 months from the initiation of Buvidal®) and III (after 12 months from the initiation of Buvidal®) survey stages. Questionnaires for the II and III stages will contain blocks of questions that will help to reveal the assessment of the experience of taking the medication by the patients, and will not contain blocks about socio-demographic characteristics and treatment experience before switching to a new treatment.

Since the completion of the survey is a mandatory condition for receiving the medication, the study participants will undergo an assisted questionnaire, similar to the procedure described in the first paragraph, during the II and III stages of data collection. To this end, the healthcare professional must contact with the study participants in advance to remind them to take part in the next stage of the survey.

During each stage of the survey, the medical staff on the OST site fills out the Log for inclusion and registration of respondents in the study cohort (Annexes 3-5) (for each stage of the survey a separate log is filled out), where information about patients is entered.

The entire questionnaire is common for the entire sample of the respondents (with the possibility of skipping individual blocks of questions in case of their irrelevance for the patient).

The electronic version of the questionnaire will be programmed on the REDCap platform. Data collection will be carried out by means of the assisted questionnaire of the respondents using a smartphone, tablet or laptop with online access to the web version of the REDCap platform. Data collection will be confidential, all social workers and healthcare professionals will sign a non-disclosure agreement to keep data obtained during the study confidential.

In case if during the I, II or III stage of the survey questions are skipped by the respondent or the questionnaire is incomplete, the data verification manager of the PHC transfers the information about this study participant to a healthcare professional and a social worker from the relevant region, who in turn contact with this respondent and ask him/her to provide information on the skipped questions or blocks of questions.

In case if the respondent withdraws from the study cohort, the healthcare professional or social worker still contacts the given patient and, depending on the stage of the study from which the patient withdrew, offers him/her to participate in the II or III stage of the survey. If the patient is available for re-survey, the healthcare professional makes a corresponding entry into the Log (Annexes 3-5) with the date of the beginning and the end of the survey window, noting out this patient's withdrawing from the previous stage.

4.2. Criteria for withdrawal from the study cohort

Patients from the study cohort will have to visit the HCF once a month, according to the date appointed by the doctor, to receive a new dose of Buvidal®. In case if the patient does not appear at the HCF within 10 days from the date appointed by the doctor, in case if it is impossible to contact with him/her during these 10 days, and due to a number of other reasons for which patients may end participation in the study, described in the list below, the patient's status changes to "Withdrawn".

The regional coordinator must inform the principal investigator from the PHC about those patients who withdrew from the study cohort and enter the relevant information into the Log for inclusion and registration of respondents in the study cohort (Annexes 3-5), indicating the date and reason for withdrawal of the patient, according to a list below:

1. Patient desires to withdraw
2. Patient changes the place of residence
3. Patient withdraws due to adverse reactions
4. Patients decides to complete the OST
5. Patient desires to return to the tablet formulation
6. Lack of contact with the patient for 10 days
7. Patient's imprisonment
8. Patient's death.

The study team of the PHC will separately analyze the number of patients and the reasons for their withdrawal from the OST program using Buvidal®.

4.3. Data collection, qualitative component

In order to obtain more information about the effectiveness and disadvantages of the medication at the OST sites, it is planned to conduct focus group interviews with healthcare professionals at the beginning and at the end of the study.

According to the Table 1, the total number of healthcare professionals involved in the introduction of the medication at all OST sites is 22 (2 per each study site). For the effective interaction of the participants during the focus group interview and in order to obtain as complete information as possible, healthcare professionals will be divided into 2 groups, 11 people in each. Thus, 2 focus

groups interviews will be conducted at the 1st and 2nd stage of the survey.

Prior to the initiation of the focus group interview, oral or written informed consent to participate in the study will be obtained from healthcare professionals (refer to Annex 8).

4.4. Data collection principles and tools

Focus group interviews will be moderated by a public health professional who is a member of the study team. Questions will be asked according to the developed guide. Upon the verbal consent of the participants (Annex ____), the interview will be recorded on an audio device. The duration of the focus group interview will be approximately 90 minutes. After the interview, the recording will be transcribed by members of the study team and kept as a transcript. The audio recording will be destroyed after transcribing.

The survey among the participants of the study group will be conducted by means of assisted questionnaires with the submission of questionnaires on the REDCap platform for the 1st, 2nd and 3rd stages of data collection.

The focus group interview guide and questionnaires will be reviewed in advance by the Ethics Committee, data collection will not be initiated until the Committee's approval.

4.5. Tools for monitoring and evaluation of the medication introduction

Healthcare professionals at the study sites will necessarily fill out the reporting documentation regarding the introduction of the new drug, in particular, the data will be entered into:

- OST module of MIS SSD,
- card for reporting the adverse reactions (more detailed in Annex 2) at the link: <https://aisf.dec.gov.ua>
- monthly report on the quantitative and qualitative non-personalized characteristics of OST patients to be submitted to the PHC in accordance with subparagraph 4, paragraph 3 of the Order of the Ministry of Health of Ukraine No. 200 of 27.03.2012 "On approval of the Procedure for conducting OST for patients with opioid addiction".

The reporting that the regional study sites will submit during the introduction of the drug will be verified by a co-investigator responsible for data management.

4.6. Security measures in the context of a full-scale invasion of Ukraine

Data collection for the qualitative and quantitative components will be conducted in compliance with wartime security measures established at the central and local levels. Focus group interviews will not be conducted: in the occupied territories; during the curfew restrictions established by the local military administration; during air-raid alarms; during active hostilities on the territory of the cities involved in the study.

If an air-raid alarm is announced during the study sites operations, study participants and site personnel shall go to a shelter.

3.0 Study restrictions

Since the target group of the study is patients with opioid addiction who have a desire to switch to a new for Ukraine treatment option, the limitation may be the patients themselves, in particular, their reluctance to switch to injectable formulation. This may result in slow enrollment or failure to enroll the full size of the sample population.

In addition, one of the inclusion criteria for the study is the patient's intention to continue the treatment for the next 12 months, however, the study team and the healthcare professionals do not have tools to ensure that the participants abide this intention, so there is a risk that some participants may complete their participation before the planned time.

4.0 Analytical stage

6.1. Data processing and analysis

Based on the results of the focus group interviews, after the I, II and III stages of the survey, a report with primary data analysis will be drawn up.

According to the results of the survey of the participants of the study cohort, 3 separate arrays of quantitative data will be processed and formed (at the beginning of the introduction of the medication and at the end of the study).

Processing will include checking for missing data, logic errors, data entry errors, etc. using REDCap's automated data management mechanisms, and correcting errors and restoring missing values where possible. After verification, the completed forms of individual respondents are blocked from further amendments.

Analysis of all received data will be provided by the study team. On the basis of reports with primary analysis of data and arrays for the quantitative component, a general report with conclusions and recommendations will be drawn up, to this end an analytical plan will be developed in advance, determining in details the direction and depth of the analysis.