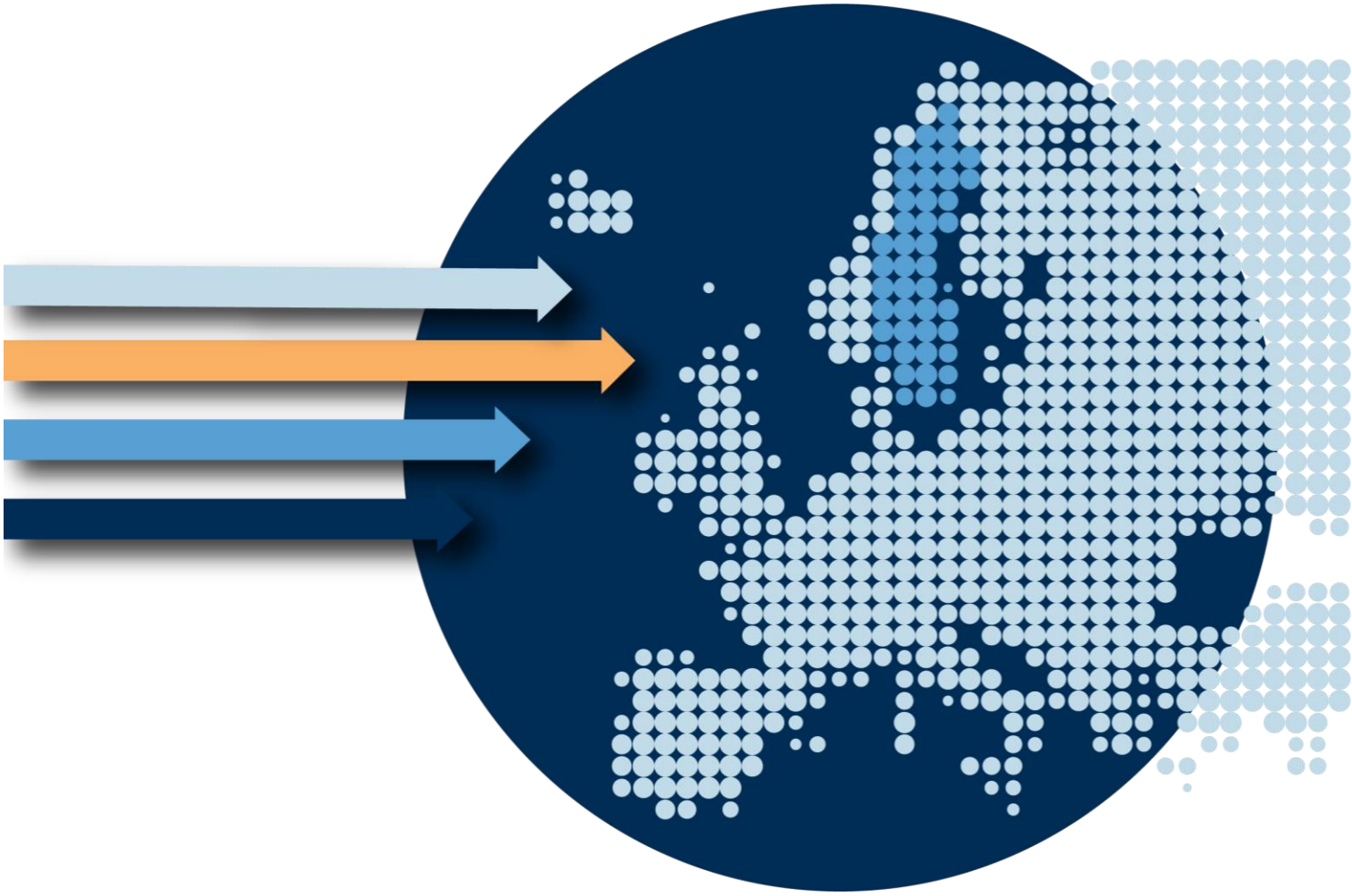
Patient pathways in the treatment of opioid drug dependency
– A register-based real world analysis using regional healthcare registers



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2020:2

PATIENT PATHWAYS IN THE TREATMENT OF OPIOID DRUG DEPENDENCY
– A REGISTER-BASED REALWORLD ANALYSIS USING REGIONAL HEALTHCARE REGISTERS

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Foreword

Medication-Assisted Treatment of Opioid Dependence, or as labelled by WHO, psychosocially assisted pharmacological treatment of opioid dependence, is a treatment that prescribes using methadone, buprenorphine, naltrexone or clonidine in combination with psychosocial support to people dependent on heroin or other opioids. The Swedish acronym for this treatment is LARO (Läkemedelsassisterad rehabilitering vid opioidberoende) The WHO considers LARO to be an important tool for reducing the health and social consequences and to improve the well-being and social functioning of people affected. LARO was first developed in the late 1960s in the US but did not become an established alternative in Sweden until the early 1980s. However, it remained controversial and the broad national introduction has been gradual with the first Swedish national regulation in 2005. Region Skåne was among the first four healthcare regions to introduce LARO in the early 90's and there is now 30 years of experience with LARO.

The main objective of this study was to analyse the current treatment pathways in terms of type of healthcare contacts and type of healthcare providers for people with opioid dependence enrolled in programmes at LARO clinics in the Skåne region. An additional objective was to describe the use of opioid dependence medicines and overall healthcare resource utilisation in other parts of the healthcare system for this group of people.

The report was sponsored by the pharmaceutical company Indivior and based on individualized data from Swedish national and regional healthcare registers. The study was approved by the Ethical Review Board in Lund (dnr 2018/617). The Swedish Institute for Health Economics was responsible for all data management and analysis. No individual level data has been shared with other parties. The responsibility for the analysis and conclusions in this report lies solely with the authors.

Lund, March 2020

Peter Lindgren
Managing Director, IHE

Executive summary

The overall objective of this study was to analyse treatment pathways for people with opioid dependence enrolled in programs at LARO clinics in the Skåne region in southern Sweden. LARO is the Swedish ackronym for Medication-Assisted Treatment of Opioid Dependence (Läkemedelsassisterad behandling vid opioidberoende). We investigated the use of healthcare resources, pharmaceutical use and contacts with social services for 2 429 persons (median age=36 years, proportion of men=70 percent) identified the Skåne Healthcare Register (SHR) with indications of new or ongoing LARO treatment in study years 2011-2017. Treatment patterns were observed and analysed for the period when LARO treatment was included in the Choice of healthcare reform in Region Skåne in 2014 and with the last observation year 2017. These analyses were conducted at the aggregate level and for three study groups defined by LARO treatment characteristics. Secondly, we studied patterns during the first year of LARO treatment for persons admitted in LARO treatment programmes at designated LARO clinics.

Five key findings from the study were:

1. Increased supply and improved access

Both the number of LARO clinics and the number of people in LARO treatment have increased over time. In 2013 there were eight LARO clinics in Skåne and in 2017 there were 18 clinics. During the same period the number of patients in LARO treatment increased from 1 289 to 1 654 (28 percent). Also, the number of visits per year per person has increased. An average increase of visits by eight percent (107 to 116) was noted from 2015 to 2017.

2. Additional healthcare use for people in LARO

Among people with LARO visits every month during their first year in treatment, more than 40 percent used also non-LARO psychiatric care indicating a presence of psychiatric comorbidity. Those with psychiatric visits outside LARO had on average 5.6 visits during the first year of LARO treatment.

3. A high proportion of people in LARO remains in treatment if stable in the first year

In this study we showed that among those who were possible to follow up until two years (288 persons out of 339 persons in stable LARO treatment) after LARO entrance, 92 percent remained in treatment after 18 months and 72 percent remained in treatment after 24 months (Figure A). An important outcome measure for LARO success is retention measured as the percentage of people who remain in treatment compared to the number who started LARO. According to research, a high degree of retention is expected to lead to reduced mortality, reduced risk of lateral abuse and a reduced relapse risk.

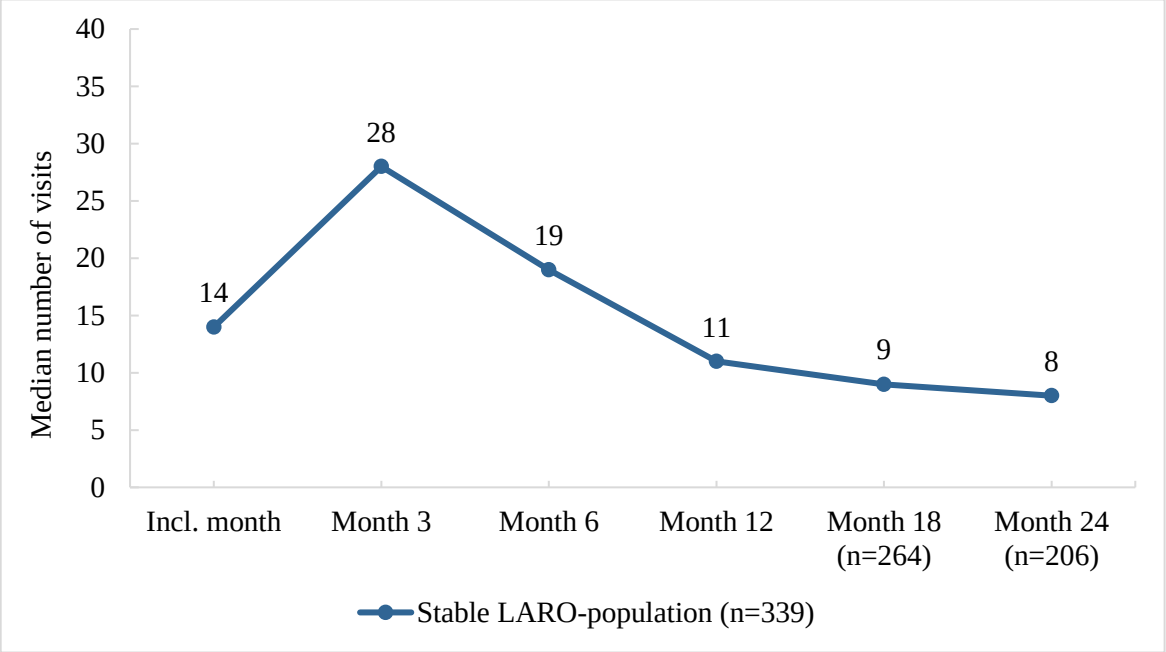

Figure A. *Median number of visits at inclusion month, months 3, 6, 12, 18 and 24 for the stable LARO population (n=339, each person with visits every month during the first year).*

4. Increasing level of central purchases of LARO treatment medications

There has been a general trend over the years towards greater proportion of study medications distributed in clinics compared to pharmacies. The results show a shift in the way the study medications (substance (ATC-code): buprenorphine mono (N07BC01), methadone (N07BC02), and buprenorphine and naloxone in combination (N07BC51)) for opioid dependence were managed (Figure B). During the period 2008 to 2011 these medications were predominately handled through prescriptions while after 2011, the persons using these medications to a higher extent received them directly from a healthcare unit. Keeping the distribution of LARO medications at the LARO clinic may interfere with the objectives of the third phase of LARO treatment where one element of increasing independence and responsibility for treatment is the transition to pharmacy-based purchases of prescribed opioid dependency medication.

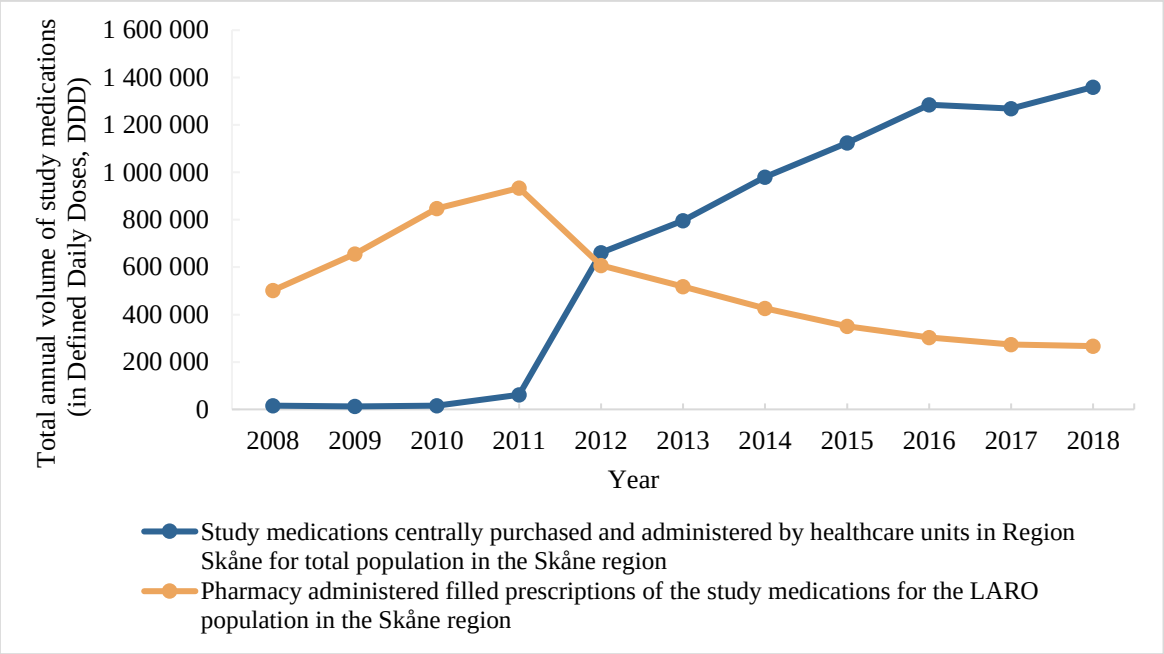

Figure B. *Annual volume of study medications buprenorphine mono, methadone and buprenorphine and naloxone in combination 2008-2018. Comparison of the trend of the centrally purchased volume administered by healthcare units and the trend of pharmacy administered filled prescriptions to LARO-population as registered in the Prescribed Drug Register. Note: Centrally purchased study medications may be used for LARO treatment and for pain treatment. The Medical Unit at Region Skåne estimates that about 2 percent of methadone is used for pain treatment.*

5. Quality improvement in LARO treatment

The overall shift in healthcare treatment pattern in terms of a larger proportion of team visits (visits where the LARO person meets with more than one types of healthcare personnel) over time may indicate a quality improvement in the LARO treatment as more types of healthcare personnel seems to be involved in treatment. During the period 2015 to 2017 the annual mean number of nurse visit decrease by 15 percent (77 to 65). At the same time the annual mean number of team visits (excl. physician) increased by 95 percent (21 to 41).

Conclusion

This report shows that LARO has increased in volume over time with more people gaining access to treatment and with more visits per individual. However, the increasing level of central purchases of LARO treatment medications may counteract the third phase (pharmacy phase) intentions in LARO treatment. In addition, the report also indicates a quality improvement in the provision of LARO treatments as more people remain in treatment and more types of healthcare personnel seems to be involved in treatment.

List of abbreviations

Abbreviation	Explanation
CDR	Dödsorsaksregistret [Cause of Death Register]
DDD	Defined Daily Dose
ICD-10	International Classification of Diseases version 10. Swedish version.
KVÅ	Klassifikation av vårdåtgärder [Classification of health care interventions; NBHW]
LARO	Läkemedelsassisterad behandling eller rehabilitering vid opioidberoende [Pharmaceutically Assisted Treatment or Rehabilitation for Opioid Dependence]
LVM	Lagen om vård av missbrukare [Care of Abusers Act]
NBHW	Socialstyrelsen [The Swedish National Board of Health and Welfare]
NPDR	Läkemedelsregistret [National Prescribed Drug Register]
NRIEFI	Registret över insatser till äldre och personer med funktionsnedsättning [National Register of Interventions for the Elderly and for Functional Impairment]
NRFTCAA	Registret över tvångsvård enligt lagen om vård av missbrukare i vissa fall [National Register on Forced Treatment in defined cases according to Care of Abusers Act]
SDAAA	Statistikdatabas för vuxna personer med missbruk och beroende (mängdstatistik kommunnivå) [Statistical Database Adults with Abuse and Addiction]
SHR	Region Skånes Vårddatabaser [the Skåne Healthcare Register]

Table of Contents

Foreword ... 2
Executive summary ... 3
List of abbreviations ... 6
1. Background ... 8
1.1 LARO treatment in a Swedish context ... 8
2. Objectives ... 11
3. Material and methods ... 12
3.1 Study design ... 12
3.2 Ethical approval and data permissions ... 12
3.3 Study population ... 13
3.3.1 Inclusion criteria ... 13
3.3.2 Exclusion criteria ... 13
3.3.3 Starting and ongoing LARO treatment – 3 subgroups ... 14
3.4 Data collection and study variables ... 15
4. Results ... 18
4.1 Characteristics of the study population ... 18
4.1.1 Identification of the study population and subgroups ... 18
4.1.2 Sex and age distribution ... 21
4.1.3 History of healthcare visits within psychiatric care ... 22
4.2 Healthcare treatment patterns 2014-2017 ... 24
4.2.1 Overall treatment ... 24
4.2.2 LARO treatment ... 25
4.3 Drug treatment patterns 2014-2017 ... 30
4.3.1 Study medications administrated at healthcare units and study medications registered in the Prescribed Drug Register ... 31
4.3.2 Study medications administrated at LARO clinics ... 34
4.3.3 Study medications registered in the Prescribed Drug Register ... 35
4.4 Use of social service 2013-2017 ... 36
4.5 Healthcare treatment patterns during the first year in LARO ... 37
4.5.1 Study population ... 37
4.5.2 Overall healthcare treatment ... 39
4.5.3 Monthly visits during first year in LARO treatment ... 40
4.5.4 Treatment retention after 12, 18 and 24 months ... 41
4.5.5 Type of LARO clinic during first year in LARO treatment ... 42
4.6 Drug treatment patterns during the first year in LARO treatment ... 44
5. Discussion ... 46
6. References ... 51

1. Background

The World Health Organization (WHO) characterizes opioid dependence by a cluster of cognitive, behavioural and physiological features (1). Six such features include a strong desire or sense of compulsion to take opioids; difficulties in controlling opioid use; a physiological withdrawal state; tolerance; progressive neglect of alternative pleasures or interests because of opioid use; persisting with opioid use despite clear evidence of overtly harmful consequences (1) (p.5). The term opioid use disorder is used in the classification system issued by the American Psychiatric Association known as DSM- 5 (Diagnostic and Statistical Manual of Mental Disorders) and corresponds to the two earlier terms opioid abuse and opioid dependence (2).

Medication-Assisted Treatment of Opioid Dependence[1], or as labelled by WHO, psychosocially assisted pharmacological treatment of opioid dependence, is a treatment that prescribes using methadone, buprenorphine, naltrexone or clonidine in combination with psychosocial support to people dependent on heroin or other opioids. The Swedish acronym for this treatment is LARO (Läkemedelsassisterad rehabilitering vid opioidberoende) and this term is used henceforth in this report. The WHO considers LARO to be an important tool for reducing the health and social consequences and to improve the well-being and social functioning of people affected (1). LARO was first developed in the late 1960s in the US but did not become an established alternative in Sweden until the early 1980s (3). However, it remained controversial and the broad national introduction has been gradual with the first national regulation in 2005. Region Skåne was among the first four healthcare regions to introduce LARO.

There are three available medications on the market today that are used in Swedish LARO treatment: mono-buprenorphine, methadone and the combination of buprenorphine and naloxone. The Swedish National Board of Health and Welfare (NBHW) gives highest priority to treatment assisted with the combination of buprenorphine and naloxone for people with opioid dependency in LARO treatment. NBHW motivates recommendation with a better treatment effect compared to alternative medications as the naloxone component reduces the risk of erroneous use and intravenous substance abuse. However, LARO treatment with mono-buprenorphine and with methadone, respectively, is also ranked high in the national guidelines.

1.1 LARO treatment in a Swedish context

LARO treatment is provided in specialized clinics, so called LARO clinics. These clinics may either be organised as sections under the psychiatric department within publicly provided healthcare at hospitals, or as private clinics with accreditation and financing from the healthcare region.

[1] Medication-Assisted Treatment of Opioid Dependence is sometimes abbreviated as MAT.

To be admitted to LARO treatment, individuals with opioid dependence need to meet certain criteria including an age over 20 years[2] and a physician-documented opioid dependence that has lasted for at least one year. The NBHW estimated that Sweden had 110 LARO clinics in November 2013 offering treatment in accordance with the legislation SOSFS 2009:27. A majority of those, 91/110, were owned by healthcare regions. The number of LARO clinics has increased over time and the government agency Health and Social Care Inspectorate listed 177 registered LARO clinics in July 2018. Nevertheless, evaluations point at persistent unmet demand with long waiting times for treatment initiation in some parts of the country (4).

A report from 2017 analysing data from Region Skåne indicate that most LARO treatment is provided by the designated public and private LARO clinics. In practice, key elements of LARO treatment including regular administration of medication for opioid dependency at a healthcare unit could be provided at a healthcare unit that is not designated LARO clinic. The report from Region Skåne indicated that this number was small (3).[3] Medications provided at healthcare units are bought by the healthcare region and may be subject to tenders. The tender price may differ from the reimbursement price approved by the national Dental and Pharmaceutical Benefits Agency (TLV) and used for subsidized prescription drugs in outpatient care distributed by pharmacies.

In general, LARO treatment in Sweden consists of three phases with an increased degree of responsibility and accountability over time (5):

- Phase 1: Expected to last for three months or longer. The person with opioid dependence makes daily visits to the LARO clinic for the administration of the medicine. These daily visits put a demand on healthcare resources and on the individual. In addition, this routine also provides an opportunity for delivering complimentary psychosocial and psychological support.
- Phase 2: The person with opioid dependence still comes to the clinic for administration of medicines, but intervals between visits are prolonged to e.g. weekly contacts.
- Phase 3: The person with opioid dependence is supposed to be stable and could assume responsibility for collecting the medicines at the pharmacy rather than at the clinic.

In practice, it is common that the LARO clinic remains as provider of medications also in Phase 3 for several reasons. If tender prices are lower than the national pharmacy price, the healthcare region in its role as payor of medications have less incentive to increase its costs through a switch from tender priced drugs provided by the LARO clinic to outpatient prescription distribution at pharmacies. There are also evaluations showing that some individuals are more comfortable continuing to retrieve their

[2] Under special circumstances, an individual may be prescribed such treatment even if he or she has not yet reached the age of 20 years.
[3] The report did not further analyse whether these registrations were people with true LARO treatment or a result of erroneous registrations.

medicines at the LARO clinic. Healthcare professionals may also prefer to keep the individuals enrolled in LARO treatment in the clinic for supervised medications (3, 6).

Swedish research points to the importance of treatment retention because it is only for ongoing treatment that positive effects have been demonstrated (reduced mortality, morbidity, and illegal drug use as well as improved social situation) (3). Results from a Swedish study in 2013 showed high retention (over 80 percent) in an historical and international perspective when retention was measured as proportion of individuals still on treatment after one year (4).

In recent years, LARO treatment has been the focus of several actions in Sweden with the aim of further developing the organization and the care programme. For example, the NBHW issued national guidelines in 2017 for care and support in the treatment of drug abuse and dependency (7). An updated version of these guidelines was published in 2019 (8). The Skåne Region included LARO treatment among treatment areas where individuals could choose provider ("Choice of healthcare provider in Skåne"- "Vårdval LARO") in 2014. Since the free choice of provider reform was introduced, the number of LARO clinics with accreditation have increased from nine in 2013 to 20 in January 2020 in Region Skåne.

In connection with the Choice of Health Care Provider in Skåne reform, several evaluations of LARO clinics as a phenomena and of LARO treatment have been published (3, 5, 6, 9). These studies have largely relied on interviews and surveys. They describe, for example, the populations treated at LARO clinics, and individuals' and professionals' experiences of the healthcare and social service provided in the clinics. Data from a survey conducted by the NBHW show that the specific organization of LARO clinics and what type of care the clinic supplies vary between healthcare regions, between single clinics, and depending on who is organizing the provision. The NBHW survey reports on principles for the provision of care. To date, less has been published about the actual provision of care and of patient pathways over time using real-world data. Given the observed practice variations from the organizational perspective, it is relevant to explore how LARO treatment in practice may vary between individuals enrolled in the programme considering for example type of provider.

2. Objectives

The main objective of this study was to analyse the current treatment pathways for people with opioid dependence enrolled in programmes at LARO clinics. Treatment pathways were explored using longitudinal individual-level register-based real-world data on healthcare contacts including contacts with the LARO clinic prior to formal enrolment. Healthcare contacts were characterised by type of contact and by type healthcare provider.

An additional objective was to describe the use of opioid dependence medicines; overall healthcare resource utilisation in other parts of the healthcare system; and use of social services registered in national registers.

3. Material and methods

3.1 Study design

This observational research on LARO treatment analysed four years (2014-2017) of longitudinal retrospective cross-linked individual-level health and social services data in Region Skåne, Sweden, starting the year of the introduction of choice of healthcare provider for LARO treatment in Region Skåne 2014. Additional retrospective healthcare data from years 2008-2013 were added and allowed analyses with reference to treatment history and of the fact that medication-assisted treatment of opioid dependence has been provided in Region Skåne for decades. However, the choice of healthcare provider reform implied a possibility for switch between providers and potential new treatment pathways for people with ongoing LARO treatment.

People meeting the inclusion criteria of enrolment at a LARO clinic and resident in the Skåne region least once during the study period 2013-2017 (see Section 3.3 Study population) constituted the core of the study database. For the study, data on healthcare utilisation, mortality, filled prescriptions of selected study medications, and social service use was added from national and regional data sources. Additional aggregated longitudinal data on study medication use in public and private LARO clinics were obtained from Region Skåne.

Study variables were included for all individuals all years in the study database. The part of the sample fulfilling inclusion criteria in some of the later study years were observed both before and during LARO treatment. LARO treatment and medication for opioid dependence may be lifelong. This study first focus on LARO treatment as provided in years 2014-2017 describing the general development of number of people in LARO treatment, types of care and medications used, empirically observed retention etc over time to describe the context. Secondly, it takes the individual perspective and describe treatment patterns from start of LARO treatment and up to 24 months after start. The study inclusion criteria were broad and captured also people not receiving LARO treatment at a LARO clinic during years 2014-2017. The analyses of this latter group were restricted to descriptive information on population characteristics. The analyses of LARO treatment focused on people with at least some visits to designated LARO clinics in 2014-2017.

3.2 Ethical approval and data permissions

The study was approved by the Ethical Review Board in Lund (Regionala Etikprövningsnämnden Lund, dnr 2018/617) provided that study information was published in newspaper with regional coverage and also publicly available at the home page of the Swedish Institute for Health Economics, IHE. This study information offered an opt-out option from the study. The study protocol was also

approved and permission to analyse individual level data was granted by all data providers of data including Region Skåne Samrådsgrupp för kvalitetsregister, vårddatabaser och beredning (KVB) [Region Skåne Consultative Board for Quality Registers, Health Care Registers and Preparation], and NBHW.

3.3 Study population

The study population was retrieved from the Skåne Healthcare Register, SHR (Region Skånes vårddatabaser, RSVD) according to the inclusion criteria and exclusion criteria as described below. The retrospective observational design included all people fulfilling criteria for LARO treatment at any time point in Region Skåne in years 2013-2017. Region Skåne had 18 LARO clinics during the study period and users of LARO treatment could switch LARO clinic while on ongoing treatment.

3.3.1 Inclusion criteria

The study used the following criteria for identifying the study population with approved ongoing or initiated LARO treatment during 2013-2017:

A. Fulfilling national criteria for LARO treatment as defined by approval from responsible physician at a LARO clinic in Region Skåne in 2013-2017; or
B. active in LARO treatment in years 2013-2017; KVÅ-codes for pharmacological treatment relevant to LARO (DT026 prescription of medication at inscription or at visits during ongoing treatment, and/or AU116 medication intake under supervision); or
C. registration of diagnosis for opioid dependence in 2013-2017 (ICD-10 codes: F11.2 Opioid dependence, F11.9 Opioid use, unspecified) for those with KVÅ-codes DT026 and/or AU116 given at a non- LARO clinic.

Individuals could fulfil one or several of these criteria. We did not apply any age limitation in inclusion criteria. The regulation for LARO treatment states that the treatment is intended for people ≥20 years old but allow younger ages under special circumstances. These inclusion criteria were broad and did not require treatment at designated LARO clinics. The combination of both diagnosis and procedure codes in criterion C aimed to include persons that had LARO-treatment through other healthcare units including regular psychiatric clinics.

3.3.2 Exclusion criteria

People not resident in the Skåne region at the time of LARO treatment were excluded because data on healthcare resource use may be incomplete. No individual used the opt-out option.

3.3.3 Starting and ongoing LARO treatment – 3 subgroups

This study used observational retrospective data for years 2008-2017 to describe LARO treatment pathways over time. It allows for heterogeneity in the study population and explores treatment pathways by subgroups characterized by indicators available from the register data analysis.

People could have medication-assisted treatment of opioid dependence prior to the initiation of the choice of healthcare provider and the introduction of registration of formal LARO clinic codes in the SHR. Empirically, LARO indication was defined using the study inclusion criteria. From 2011 and onwards, people could have first LARO indication based on the combination of KVÅ codes DT026 and/or AU116, and the ICD-10 codes F11.2 and/or F11.9. Starting from 2014, the first observation of LARO indication could also be based on a registration of healthcare contacts with designated LARO clinics. These two tracks for inclusion in the study was also used to create subgroups where treatment patterns may differ. Of special interest was to allow for initiation of LARO treatment in other healthcare units than LARO clinics also after the introduction of the choice of healthcare provider reform and expansion of the LARO treatment capacity from the growing number of LARO clinics. The analyses also explored the extent of LARO treatment provided outside LARO clinics in 2014-2017. Treatment patterns were described for three subgroups of people meeting study inclusion criteria:

- Group 1: persons with the first LARO indication at a LARO clinic and visits to a LARO clinic 2014-2017.
- Group 2: persons with the first LARO indication in another healthcare unit than a LARO clinic but with visits at a LARO clinic 2014-2017.
- Group 3: persons with the first LARO indication in another healthcare unit than a LARO clinic and no visits to a LARO clinic 2014-2017.

By design, the inclusion strategy implied that significant proportions of people with first observed indication of LARO treatment in 2011 or 2012 in study data were in fact enrolled since before in ongoing LARO treatment.[4]

The first phase of LARO treatment, with recommended duration of at least three months, involves daily visits to the LARO clinic for supervised intake of medication, and psychological and psychosocial support. To explore the treatment pathways for people initiating LARO treatment as observed in register data, we conducted further analysis of the Group 1 as this group was expected to have all LARO treatment provided by designated LARO clinics. This group was stratified by patterns of regularity of visits to the LARO clinic up to 24 months after initiation:

- Stable LARO population: Registered visits each month during the first 12 months of LARO treatment

[4] Available data did not have information on of first decision ever to start LARO treatment.

- Irregular users: No visits in at least one month during the first 12 months after initiation of LARO treatment

Irregular users were further described by proportion with at least one visit in the month and the proportion without visits to the LARO clinic in each month.

It is possible that people with first observation of LARO treatment in 2011-2017 have had previous spells of LARO treatment before the study period, but such information was not available in this register-based analysis. All three study groups may contain people with a history of prior spells of medication-assisted treatment of opioid dependence at some point in time which should be acknowledged in the interpretation of the results. However, during the main study period 2014-2017 we had people with treatment in LARO clinics without prior indication of LARO treatment in up to six years. For the purpose of this study, we considered them as eligible for the analysis of treatment pathways during the first two years of LARO treatment.

3.4 Data collection and study variables

Study variables on healthcare use came from the regional SHR and variables on dispensed prescriptions, social services, and cause of death from national registers at the NBHW. Complementary information on hospital and LARO clinic-based purchase of buprenorphine, methadone and the combination of buprenorphine and naloxone were retrieved from the Region Skåne Medication Unit (Läkemedelsenheten). These data were available as monthly data on aggregate use of opioid dependence medications at the Region Skåne level for years 2008-2018.[5] For years 2014-2017, aggregate data on monthly purchases of opioid dependence medications to LARO clinics was available in total and for research split by type of LARO clinic (public, private).

After identification of the study population in SHR, Region Skåne sent the "LARO treatment population" file including personal identity numbers and SHR study variables to the NBHW for retrieval of prescription drug data, social services data and cause of death data. Unique personal identification numbers were used to link data from the selected population registers. The NBHW replaced personal identity numbers with study numbers before sending the data to the Swedish Institute for Health Economics. The SHR and NBHW data together constituted the study database.

Table 1 lists study variables from the SHR used in the analysis of treatment pathways for LARO treatment as well as other healthcare use in Region Skåne.

[5] Centrally purchased study medications may be used for LARO treatment and for pain treatment. The Medication Unit at Region Skåne has estimated that the use of methadone for treatment of pain is around two percent of the total volume of the centrally purchased volume.

Table 1. *Key variables for healthcare contacts (visits, hospitalizations) at LARO clinic and in other units providing care in Region Skåne (2008-2017). Source: Skåne Healthcare Register (SHR).*

Variable	Comment
Year of birth	
Sex	
Residency	Healthcare region of residence
Producer	Public and private
Admission date	
Discharge date	Hospitalizations only
Unit of treatment	Used to identify LARO clinics
Diagnoses	
Procedure codes and other (KVÅ)	All registered procedure codes
Other activities by KVÅ-codes	Type of investigation (for LARO clinics e.g. prescription of medication (start, dispense at visit), supervised medication, psychologist treatment (different forms), neuropsychiatrist investigation). All KVÅ-codes (up to 15) will be included
Level of care (1)	Primary care, specialized outpatient care, inpatient care
Level of care (2)	Psychiatric care, somatic care
Type of contact	Visit/non-visit (phone, mail, letter)
Health provider category	SHR specifications: team including physician; nurse; keeper; physiotherapist, almoner, psychologist, team excluding physician

Information on filled prescriptions of methadone, buprenorphine and buprenorphine in combination with naloxone for opioid dependence treatment were retrieved from the Läkemedelsregistret (the National Prescribed Drug Register, NPDR) at the NBHW. **Table 2** lists variables for categorization of drug treatment type that are of relevance for describing opioid dependency treatment at LARO clinics.

Table 2. *Key variables describing use of prescribed drugs in outpatient care 2008-2017. Source: National Prescribed Drug Register (NPDR).*

Variable	Inclusion criteria
ATC-code (7 digit level)	N07BC01 Buprenorphine N07BC51 Buprenorphine, combinations N07BC02 Methadone
Date of dispense	
Number of dispensed defined daily doses (DDD)	

Outcome variables describing use of social services were obtained from two sources at NBHW with individual level data: Registret över tvångsvård enligt lagen om vård av missbrukare i vissa fall (National Register on Forced Treatment in defined cases according to Care of Abusers Act NRFTCAA) and Registret över insatser till äldre och personer med funktionsnedsättning (National Register of Interventions for the Elderly and for Functional Impairment, NRIEFI). **Table 3** below lists variables for describing interventions within forced treatment according to Care of Abusers Act

in the NRFTCAA.[6] Variables focus on date of decision for forced treatment, admission and discharge; on type of substance abuse; and by whom the decision was made.

***Table 3**. Key variables describing use of social services for people with forced treatment 2013-2017. Source: National Register on Forced Treatment in defined cases according to Care of Abusers Act (NRFTCAA).*

Variable (register)	Description
Date of decision	Year, month and day
Date of admission and discharge	Year, month and day
Type of substance abuse	Different types of abuse: alcohol, narcotics etc

The NRIEFI collates data on social services provided by municipalities for elderly and people with functional impairments (physiological and mental) at the individual level. **Table 4** lists selected variables used to describe use of five interventions in social services which may, or may not, correlate with health interventions at LARO clinics for the study population.

***Table 4**. Variables describing use of social services for individuals with concomitant mental illness in 2013-2017. Source: National Register of Interventions for the Elderly and for Functional Impairment (NRIEFI).*

Variable	Description
Period	Year and month
Type of services	Day care, escort service, supported dwelling, contact person)
Short-term residence	Decision, number of days, indicator of use at the end of period

Date of death was obtained from Dödsorsaksregistret (the Cause of Death Register, CDR) at NBHW to account for possible death in the analyses of LARO treatment pathways. In addition, cause of death was obtained with an aim to describe the proportion of deaths with registration of ICD-10 code T40 (Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics) if number of observations allowed further analyses into cause of death.

[6] In Swedish: Lagen om vård av missbrukare, LVM.

4. Results

4.1 Characteristics of the study population

4.1.1 Identification of the study population and subgroups

During the 7-year (2011-2017) inclusion period we identified 2 767 potential study subjects in SHR (**Figure 1**). Out of those, 2 429 (88%) fullfilled the inclusion criteria and were residents in the Skåne region at the date of inclusion. The total study population was divided into three groups based on where they were identified for the first time during the inclusion period. Group 1 consisted of persons identified via LARO clinic and visit at LARO clinic 2014-2017 (28.8%). Treatment pathways in Group 1 were expected to reflect those of people starting medication-assisted treatment for opioid dependence in the focused treatment context with the mission of LARO clinics. Group 2 consisted of persons identified via a non-LARO clinic at any point in time from 2011 and who had at least one visit at a LARO clinic 2014-2017 (49.5%). As such, Group 2 captured also people with ongoing LARO treatment when the concept of "LARO clinic" was introduced in SHR in 2014. The large number of new entrants in 2012 (**Table 5** below) also indicates an existing group of people with ongoing long-term LARO treatment. Data did not contain information on date of start of LARO treatment. Group 3 included persons who fulfilled inclusion criteria ICD-10 diagnostic code for psychiatric disorder due to opioids and together with KVÅ-code for visits and supervised medical treatment in non-LARO clinics and with no visits to a LARO clinic in study years 2014-2017 (21.7%). Group 3 could differ from Group 2 as they during the observation period did not enroll in the designated LARO clinics.

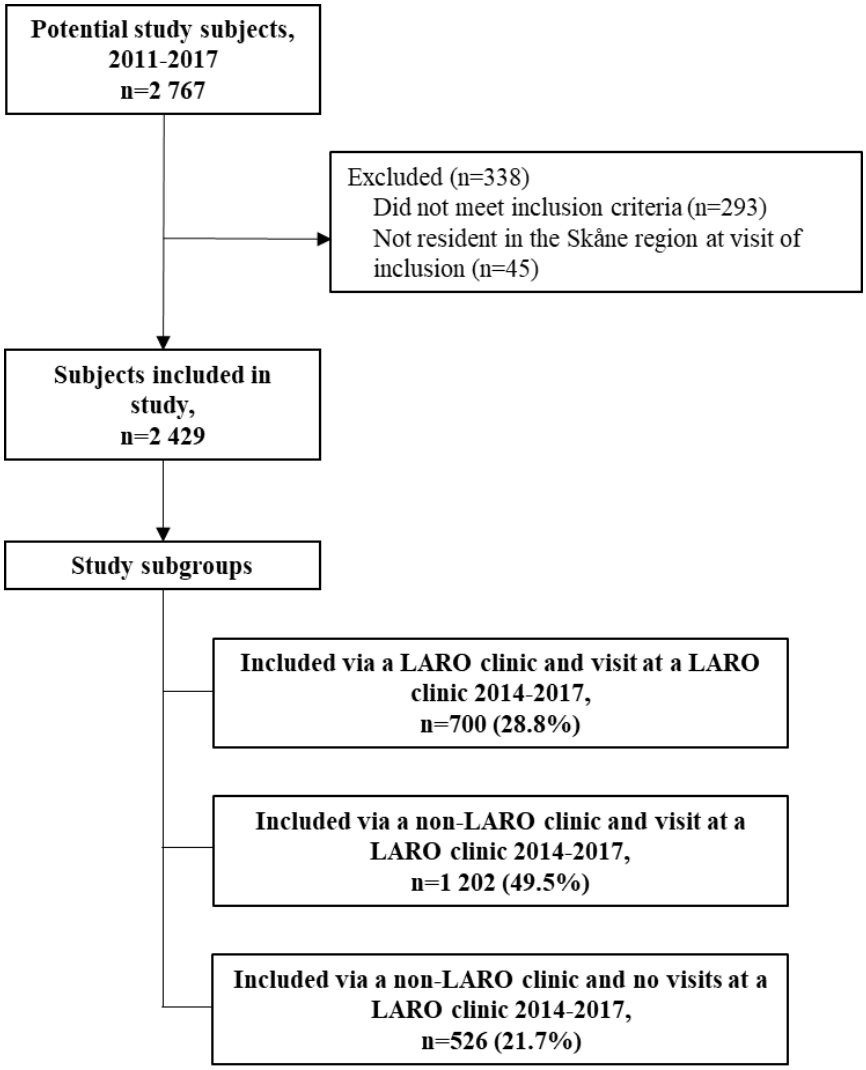

***Figure 1**. Flowchart of inclusion and exclusion of the LARO population and subgroups of the LARO population.*

Figure 2 shows the accumulated percentage of persons included in the study from 2011 to 2017 in total, and across the three subgroups. More than half of the study population (54 percent) was included in the years 2011-2013. The inclusion patterns for Group 1- Group 3 differs as shown in **Figure 2** where the majority of Group 2 were included early while Group 1 steadily increased number of included from 2014 and onwards. Group 3, the smallest group, had a stable increase in number of included from 2012 and onwards indicating that not all LARO treatment was provided at LARO clinics also four years after the introduction of choice of provider reform for LARO treatment in Region Skåne. These persons are identified with the predefined ICD-10 coded and KVÅ-codes at a non-LARO clinic.

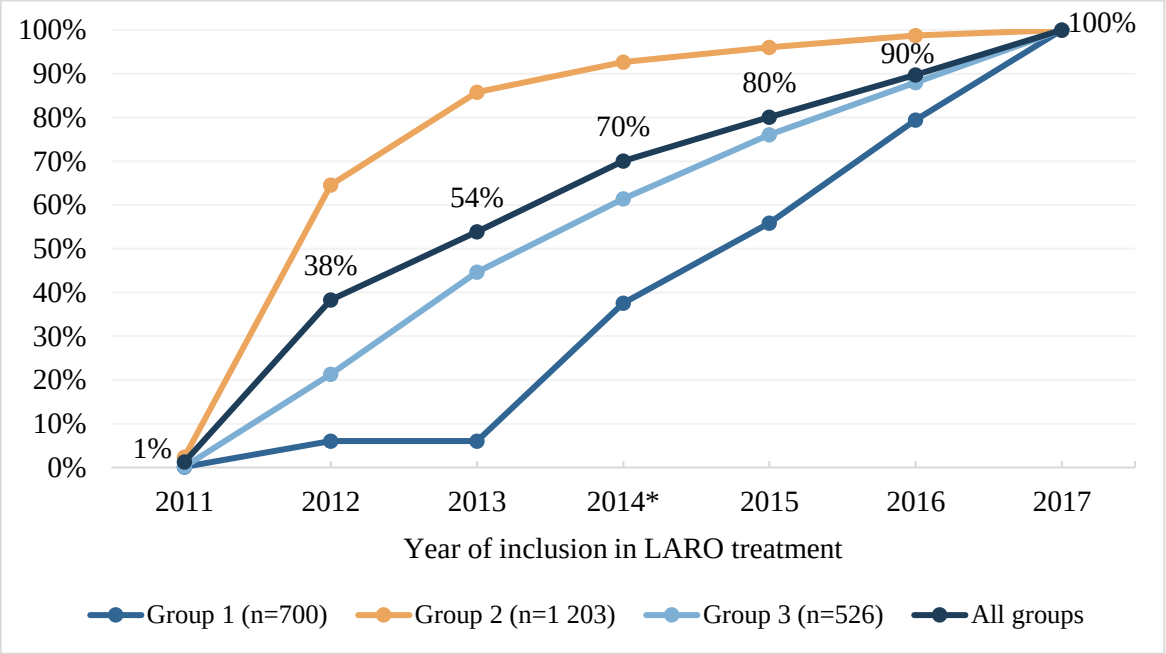

***Figure 2**. Year of inclusion in LARO treatment for persons in the LARO population. Accumulated percentage for the total number of persons and by subgroups. *= year of start of "Vårdval LARO" in the Skåne region.*

Figure 3 presents the same data as **Figure 2** but as the accumulated number of persons by first indication of LARO treatment over the study period. The large increase in the number of patients from 2011 to 2012, 900 persons of which 748 (83 percent) belonged to Group 2, reflected the new registration practices in SHR. For the total study population, 181 persons (7.5 percent) were lost to follow-up due to deaths up to December 31, 2017 (**Figure 3**, **Table 6**).

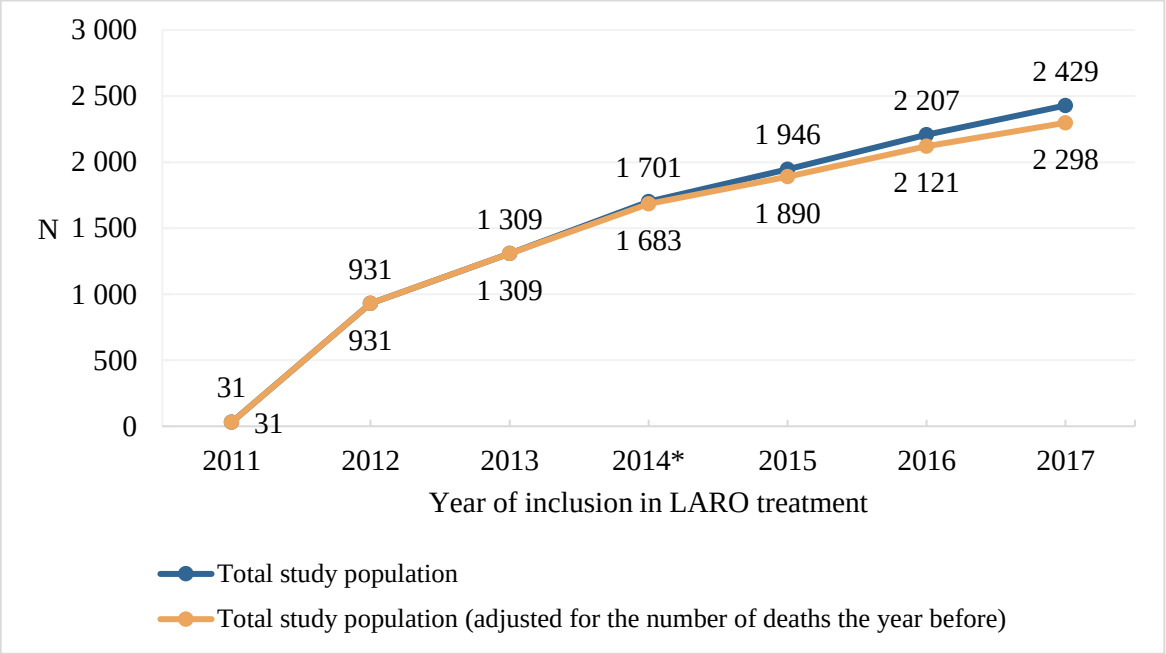

Figure 3. *Year of inclusion in LARO treatment for the LARO population. Accumulated number of persons and adjustments for deaths in preceding years for the total study population. *= year of start of "Vårdval LARO" in the Skåne region.*

Table 5 presents the same data as the number of persons with first indication of LARO treatment by year. There was on average 300 per year during the study period 2014-2017, but the number of first indications tended to decrease from nearly 400 in 2014 to the lowest number of new LARO indications (n=222) in the last year of the observation period 2017.

Table 5 *Number of people with first indication of LARO treatment in study data.*

Year	First indication of LARO treatment in study data
2011	31
2012	900
2013	378
2014	392
2015	245
2016	261
2017	222

4.1.2 Sex and age distribution

Most of the persons in the total LARO population, and in all three subgroups, were men (**Table 6**). The overall median (p25; p75) age was 36 years (29; 46) with small differences between the sexes. There was a tendency of slightly higher age in Group 2 and some greater variation in Group 3 for

men and women. More than half of the deaths during the study period were registered as related to the dependency disorder (ICD 10 diagnosis T40).

Table 6. *Demographic characteristics of the study population: Sex and age at date of inclusion and mortality by the end of 2017.*

	All patients (n=2 429)	Group 1 (n=700)	Group 2 (n=1 203)	Group 3 (526)
Number	2,429	700	1,203	526
Men, n (%)	1,688 (70)	511 (73)	851 (71)	326 (62)
Age at date of inclusion				
Median age (p25;p75), all	36 (29; 46)	35 (28; 46)	37 (30; 46)	35 (26; 48)
Median age (p25;p75), men	36 (29; 46)	36 (28; 46)	37 (31; 46)	32 (24; 44)
Median age (p25;p75), women	37 (29; 48)	34 (28; 46)	36 (29; 47)	39.5 (29; 52)
Age groups				
<20	23 (1)	1 (<1)	7 (1)	15 (3)
20-29	654 (27)	206 (31)	255 (21)	183 (35)
30-39	780 (32)	220 (31)	437 (36)	123 (23)
40-49	504 (21)	132 (19)	287 (24)	85 (16)
50-59	371 (15)	96 (14)	191 (16)	84 (16)
60-69	83 (3)	29 (4)	26 (2)	28 (5)
≥70	14 (1)	6 (1)	0 (0)	2 (2)
Mortality by December 31, 2017				
Total, of which	181 (8)	30 (4)	83 (7)	68 (13)
Diagnosis T40*	98	18	44	36
Other diagnosis	24	2	11	11
Missing information on main cause of death	59	10	28	21

p25=25th percentile, p75=75th percentile. * ICD 10 code T40 Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics

4.1.3 History of healthcare visits within psychiatric care

Irrespective of year of inclusion in LARO treatment, most persons were registered with a visit to psychiatric care during the year before start of registered LARO treatment, ranging from 91 percent of the persons included in 2012 to 53 percent of the persons included in 2016 (**Figure 4**). The higher proportions of persons with visits to psychiatric care in the beginning of the period (2011-2013) mainly depends on the integration of LARO treatment in the "conventional psychiatric care" at that time and the large portion of people with ongoing LARO treatment when included in 2012 but also in 2013.

Figure 5 shows the mean and median number of visits to psychiatric care the year before formal registration of LARO treatment in our data for the total study population (N=2 429). Data illustrates that the number of visits to "conventional psychiatric care" decreased with the introduction of "Vårdval LARO". The mean number of visits were higher than the median number of visits across the period, indicating a skewed distribution with a limited number of persons had high use of

psychiatric care. However, after 2013 the median number of visits to non-LARO psychiatric care the year before inclusion in LARO treatment seem stabilize at about five visits, with mean number of visits around 14.

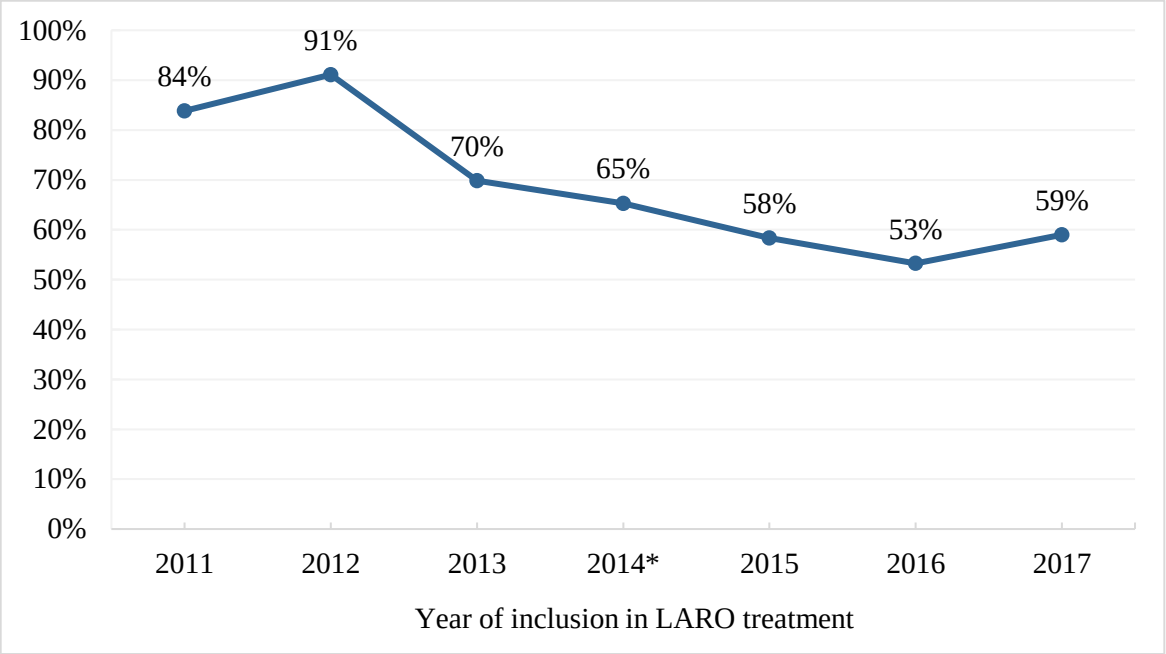

Figure 4. *Percentage of persons with at least one visit to psychiatric care one year before inclusion in LARO treatment. *= year of start of "Vårdval LARO" in the Skåne region.*

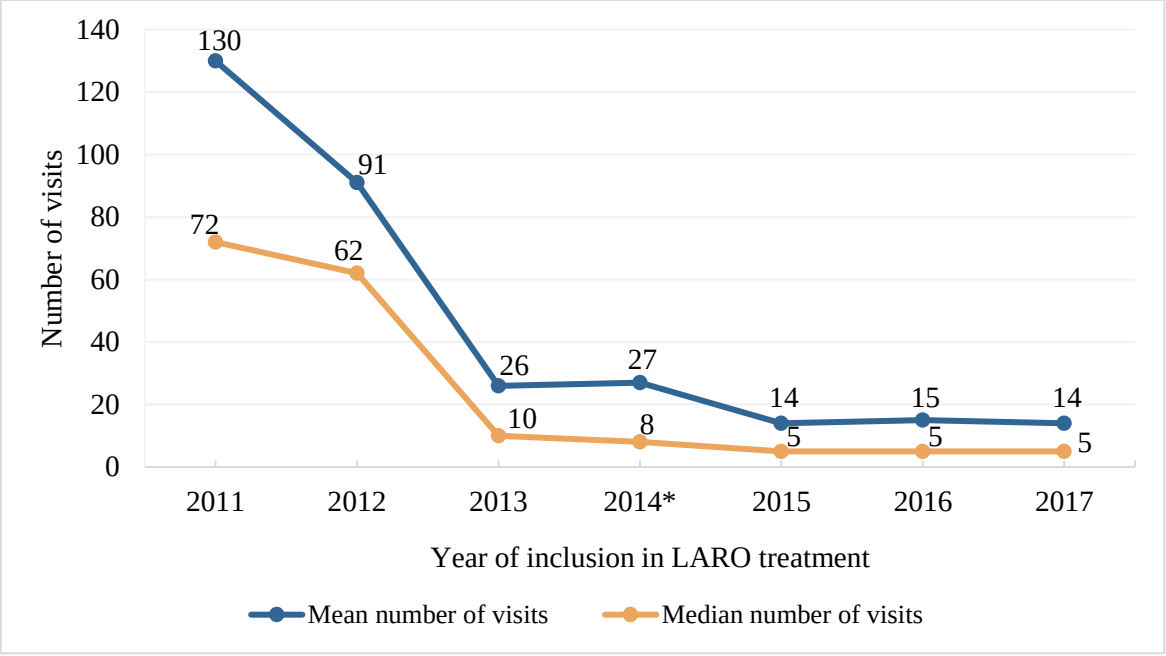

Figure 5. *Number of visits to psychiatric care among persons with at least one visit to psychiatric care the year before start of LARO treatment. *= year of start of "Vårdval LARO" in the Skåne region.*

4.2 Healthcare treatment patterns 2014-2017

4.2.1 Overall treatment

The overall healthcare treatment patterns for the total study population (n=2 429) showed that LARO visits counted for 67 percent of all healthcare visits followed by visits to non-LARO psychiatric care (22 percent) during 2014-217 (Table 7). The proportion of visits to the LARO clinic was highest in Group 1, which can be explained by the difference in distribution of newly onset and ongoing LARO treatment in Group 1 and Group 2. Phase 1 of LARO treatment according to the programme normally means a higher intensity of visits. Notably, Group 3 defined by no visits to LARO clinics during the study period, had as expected a high proportion of care provided in non-LARO psychiatric units. An analysis of the primary ICD-10 diagnostic codes registered for the visits in psychiatric care (LARO and non-LARO clinics) showed that the diagnostic code F11.2 (opioid dependence) was the main diagnosis for 85 percent of the visits in Group 1 and 2 (data not shown). The corresponding figure in Group 3 was 40 percent. Diagnostic codes related to other forms of abuse (sedatives, cannabis, multiple drug use) or healthcare problems (depression, schizophrenia) were more common in Group 3 compared to the other two groups. The requirements for treatment in formal LARO clinics may be more difficult to meet for people with more complex history of abuse. Interestingly, Group 3 had 25 percent of the overall healthcare visits in primary care. This share was a considerably higher proportion compared to Group 1 and Group 2 (Table 7).

Table 7. *Overall treatment pattern for the total study population and across groups 2014-2017.*

	All groups (N=2 429)	Group 1 (n=700)	Group 2 (n=1 203)	Group 3 (n=526)
Total healthcare visits, n (%)	923 909 (100)	250 917 (100)	612 386 (100)	60 606 (100)
LARO care	622 282 (67)	203 880 (81)	418 402 (68)	0 (0)
Non-LARO psychiatric care	203 502 (22)	22 216 (9)	147 074 (24)	34 212 (56)
Specialized non-psychiatric care	46 648 (5)	11 892 (5)	23 580 (4)	11 176 (18)
Primary care	51 477 (6)	12 929 (5)	23 330 (4)	15 218 (25)

4.2.2 LARO treatment

4.2.2.1 Total number of patients and total number of visits

The results in this section describe healthcare utilisation for Group 1 and Group 2 who by design had LARO treatment at LARO clinics.[7] The number of people in LARO treatment increased from 1 289 in 2014 to 1 654 in 2017, which corresponded to an increase of 28 percent (**Figure 6**). Most people who entered LARO treatment after 2014 belonged to Group 1. However, there were a few persons entering LARO treatment after 2014 who are identified with the stipulated inclusion criteria also outside the regular LARO organization (Group 2).

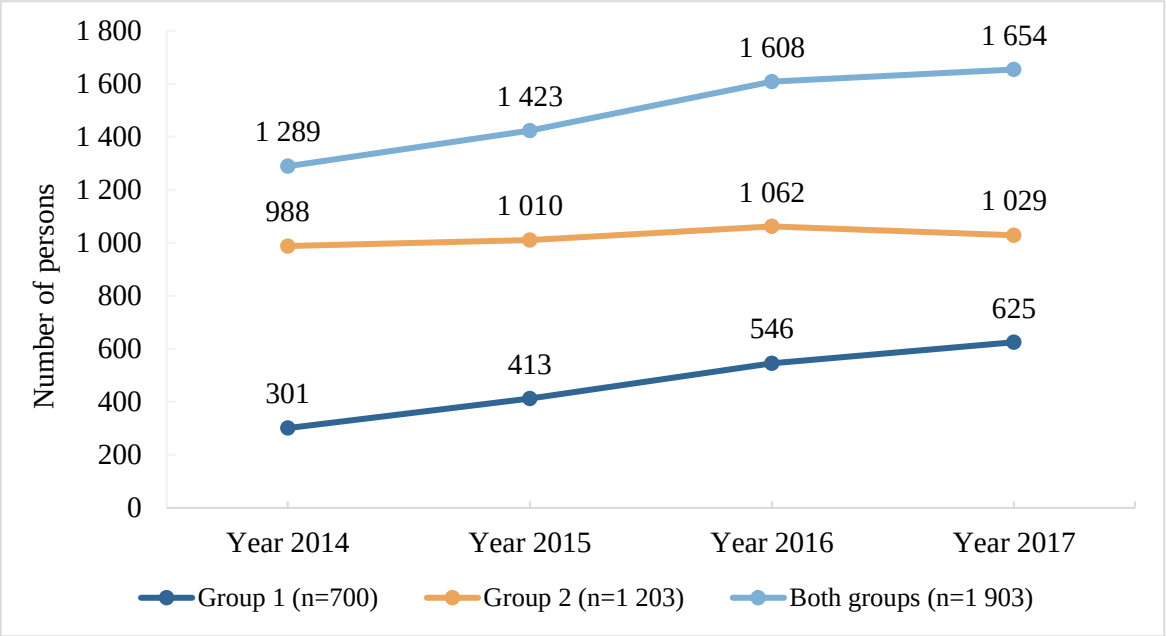

Figure 6. *Total number of persons in LARO treatment per calendar year 2014-2017.*

In parallel with increasing numbers of accredited LARO clinics and increasing numbers of persons in LARO treatment between 2014 and 2017, the volume of visits produced also increased. The total number of registered visits to LARO clinics increased from around 97 000 in 2014 to around 192 000 in 2017[8] which corresponded to nearly doubling the production (+98 percent) (**Figure 7**).

[7] Group 3 did not have observations of use of LARO treatment as provided by LARO clinics.
[8] From 97 200 visits in 2014 to 192 276 visits in 2017.

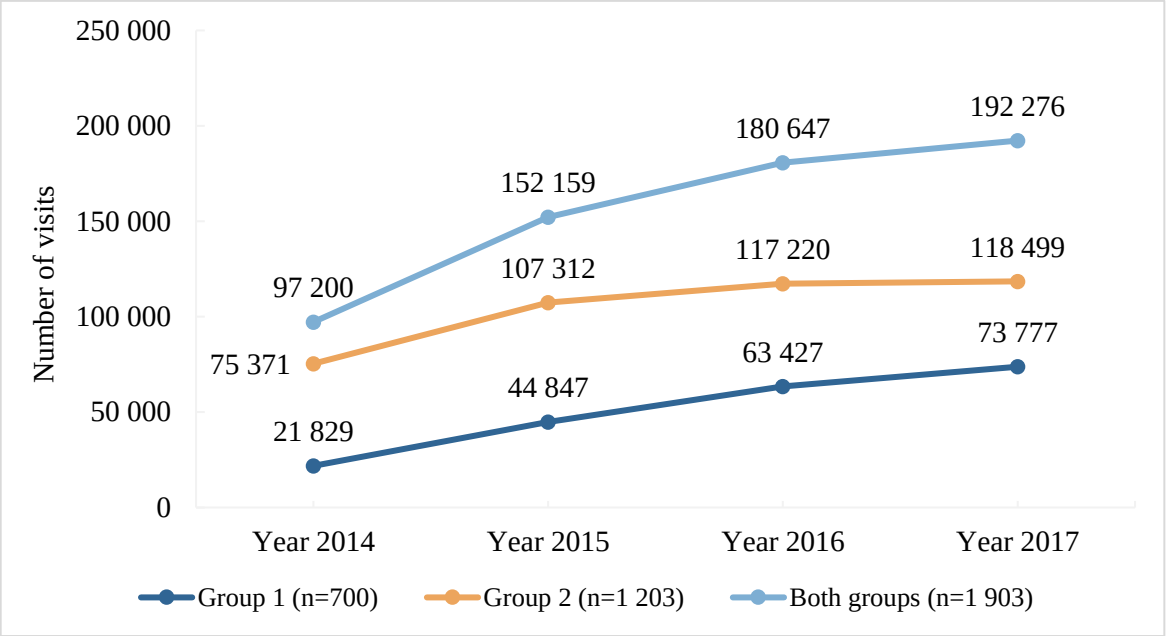

Figure 7. *Total number of visits to LARO treatment per calendar year 2014-2017.*

Persons enrolled in LARO treatment meet with different healthcare personnel. The initial enrolment involves meeting a physician, but the bulk of the following treatments is supervised medication intake which is usually provided by a nurse. The psychological and psychosocial support are also key components of LARO treatment, and this is typically registered as "team visit without involvement of a physician". The person in question then meets with at least two different types of healthcare personnel at one visit. Almoner, psychologist and psychotherapist are examples of other healthcare personnel involved in LARO treatments. **Figure 8** shows that the distribution of different types of visits has changed somewhat over the years 2014-2017 towards more team-based visits. Team visits increased from 30 percent to 37 percent and the proportion of nurse visits decreased from 65 percent to 58 percent. The proportion of physician visits remained stable at five percent over time. This change in healthcare treatment pattern may indicate a quality improvement in the LARO treatment as more types of healthcare personnel seems to be involved in treatment. In addition to supervised drug intake, other type of treatments is offered at LARO visits. An ambition expressed by the Region Skåne is to increase the proportion of neuropsychiatric examinations carried out at LARO clinics. Our data analysis showed that the registered number of such examinations were 70 in 2015, 97 in 2016 and 66 for 2017 in SHR (the KVÅ code for this examination did not exist before 2015). It is noteworthy that out of the total 233 registrations of completed neuropsychiatric examinations 2015-2017, 80 percent were registered at private LARO clinics.

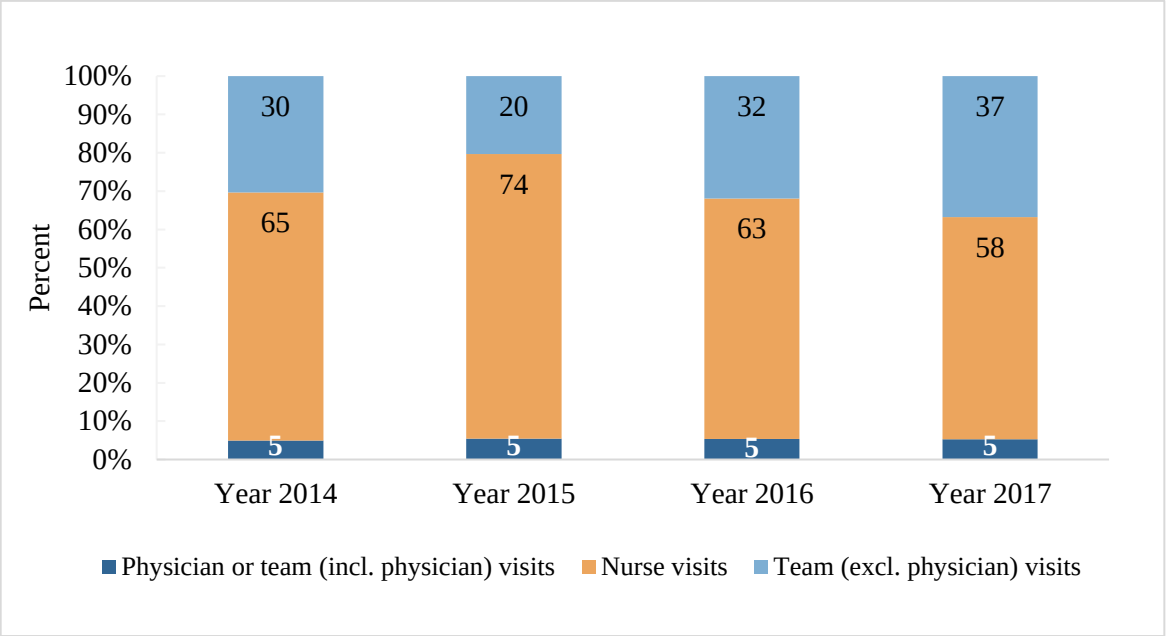

Figure 8. *Percentage of visits across different healthcare personnel involved in LARO treatment 2014-2017.*

4.2.2.2 Mean number of visits to LARO treatment

Table 8 tells that at the aggregated level, the mean number of total visits per person involved in LARO each year has increased over time, from 75 visits in 2014 to 116 visits in 2017. However, registration of data on designated LARO treatment was fully implemented from April 2014 and the shift in average number of visits to year 2015 may reflect both a real increase and a change in registration coding. Still, the average number of visits increased also 2015 and onwards. This may reflect the increasing proportion of people in Phase 1 of LARO treatment with around 300 new entrants each year who according to the standard schedule should have at least three months with daily visits corresponding to 90 visits. The overall mean number of visits was higher in Group 1 compared to Group 2 all years apart from the first year. However, no systematic pattern between the groups regarding mean visits to the different types of healthcare personnel over time could be distinguished. The use of services of psychologist, psychotherapists, and almoners outside the team-based visits was limited to a handful of occasions per year on average.

Table 8. *Mean number of visits to different healthcare personnel involved in LARO treatment 2014-2017.*

Visits to LARO clinic	All persons (n=1 903)	Group 1 (n=700)	Group 2 (n=1 203)
Mean number of total visits			
2014	75	73	76
2015	107	109	106
2016	113	116	110
2017	116	118	115
Mean number of visits to a physician or team incl. physician			
2014	4	5	4
2015	6	7	6
2016	6	7	6
2017	6	7	6
Mean number of visits to a nurse			
2014	47	46	47
2015	77	70	79
2016	69	75	67
2017	65	69	63
Mean number of visits team excl. physician			
2014	22	20	23
2015	21	29	18
2016	35	35	35
2017	41	39	43
Mean number of visits to other healthcare personnel*			
2014	3	2	3
2015	4	4	4
2016	4	5	3
2017	5	8	5

*psychologist, psychotherapist, almoner

4.2.2.3 Type of LARO clinic

In 2013, hence one year before the introduction of "Vårdval" LARO in the Skåne region, there were eight public LARO clinics and one private clinic in the Skåne region. During the first year of "Vårdval LARO" the number of clinics increased rapidly to 15, and in 2017 there were 18 LARO clinics in the Skåne region. All new clinics are privately organised (**Figure 9**).

Figure 10 shows the aggregated number of visits to LARO clinics distributed across publicly and privately driven clinics over the years 2014-2017. The total number of visits increased in both public and private LARO, but the increase was most pronounced in the private clinics. Between 2014 and 2017, the total number of visits to private LARO increased by more than 200 percent, which is explained by an increase in both the number of clinics and patients. The increase in the number of visits to public LARO during the same period was 31 percent. About 10 percent of the persons visit both a public and a private LARO clinic during the same year.

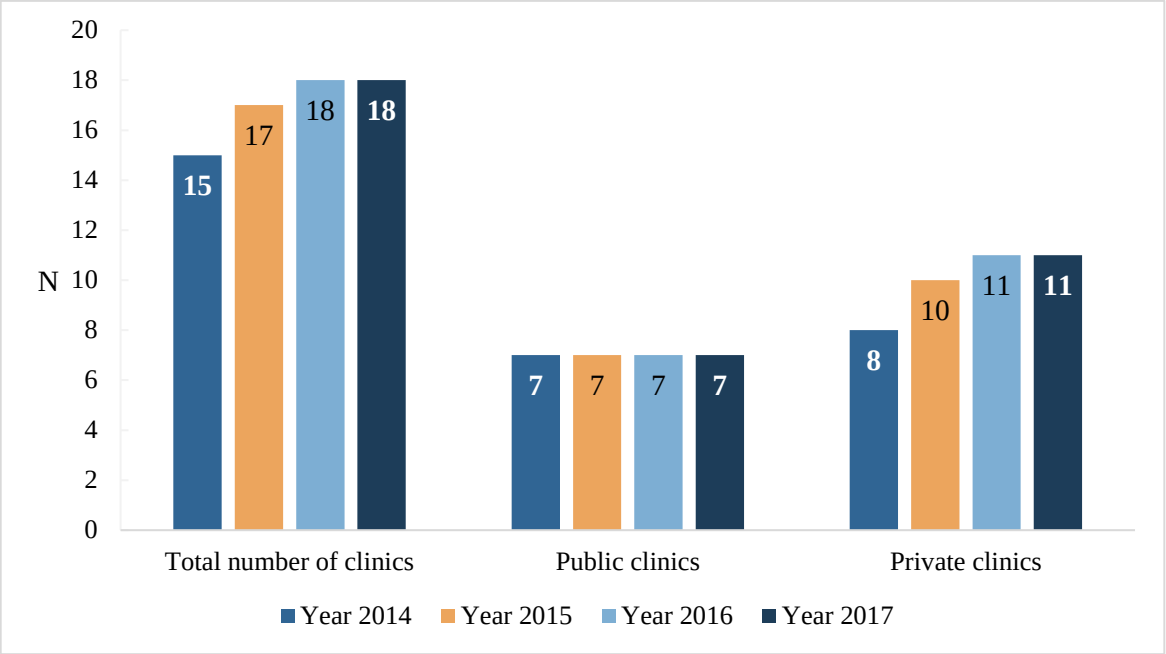

Figure 9. *Number of LARO clinics in the Skåne region 2014-2017. Total number of clinics and distribution between public and private clinics.*

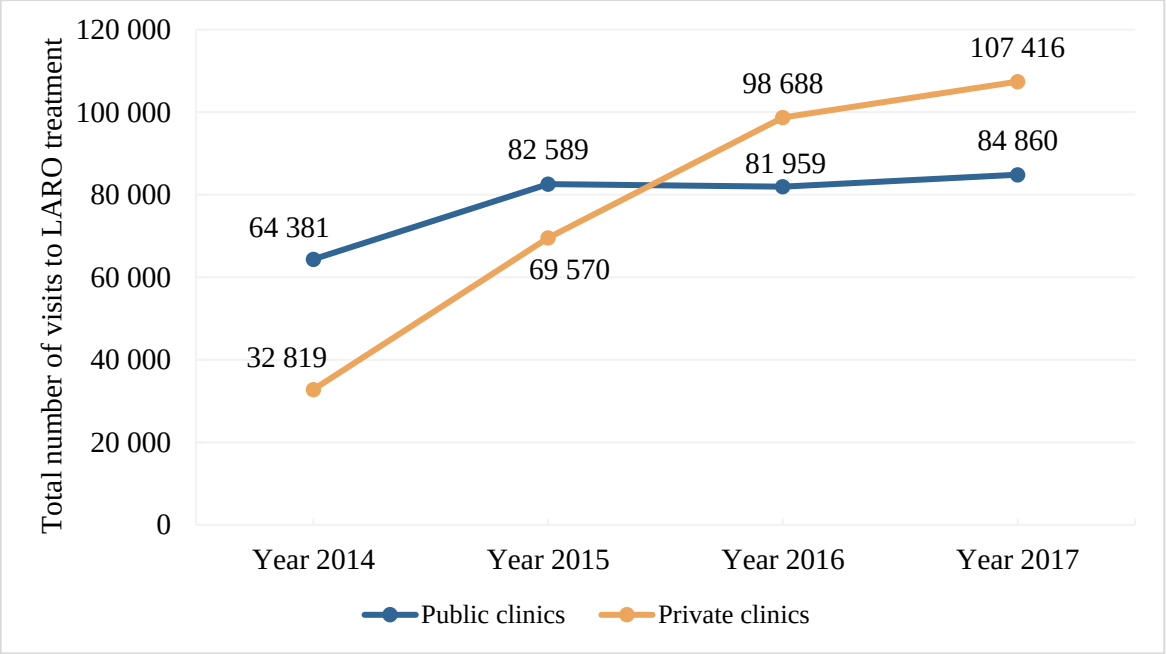

Figure 10. *Total number of visits to public and private LARO clinics 2014-2017.*

In addition to analysing how the total volume of LARO has developed over time, we have also looked at how the number of visits per person in LARO treatment developed across type of clinic during the years 2014-2017. **Figure 11** illustrates that for all LARO clinics the annual mean number of visits increased from 75 till 116, which corresponded to an increase of 55 percent. The increase in the

number of visits per individual and year has been positive in both public and private LARO, but the increase has been more accentuated in private LARO. Irrespective of year, data shows that the average number of visits to private LARO was higher compared to public clinics. In 2014, an average of 15 more visits were made per person and year in private LARO compared to public clinics. In 2017, the difference had increased to 34 more visits in private clinics. However, these figures were partly driven by private clinics attracting a higher proportion of starters of LARO treatment and thus people who were in the first phase and had more visits according to the programme.

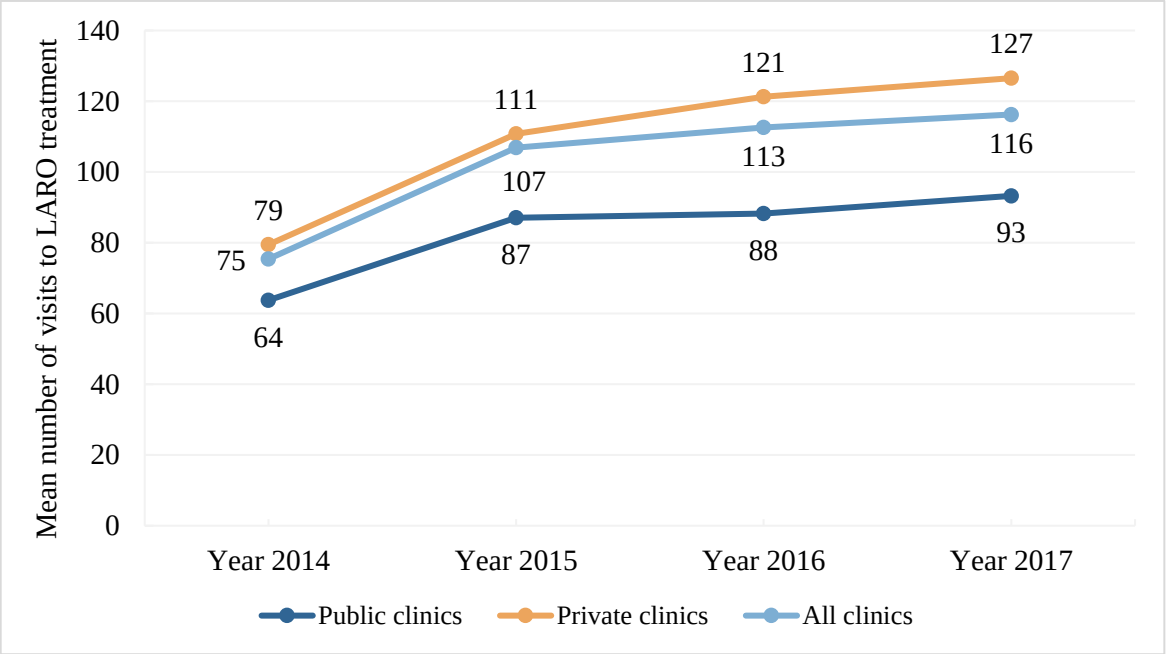

Figure 11. *Mean number of visits for persons with at least one visit to a LARO clinic across public and private clinics 2014-2017.*

4.3 Drug treatment patterns 2014-2017

National sales data indicated an increase over time for medications used in the treatment of opioid dependency (methadone, buprenorphine and buprenorphine in combination with naloxone) but there was also a shift towards central purchases by healthcare regions through procurement processes and tenders. Central purchases of medications do not have to follow the national prices for prescribed outpatient medications distributed at pharmacies. These purchases supply medications for use within the healthcare services. Although LARO treatment is provided on an outpatient basis, the person enrolled receives the medication under supervision by healthcare personnel at least in the first phase. Thus, there are multiple reasons to assume that a high proportion of study medications are distributed through the LARO clinic and that pharmacy distribution of study medications will be limited to those in the late phase of LARO treatment. Drug use within clinics is not to date registered on an individual level in national registers.

4.3.1 Study medications administrated at healthcare units and study medications registered in the Prescribed Drug Register

Figure 12 shows the defined daily dose (DDD) of the study medications (substance (ATC-code): buprenorphine mono (N07BC01), methadone (N07BC02), and buprenorphine and naloxone in combination (N07BC51)) administrated at healthcare units for the total population of the Skåne region compared to DDD for the study medications as registered in the Prescribed Drug Register (PDR) for the LARO population in the Skåne region during the period 2008-2018. The figures indicate a shift in the way the study medications for opioid dependence were managed. During the period 2008 to 2011 these medications were predominately handled through prescriptions while after 2011, the persons in need of these medications to a higher extent received them the directly from a healthcare unit. The patterns are similar for all three study medications (**Figure 13**).

There are several reasons for this shift. First, advantageous procurement has lowered the prices for drugs administered directly at a healthcare unit. Second, there is a central cost responsibility which means that an individual LARO clinic is not responsible for the costs of the study medications. Third, some LARO clinics expresses a desire to aim at continuity in treatment provision with medication management at the clinic, and a reluctance to shifting over to prescriptions and distribution through pharmacies. Fourth, costs to the opioid dependent person are increased when switched to pharmacy distribution where prescription drugs are subject to the general system with a high-cost ceiling and payment out of pocket each year. Medications provided at the clinic are free of user-charges.

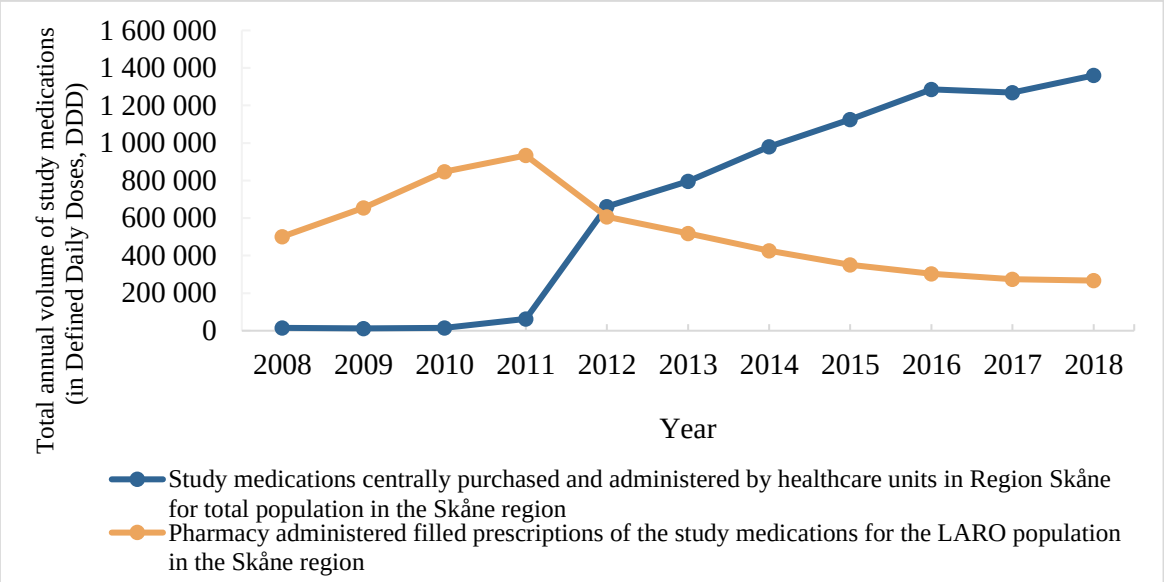

Figure 12. *Annual volume of study medications buprenorphine mono, methadone and buprenorphine and naloxone in combination 2008-2018. Comparison of the trend of the centrally purchased volume administered by healthcare units and the trend of pharmacy administered filled prescriptions to LARO-population as registered in the Prescribed Drug Register. Note: Centrally purchased study medications may be used for LARO treatment and for pain treatment. The Medical Unit at Region Skåne estimates that about 2 percent of methadone is used for pain treatment.*

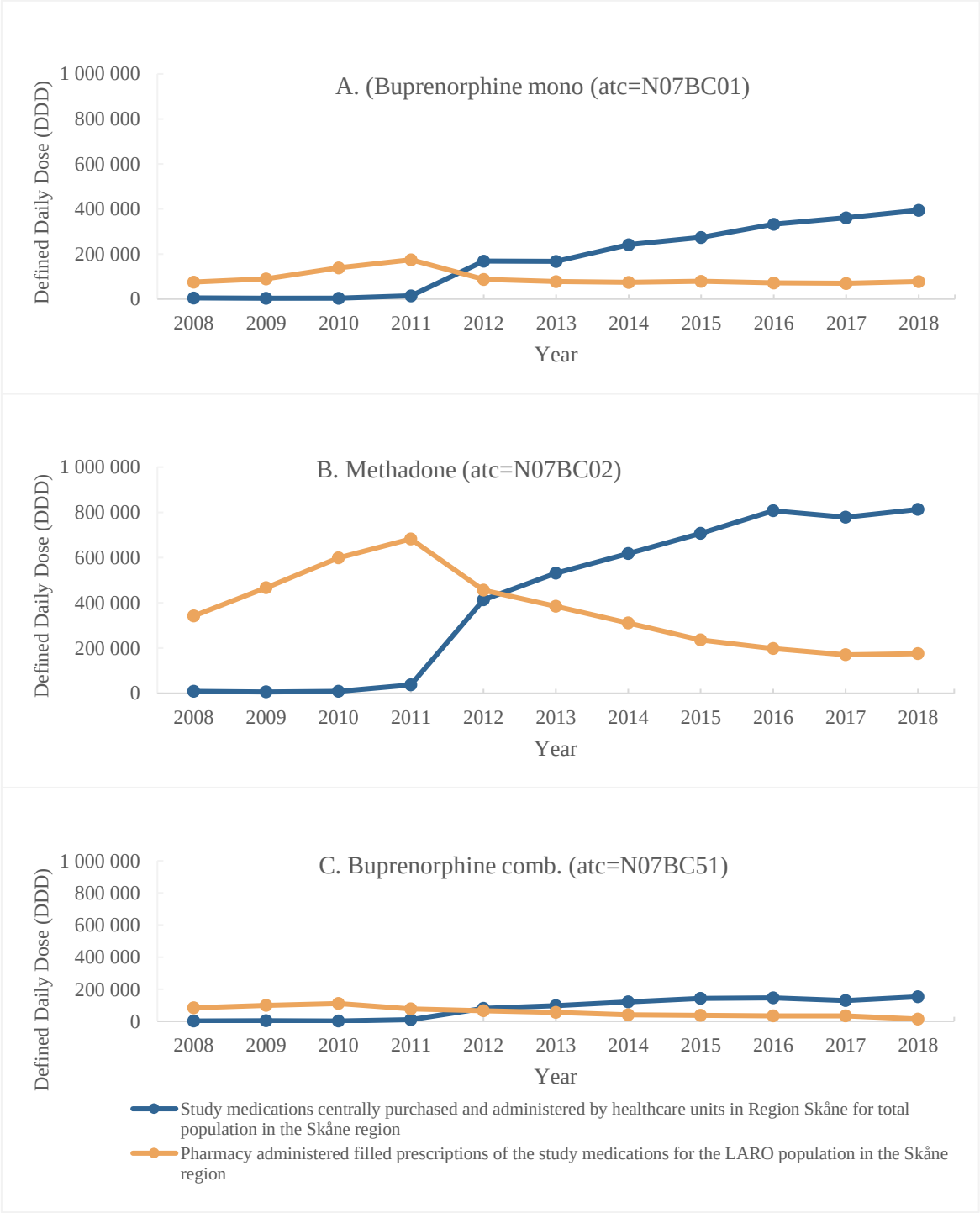

***Figure 13**. Volume of study medications, in DDD 2008-2018: Panel A: buprenorphine mono, Panel B methadone and Panel C buprenorphine and naloxone in combination. Comparison of the trend of the centrally purchased volume administered by healthcare units and the trend of pharmacy administered filled prescriptions to LARO-population as registered in the Prescribed Drug Register. Note: Centrally purchased study medications may be used for LARO treatment and for pain treatment. The Medical Unit at Region Skåne estimates that about 2 percent of methadone is used for pain treatment.*

4.3.2 Study medications administrated at LARO clinics

For the study medications administrated directly at the LARO units we had aggregated data on DDD across type of clinic from the pharmaceutical unit in Region Skåne. By use of this information and information on the number of persons in LARO treatment in public and private clinics across different years as registered in the SHR we estimated the DDD per person across years. **Table 9** illustrate the pattern of use of the three study medications over time in public and private LARO clinics, and in total. Information for each year relates to the period April to September due to gaps in data for some years. These data shows that while buprenorphine and naloxone in combination had the highest recommendation in the NBHW national guidelines published in the 2017, it is the least used of the three study medications. The most common (DDD per person) administrated drug at both public and private LARO clinics was methadone followed by buprenorphine mono (**Table 9**). A comparison between the public and private clinics reveals that the DDD per person and year of buprenorphine mono decreased at public clinics during 2014-2017 while the opposite patterns was shown for private clinics.

Table 9. *Defined Daily Dose (DDD) of the study medications for persons with at least one LARO visit in any of the years 2014-2017 per person from April to September each study year (6-months' of use) of the study medications for persons with at least one LARO visit in any of the years 2014-2017.*

	DDD (% of total average DDD)		
	All clinics	**Public clinics**	**Private clinics**
Buprenorphine mono (atc=N07BC01)			
2014	101 (25)	99 (25)	72 (28)
2015	100 (24)	88 (20)	95 (30)
2016	109 (25)	83 (20)	121 (33)
2017	108 (29)	81 (23)	124 (36)
Methadone (atc=N07BC02)			
2014	242 (61)	241 (60)	168 (66)
2015	273 (64)	282 (66)	196 (62)
2016	267 (62)	275 (65)	213 (59)
2017	225 (60)	226 (63)	196 (57)
Buprenorphine comb. (atc=N07BC51)			
2014	55 (14)	63 (16)	16 (6)
2015	51 (12)	60 (14)	27 (8)
2016	52 (12)	63 (15)	30 (8)
2017	40 (11)	50 (14)	24 (7)
Sum of study medications			
2014	398	403	256
2015	424	430	318
2016	428	421	364
2017	373	357	344

Table 9 also shows some differences in distribution of choice of type of study medications used for persons treated in public and private clinics. Public LARO clinics appear to increase use of

methadone measured as the proportion of the volume prescribed over study years from 60 percent to 63 percent. Private LARO clinics appear to reduce the proportion to have a reversed trend and use of methadone decreased from 66 percent to 57 percent. The use of buprenorphine in combination with naloxone varied marginally for private clinics but was a clearly lower level compared to public clinics. The proportion of buprenorphine mono increased from 28 percent in 2014 to 36 percent in 2017.

4.3.3 Study medications registered in the Prescribed Drug Register

From the National Prescribed Drug Register (NPDR) we have individual-based data on the study medications. Out of the total study population (N=2 429), we identified 840 persons (35 percent) with a registration with any of the study medications in the PDR 2014-2017 (**Table 10**). The highest proportion of persons with PDR registrations was observed for Group 2, which partly can be explained by the fact that in this group there was a relatively high proportion of people who had been in LARO treatment for a long time and thus more likely to have reached Phase 3 of the treatment stages and hence according to the process of LARO treatment collecting medications at the pharmacy. The data also showed that 151 persons (18 percent) were prescribed more than one type of the study medications during the period.

Table 10. *Percentage of the LARO study population with at least one expedition of a prescription of the study medications in the Prescribed Drug Register (PDR) 2014–2017.*

	All groups (N=2 429)	Group 1 (n=700)	Group 2 (n=1 203)	Group 3 (n=526)
Registration in PDR 2014-2017, n (%)	840 (35)	245 (35)	571 (47)	24 (5)

Table 11 shows the number and proportion of persons with a registered use of each study medications at some point during 2014-2017. More than half of the persons had been prescribed methadone and one third of the persons had been prescribed buprenorphine and buprenorphine in combination. The percentage of persons with a prescription of methadone was highest in Group 2 and lowest in Group 3.

Table 11. *Number (percentage) of persons with at least one expedition of a prescription of the study medications across type of substance 2014-2017 in the Prescribed Drug Register.*

	All groups (N=840)	Group 1 (n=245)	Group 2 (n=571)	Group 3 (n=24)
Number of persons (%)*				
Buprenorphine mono (ATC=N07BC01)	267 (32)	75 (31)	187 (33)	5 (21)
Methadone (ATC=N07BC02)	469 (56)	121 (49)	337 (59)	11 (46)
Buprenorphine comb (ATC=N07BC51)	241 (29)	88 (36)	142 (25)	11 (46)

* This percentage totals to over 100 as a patient may have received several different substances during the period.

Figure 14 shows that the yearly proportion of persons with a registration of drugs in PDR out of the persons with a registration of at least one LARO during the same year has decreased from 37 percent in 2014 to 23 percent in 2017. One explanation for this pattern may be that, for the years 2014-2017, there has been an inflow of new persons in LARO treatment receiving their study medication directly at the LARO clinic.

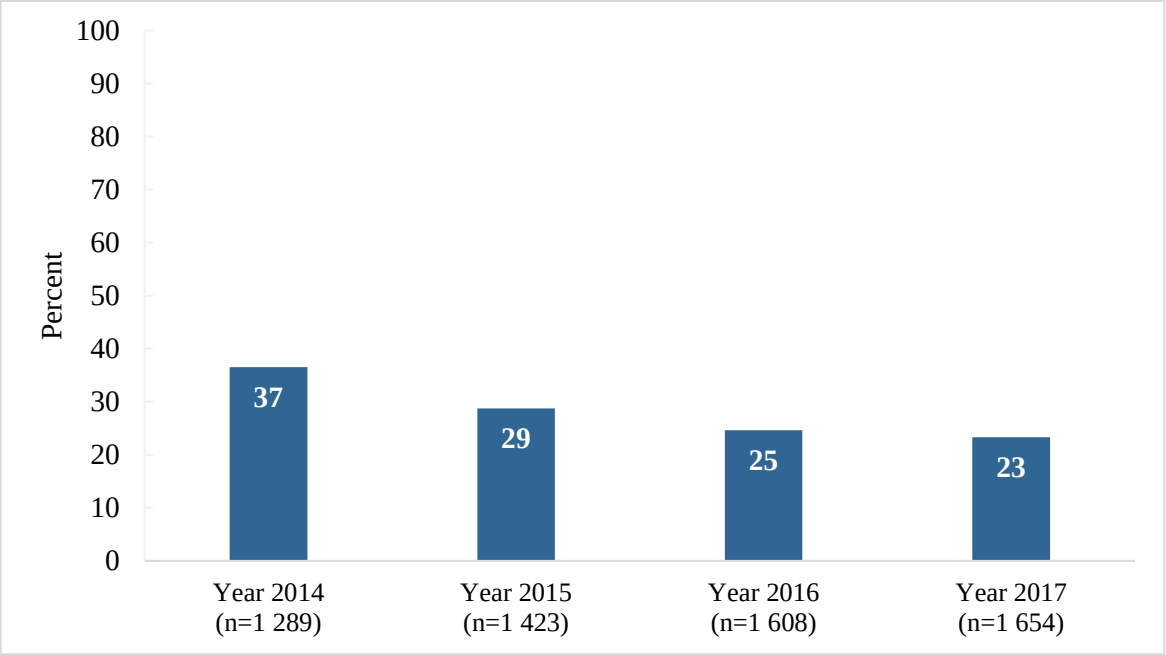

Figure 14. *Percentage of the total LARO population registered with at least one expedition of a prescription of any of the study medications in the Prescribed Drug Register (PDR) 2014–2017.The numbers in parenthesis below the years shows the number of persons with LARO visits for each year.*

4.4 Use of social service 2013-2017

Not all persons in LARO treatment are continuously stable; they may leave LARO treatment or need additional treatment to be stabilized. Therefore, we were interested in the use of forced treatment according to Care of Abusers Act as registered in National Register on Forced Treatment in defined cases according to Care of Abusers Act (NRFTCAA). Out of the total study population (N=2 429), about eight percent (n=189) were treated according to the NRFTCAA during the period 2013-2017 (**Table 12**). Most persons were treated according to NRFTCAA one time 2013-2016 and a period of treatment lasted on average for 160 days. We note that few people in Group 3 had been subject to NRFTCAA intervention.

We also investigated the extent to which people in our LARO population used social service for elderly and people with functional impairments (physiological and mental) by using the national register of Interventions for the Elderly and for Functional Impairment (NRIEFI). **Table 12** shows

that about one percent of the total LARO study population used any of the social service registered in the NRIEFI during 2013-2017.

Table 12. *Number (percentage) of persons registered in the NRFTCAA and NRIEFI 2013-2017.*

	All patients (N=2 429)	Group 1 (n=700)	Group 2 (n=1 203)	Group 3 (n=526)
National Register on Forced Treatment in defined cases according to Care of Abusers Act (NRFTCAA), n (%)	189 (7.8)	80 (11.4)	98 (8.0)	11 (2.1)
Register of Interventions for the Elderly and for Functional Impairment NRIEFI, n (%)	24 (1.0)	10 (1.4)	13 (1.1)	1 (<1)

Table 13 reveals that majority of the persons (75 percent) with a registration in NRFTCAA also had a registration of the study medications in PDR.

Table 13. *Number (percentage) of persons with at least one expedition of a prescription of the study medications ever (2008-2019) in the Prescribed Drug Register (PDR) among the persons with a registration in NRFTCAA 2013-2017.*

	All patient (n=189)	Group 1 (n=80)	Group 2 (n=98)	Group 3 (n=11)
Ever (2008-2019) in the Prescribed Drug Register out of those with a registration in the NRFTCAA	141 (75)	55 (69)	80 (82)	6 (55)

4.5 Healthcare treatment patterns during the first year in LARO

4.5.1 Study population

In the study of LARO treatment during the first year we included only Group 1, i.e. the 700 persons identified in the SHR by at least one visit to a LARO clinic with a registration of any of the KVÅ-codes for supervised medication intake[9] , establishment of structured plan for healthcare and care[10], or prescription of medication[11] during the period 2014-2017. The reason for this was that we wanted to define people who had not been in any form of LARO treatment before.

[9] In Swedish: övervakat läkemedelsintag, KVÅ code AU116.
[10] In Swedish: upprättande av strukturerad vård- och omsorgsplan, KVÅ code AU120.
[11] In Swedish: ordination av läkemedel, KVÅ code DT026.

Out of the 700 persons included in Group 1, we identified 339 persons (48 percent) with visits to a LARO clinic each month during the first year of LARO treatment (**Figure 15**). This group of persons is labelled "stable LARO population" in the following. The remaining 361 persons (52 percent) had an irregular pattern of LARO clinic visits during the first year. After the identification visit during the first month which all persons had, the number of persons with visits decreased gradually during the remaining months. We use the label "irregular LARO population" in the following for this group. We are aware of that the criteria of having LARO visits every month during the first year to be included in the stable LARO population is strict. If we had allowed no LARO visits for any six of the 12 months we would have included an additional 222 persons (64 percent) in the study population. However, we chose a strict criterion to enable the analysis of healthcare patterns for the persons in whom the treatment appeared to work well.

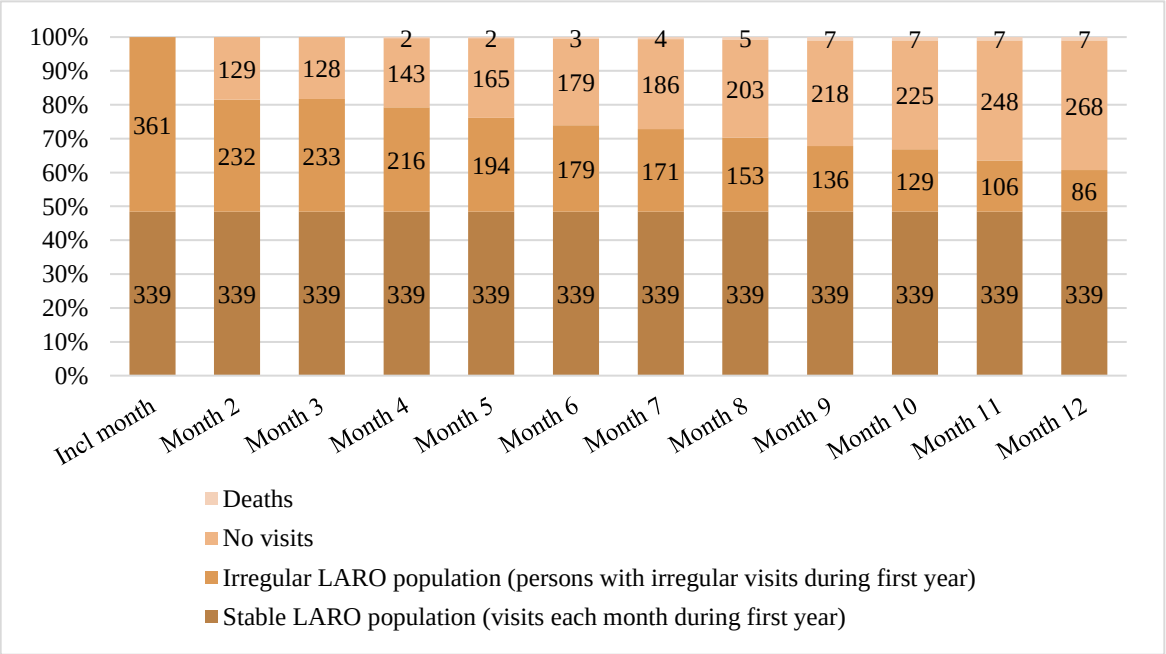

Figure 15. *Persons included in the study by fulfilment of the inclusion criteria at a LARO clinic and visit to a LARO clinic 2014-2017 (n=700) and subgroups of stable LARO population and irregular LARO population. First month of treatment represents any month between January 2014 and December 2017.*

4.5.2 Overall healthcare treatment

4.5.2.1 LARO treatment

The mean number of visits during the first year in LARO treatment was 211 for the stable LARO population (**Figure 16**). The corresponding figure for the irregular LARO population was 85.

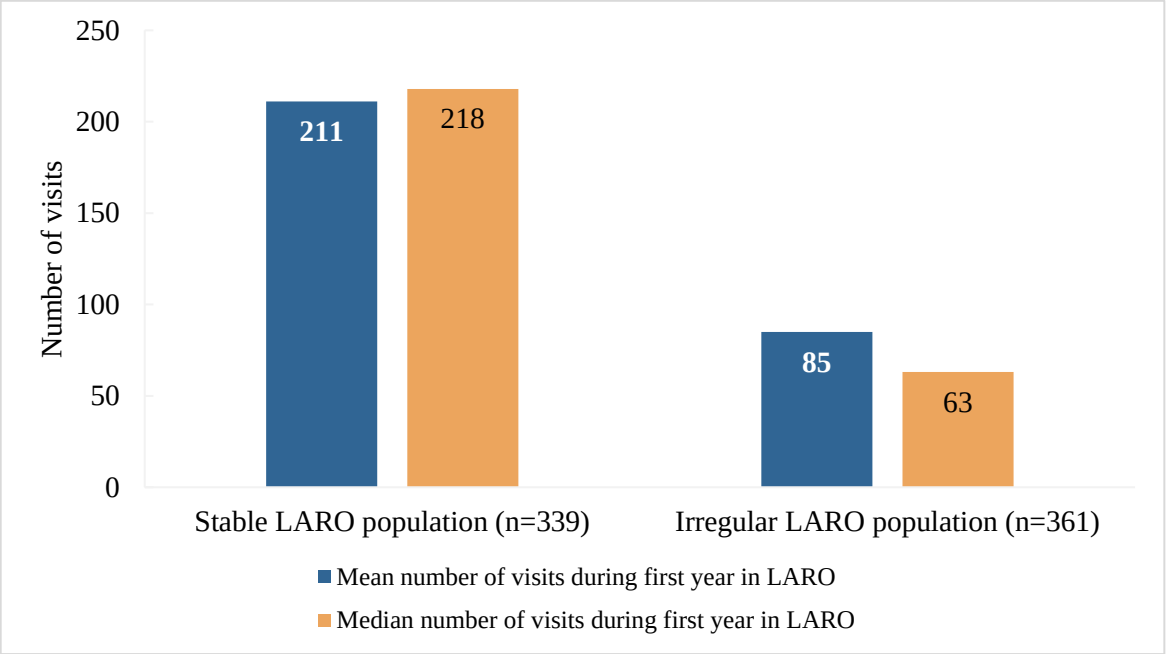

Figure 16. *Mean and median number of visits per person during first year in LARO treatment for the stable LARO population and for the irregular LARO population. Mean and median.*

4.5.2.2 Non-LARO treatment

In addition to visits to the LARO clinic, persons in LARO treatment also visited other healthcare units during their first year of LARO (**Table 14**). In both the stable and irregular LARO populations, more than half of the patients visited primary care and those who did had on average 3.5 visits. Many persons also visited the specialized care and more than 40 percent in both LARO groups had non-LARO psychiatric care which indicated that there was need for psychiatric healthcare that would not be handled the LARO treatment organization. The mean number of visits to non-LARO psychiatric care was 5.6 and 4.5 for the stable and irregular LARO populations, respectively.

Table 14. *Non-LARO healthcare visits for first year (month of start of LARO treatment and the following 11 months) of LARO treatment among the stable LARO population and the irregular LARO population.*

	Stable LARO population (n=339)	Irregular LARO population (n=361 at first month of LARO treatment)
Primary care		
Persons with at least one visit (n)	244 (72)	229 (63)
Mean number of visits (sd)*	3.5 (4.8)	3.6 (7.4)
Non-LARO psychiatric care		
Persons with at least one visit (n)	142 (42)	161 (45)
Mean number of visits (sd)*	5.6 (19.4)	4.5 (17.1)
Specialized non-psychiatric care		
Persons with at least one visit (n)	220 (65)	226 (63)
Mean number of visits (sd)*	4.4 (12.6)	(5.6)

sd=standard deviation. * for people with ≥1 visit.

4.5.3 Monthly visits during first year in LARO treatment

Figure 17 shows that the stable LARO population on average visits a LARO clinic almost every day during the three months following the inclusion month. The overall pattern looks similar for the irregular LARO population group, but with a slightly lower average number of visits. The inclusion month represents the first calendar month and the lower average number of visits is explained by starting day being any day of the month which gives an expected number of visits around 15 if the newly enrolled person goes to the LARO clinic every day.

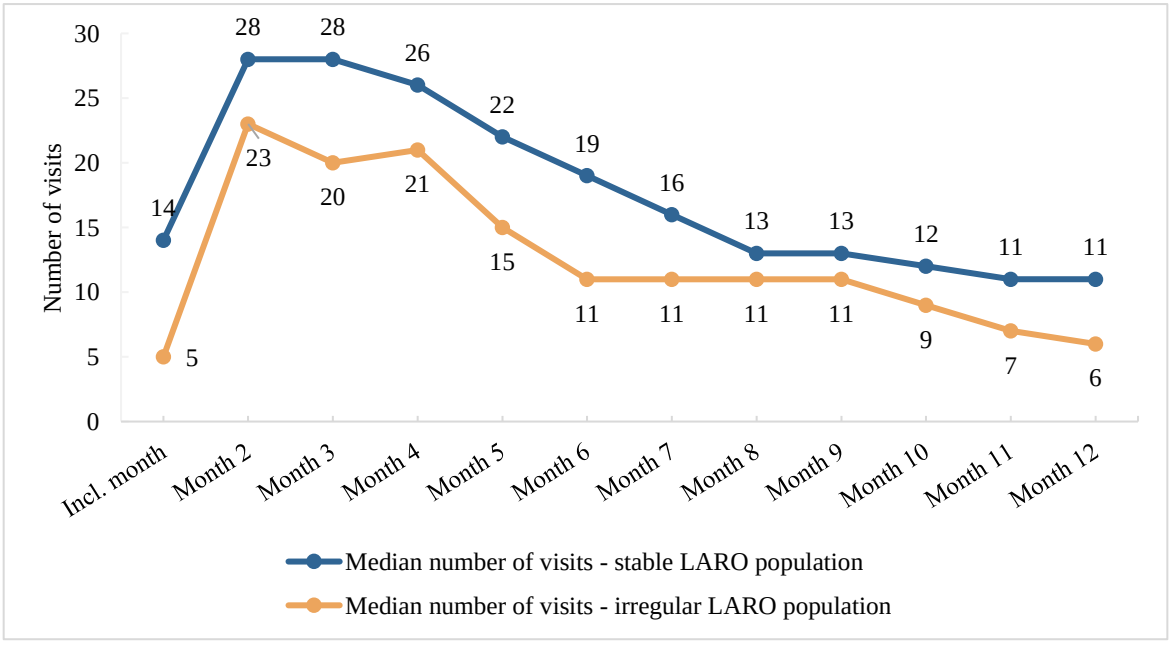

Figure 17. *Median number of visits for first year in LARO treatment for the stable LARO population and the irregular LARO population.*

For the stable LARO population we also investigated the use of different healthcare personnel available at LARO clinics (**Figure 18**). Most of the visits (≥60 percent) were to a nurse at the LARO clinic followed by team (excl. physician) visits (around 30 percent). In the inclusion month, around 10 percent of the visits were to a physician which can be explained by the fact that it is a physician who enrols a patient in LARO treatment.

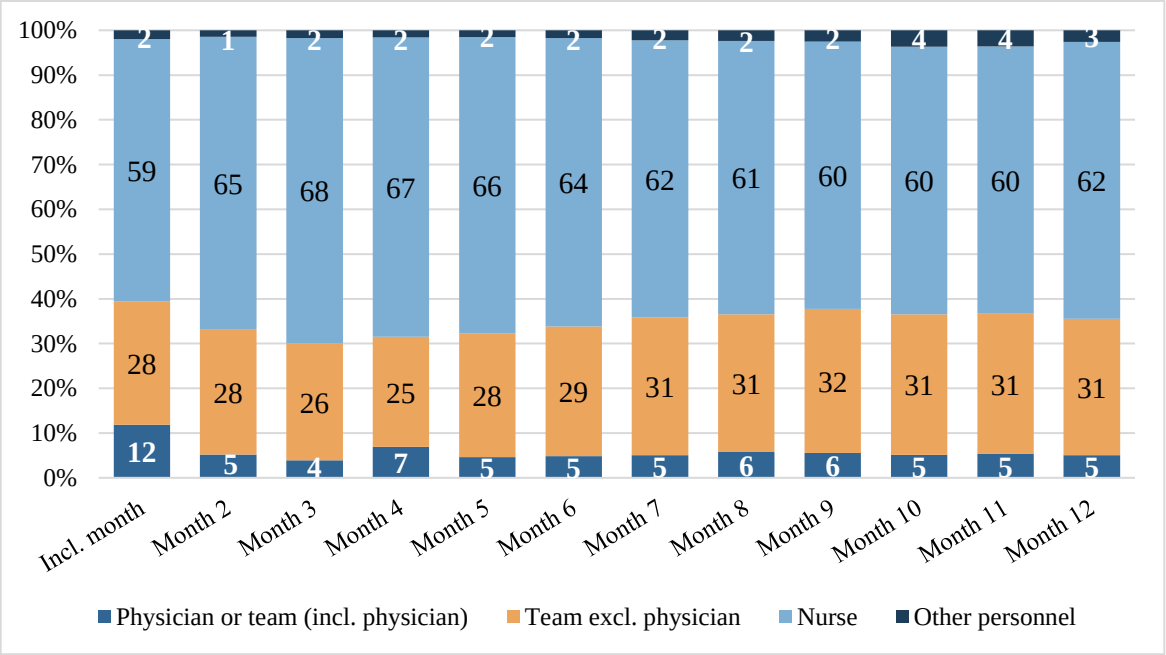

Figure 18. *Visits to LARO clinic across type of healthcare personnel for the stable LARO population (n=339)*

4.5.4 Treatment retention after 12, 18 and 24 months

In the evaluation of LARO treatment, the percentage of persons in treatment that remain in treatment (retention) is an indication of treatment quality. All people in the stable LARO population (n=339) was followed up to 12 months after initial start of LARO treatment. Among those who were possible to follow up until two years after LARO entrance, 92 percent remained in treatment after 18 months and 72 percent remained in treatment after 24 months (Figure 19). The median number of visits in month 18 and 24 was nine and eight respectively for those who remained in treatment.

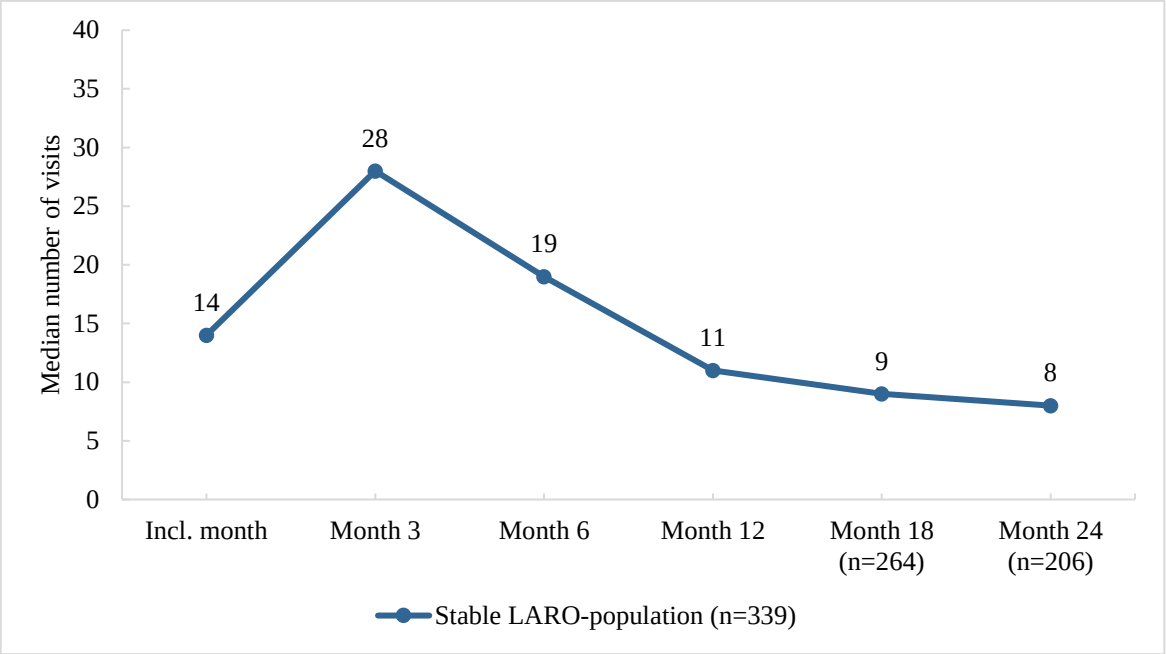

Figure 19. *Median number of visits at inclusion month, months 3, 6, 12, 18 and 24 for the stable LARO population (n=339, each person with visits every month during the first year).*

4.5.5 Type of LARO clinic during first year in LARO treatment

Fifty-five percent (n=186) of persons in the stable LARO population (n=339) used only private clinics for LARO treatment. The corresponding proportion for only public clinics and a mix of private and public clinics were 24 percent (n=80) and 22 (n=73) respectively. The median age of the persons using only private clinics was 33 years, compared to 35 years of age of the other persons in the stable LARO population. On average, more visits per patient were made each month at the private clinics compared to the public ones (**Figure 20**).

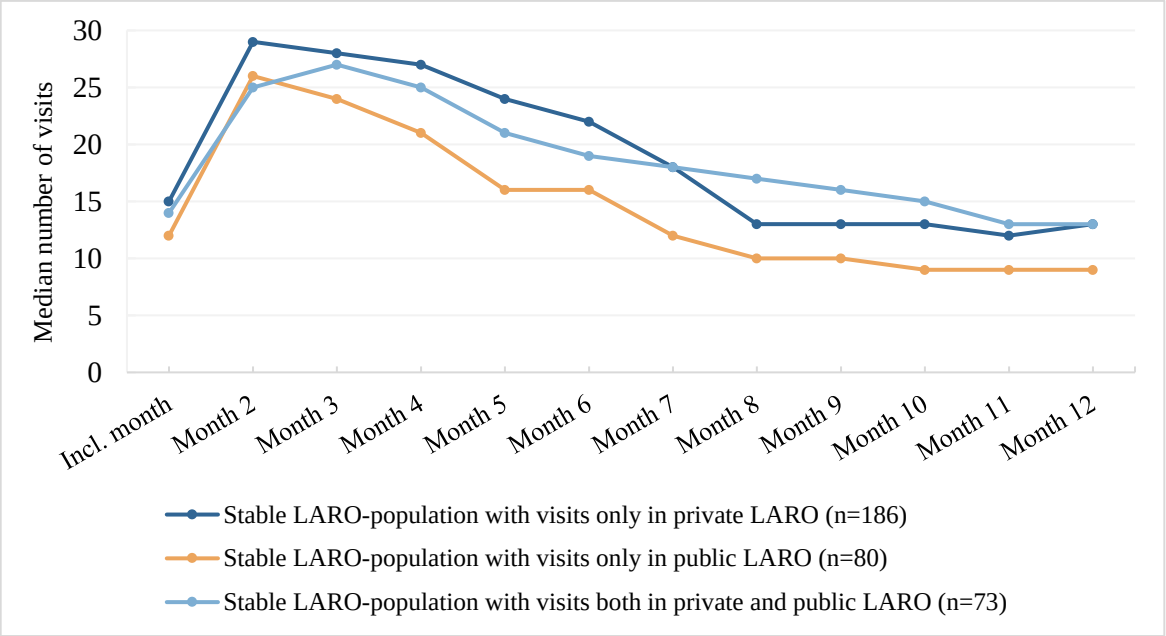

Figure 20. *Median number of visits across type of LARO clinic for stable LARO population.*

Most visits to LARO clinics were with a nurse as the nurse are involved in the supervised medication intake (Figure 21). Notably, the proportions of team visits (excl. physician) and visits to other healthcare personnel were higher for private clinics compared to public clinics.

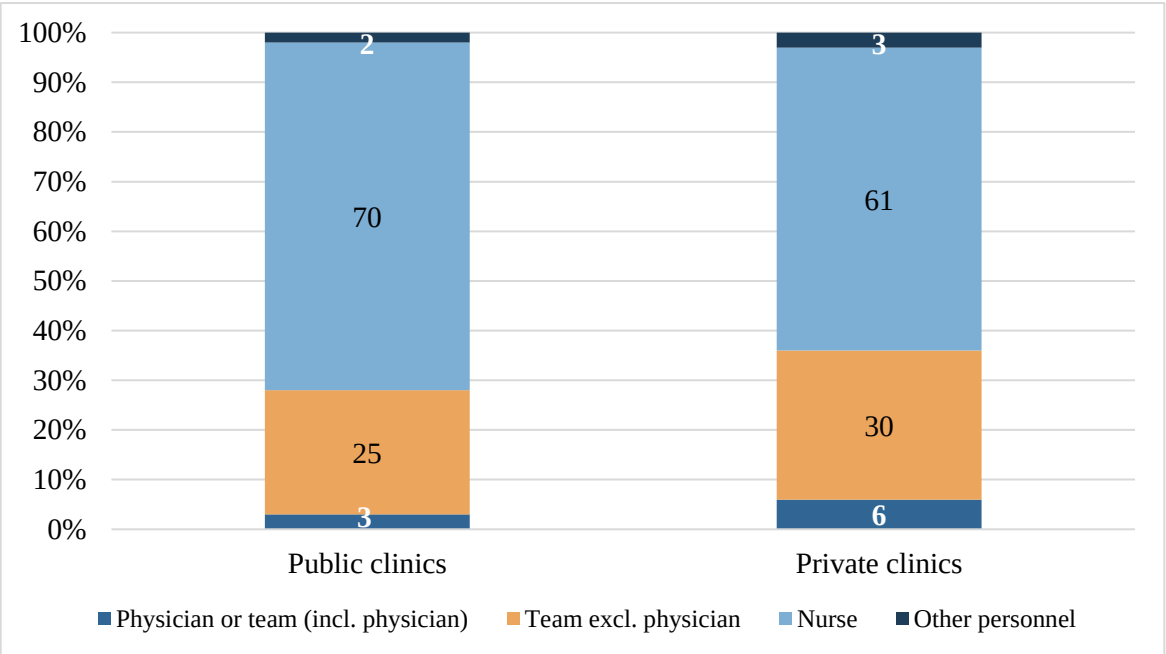

Figure 21. *Proportion of visits to different healthcare personnel out of all LARO visits across type of clinic for the stable LARO population during first year in LARO treatment.*

4.6 Drug treatment patterns during the first year in LARO treatment

Almost half of the persons in the stable and irregular LARO populations (n=700) registered a filled prescription at least once in the PDR during 2008-2019 (Table 15). One third of the persons in both groups had a filled prescription of the study medications before start of LARO treatment according to our inclusion criteria. One likely explanation for this pattern was that buprenorphine may be indicated for pain in addition to opioid dependence. Another, less likely, explanation is that certain persons may have received the study medications while living in other regions than Skåne, which means that they are registered in PDR but not in SHR.

Table 15. *Percentage of persons with at least one expedition of a prescription of the study medications in the Prescribed Drug Register (PDR) in relation to year of start of LARO treatment*

	Both groups (n=700)	Stable LARO population (n=339)	Irregular LARO population (n=361 at first month of LARO treatment)
Ever in PDR (2008-2019), n (%)	340 (49)	168 (50)	172 (48)
In PDR before year of LARO treatment start, n (%)	216 (31)	105 (31)	111 (31)
In PDR after start of LARO treatment (up to 2 years after start year), n (%)	230 (33)	96 (28)	134 (37)

Around 20 percent of the persons in the stable and irregular LARO populations (n=700) had at least one filled prescription of the study medication during their first year in LARO (**Figure 22**). This proportion was relatively stable also during the second year while it decreased to 18 percent in the third year. In the stable LARO population, 13 percent had at least one filled prescription of the study medication during their first year in LARO and this proportion increased to 16 percent in the third year.

During the first year in treatment for the stable LARO population, 68 percent of all expeditions of prescriptions was methadone (**Figure 23**). This proportion decreased to 58 percent and 49 percent during the second and third year respectively. At the same time the proportion of expeditions of prescriptions for buprenorphine comb. increased from 12 percent to 30 percent.

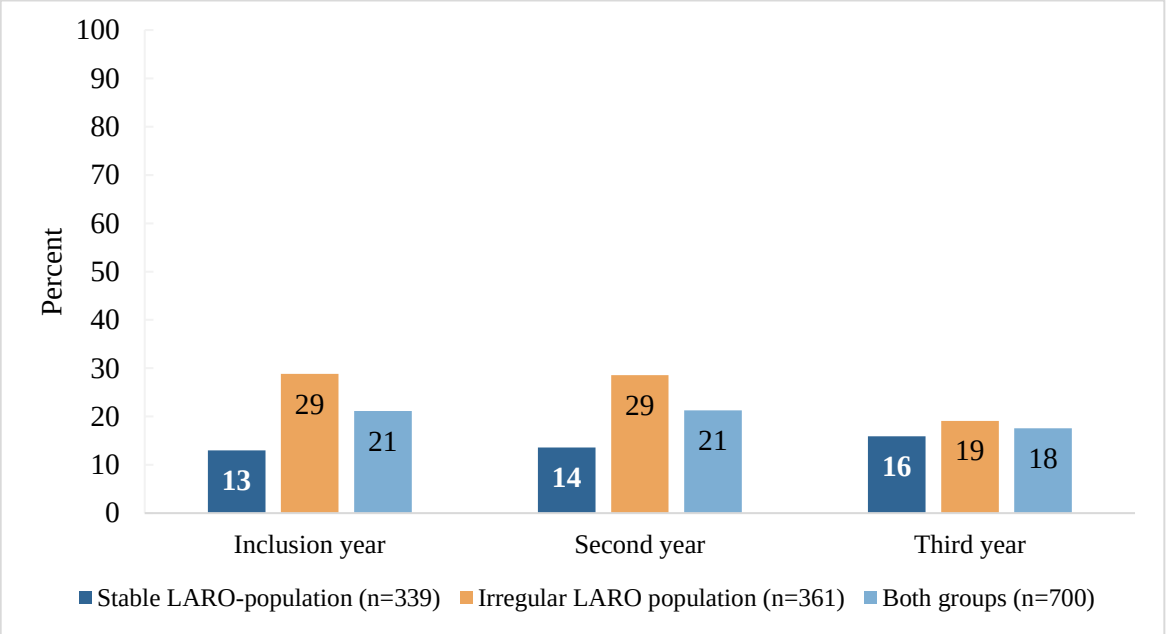

Figure 22. *Percentage of persons with at least one expedition of a prescription of the study medications in the Prescribed Drug Register in the first, second and third year of LARO treatment.*

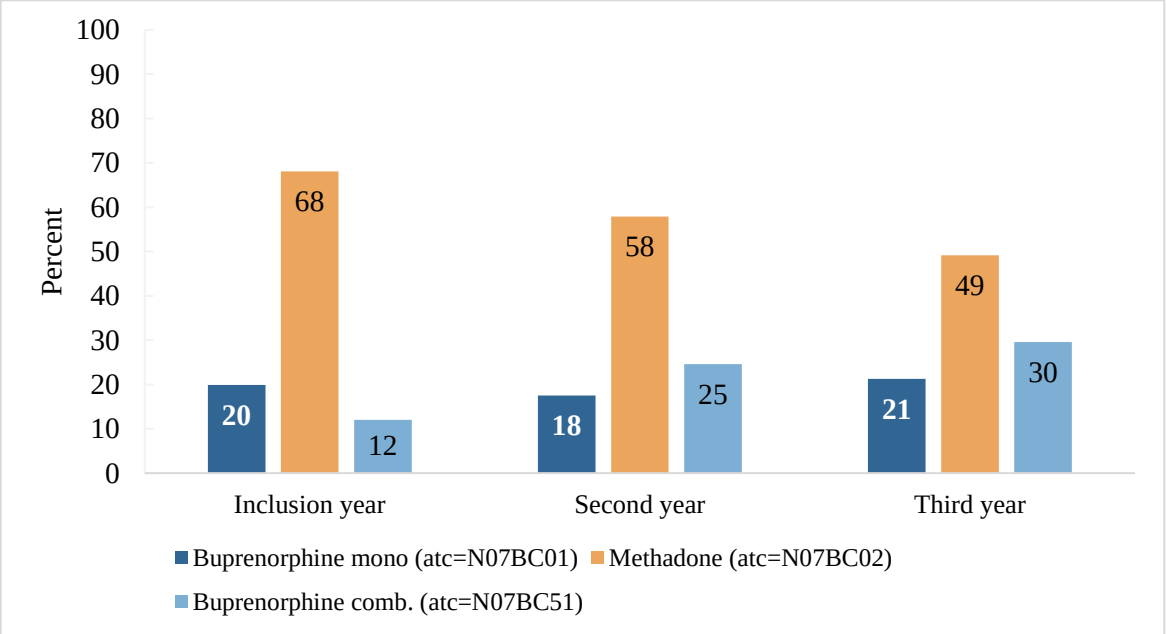

Figure 23. *Percentage of expedition of a prescription for each drug out of the total number of expeditions of a prescription for the three study medications. Data from the Prescribed Drug Register (PDR) for the stable LARO population (n=339).*

5. Discussion

The overall objective of this study was to analyse treatment pathways for people with opioid dependence enrolled in programs at LARO clinics. We investigated the use of healthcare resources, pharmaceutical use and contacts with social services. Firstly, we studied the development over time from the inclusion of LARO clinics in the choice of care reform in Region Skåne in 2014 until 2017. Secondly, we studied patterns during the first year of LARO treatment for persons admitted in LARO treatment programmes.

The study was based on data from the Skåne Healthcare Register (SHR) and from the National Patient Register (NPR), the National Prescribed Drug Register (NPDR) and Social Service registers at NBHW. The study population of persons with opioid dependence was retrieved from the SHR.

We identified 2 429 persons with a LARO indication during the period 2011-2017. One challenge in the study was to identify a population with continuous use of LARO in line with the three phases of LARO treatment. As LARO has a long history in the Skåne region, we knew from start that any real-world data would identify both new entrants to LARO treatment but also people with varying duration of enrolment, and retention to the programme. We have worked with empirically defined subgroups to explore treatment pathways for people in LARO treatment. The study also reports treatment patterns for people fulfilling study inclusion criteria for LARO treatment but with less regular participation or people who never use LARO-clinics but have LARO treatment at some other unit.

The SHR data on people with LARO treatment shows a median age of 36 years for men and 37 years for women (**Table 6**) at inclusion, which was somewhat below the general population median 39.5 years for men and 41.7 years for women. In the LARO population in this study, the proportion of men was 70 percent, which is in line with the overall LARO population in Sweden (9). However, other studies from Region Skåne with selected population subgroups have shown that the proportion of men varies from 50 to 80 percent (9).

Our longer-term follow-up data matches earlier findings underlining the heterogeneity of the group eligible for starting LARO treatment. Previous studies have created subgroups based on adherence to the LARO program itself; and found that a third of the people who start the program are successful in adherence, just under a third were unable to meet criteria for starting LARO treatment and the remainder had issues with side use of other substances as well as compliance and motivation (9, 10). One study analysed the LARO programme contents and found that a one-sided focus on the drug treatment itself and too little on the rehabilitation lead to reduced treatment success as measured by retention (9).

Since the introduction of the choice of care in Region Skåne, both the number of LARO clinics and the number of people in LARO programmes have increased. In 2013, there were eight LARO clinics (of which one private) in Skåne (3) and in 2017 there were according to registration in the SHR 18 LARO clinics (of which 11 private). During the same period the number of patients in LARO treatment increased from 1 289 to 1 654 (28 percent). The number of people in LARO treatment has increased for a longer period from 2009 onwards (3). However, our data are in line with previous studies from the area highlighting the increased supply and, the increased access to LARO has generated around 300 people initiating LARO each year, but also that the trend may be declining somewhat. It was beyond the scope of the current study to analyse whether this decline reflects lack capacity to meet need or if the waiting queue has been reduced. After the choice of care, there has been a stronger annual increase in the number of people in LARO treatment, which our data and data produced in other reports show (5).

With the extension of LARO, waiting times were significantly reduced (5). Waiting times have remained shorter, although they may occur at different clinics (personal communication with Region Skåne). According to the KEFU report, it is believed that after the introduction of the Choice of healthcare reform-"Vårdval LARO", Skåne is at about the same level as the rest of the country regarding opioid abusers treated with LARO (5). Furthermore, the KEFU report shows that the improved accessibility to LARO appears to have primarily benefited people with opioid dependence who have more complex needs (5).

In our data we observed that the number of LARO clinic visits per year per person with LARO treatment increased over the study period (**Table 8**). While our data may be incomplete in coverage of true LARO visits in the first quarter of 2014 and therefor underreport the true number of visits produced, we observed a continuous increase in the number of annual visits in years 2015-2017 where registration should be complete. An average increase of visits by 8 percent (107 to 116) was noted from 2015 to 2017 with similar increases in Group 1 and Group 2. This pattern may be expected on the aggregate level with around 300 new entrants to LARO treatment each year who according to LARO Phase 1 programme should have daily visits to the LARO clinic. For example, this explanation matches the observation that Group 1 had 133 entrants to LARO treatment in 2016, but only 79 entrants in 2017, and we observe that most of the increase in mean number of visits was between 2015 and 2016. Interestingly, the mean number of visits remained high despite a lower number of new entrants in 2017. A second explanation for increasing mean number of visits would be increasing treatment success as measured by increased retention in the LARO programme.

An analysis of the type of healthcare personnel shows that the proportion of team visits (excluding involvement of a physician) increased during the period while the proportion of nurse visits (i.e. single personnel category visits) decreased. A team visit means that the person visiting the LARO clinic has contacts with more than one type of healthcare personnel. For example, medication

retrieval can be combined with psychological treatment or treatment of somatic healthcare needs (according to the accreditation conditions). It is difficult to systematically study the content of the different visits based on SHR as many visits lack registration of a KVÅ code (code of action). Of the visits that contained a code of action, most of the visits involve monitoring of drug intake or medication prescription. Then followed "other specific investigation" and "systematic psychological treatment". Interestingly, our data pointed at a higher number of completed neuropsychiatric examinations compared to an earlier study in Region Skåne (5), although it varied between years with 97 such examinations completed in 2016 compared to 66 in 2017.

However, the overall shift in healthcare treatment pattern in terms of a larger proportion of team visits over time may indicate a quality improvement in the LARO treatment as more types of healthcare personnel seems to be involved in treatment. These register data observations do not allow deeper analyses into the type and extent of interaction during team visits. Furthermore, it does not say if there have been any changes in principles for labelling visits to LARO clinics over time or practices across health care units. Other research methods are needed to further explore such aspects of the quality in delivery of LARO treatment.

When it comes to the type of clinic, there is a difference between public and private LARO clinics in terms of both the number of visits and the type of intervention. Our results are in line with earlier observations in a report published in 2015, one year after the inclusion of LARO clinics in the Choice of healthcare provider-“Vårdval LARO” (5). According to our analysis of the LARO treatment patterns over time, the number of visits per patient to private LARO clinics seems to have been higher compared to public clinics all years 2014- 2017. In 2017, each patient at a private LARO clinic made an average of 127 visits compared to 93 at public LARO clinics. Furthermore, a comparison of registered KVÅ codes at public and private clinics seems to indicate that the latter account for a larger proportion of visits with content as other specific investigation" and "systematic psychological treatment". They also have more registrations of completed neuropsychiatric examinations. Out of the total number of registrations of completed neuropsychiatric examinations 2017-2016 (n=233), 80 percent was registered at private LARO clinics.

The central part of the LARO treatment is the drug treatment for opioid dependence and as mentioned earlier it can be divided into three phases (see Section 1.1 LARO treatment in a Swedish context). During the first three months, drug treatment is monitored and done at daily visits in what is sometimes labelled a stabilization phase. Thereafter, treatment can be prescribed with a progressively increased individual responsibility during a rehabilitation phase based on the treating physician's assessment of progress and potential. Patients who have reached a certain level of rehabilitation as assessed by the clinic may gradually move on to the third treatment phase, the so-called pharmacy phase, when the patient himself retrieves the drug from a pharmacy. In this phase, the contacts and follow-up visits with the LARO clinic are expected to decrease.

Our data showed that the context with increasing level of central purchases of LARO treatment medications may counteract the third phase intentions in LARO treatment. Although other aims may motivate central purchases, it may introduce difficulties for the transition to an independent stage involving buying opioid dependence medication at the pharmacy. Instead we observed a general trend over the years towards greater proportion of study medications distributed in clinics compared to pharmacies (Figure 12 on page 32). Thirty-five percent of the total number of persons in our LARO population had a registration of a filled prescription of the study medications in PDR. The proportion with a filled prescription was highest (50 percent) in the group of persons with a LARO indication in a non-LARO clinic but a visit to a LARO clinic 2014-2017 (Group 2) which may be associated with a higher proportion in this group with ongoing LARO treatment than the other study groups.

There are several reasons for the shift from purchases of study medications at pharmacies. First, advantageous procurement has lowered the prices for drugs administered directly at a healthcare unit. Second, there is a central cost responsibility which means that an individual LARO clinic is not responsible for the costs of the study medications by either line of distribution. From a healthcare budget perspective, LARO clinics had no incentive to favour a switch to pharmacy-based distribution. Third, it has been argued that some LARO clinics express a desire to keep treatment continuity and to continue with medication management at the clinic instead of shifting over to prescriptions (3). Fourth, from the private individual budget perspective, the system with co-payment subject to high-cost ceiling for prescription drugs imply that medication costs are lower for the opioid dependent person if he or she receives the drug as part of visits through the clinic and free of charge.

In accordance with the National Board of Health and Welfare's national guidelines the recommended study medications for new patients in LARO treatment is buprenorphine in combination with naloxone. The results from this study however show that the most common study drug over the years is methadone, and its use seems to be increasing. The NBHW first line recommendation is stable over time without tendencies of increase. One reason for the large percentage use of methadone is habits and tradition in LARO treatment. Further there may be medical reasons for not switching persons in stable treatment on methadone to another substance (personal communication with Indivior). For this report we had access to aggregate use by public and private LARO clinic, and it did not allow for a breakdown between old and newly established LARO clinics. Previous studies have reported a higher use of methadone among those with ongoing LARO treatment since long. In line with this, we observed that public clinics seemed to increase use of methadone over the study years while private clinics increased use of buprenorphine mono. The use of buprenorphine in combination with naloxone remained as third alternative throughout the study years for both public and private LARO clinics. The data available to this study did not allow for further description of patterns at the individual level and we cannot say whether the change in average doses are the results of general changes similar in all people with LARO treatment or if results are driven by subgroups with larger changes.

The second part of this study investigated the healthcare and drug treatment patterns during the first year in LARO treatment using persons included in Group 1 (n=700), as this group was expected to have all LARO treatment provided by designated LARO clinics. Group 1 was stratified by patterns of regularity of visits: a stable population with visits each month for first year and an irregular population with at least one month without visits during the first 12 calendar months. The results based on data from SHR showed that 339 patients (48 percent) were stable LARO users during the during the first 12 months of treatment. The stable LARO population received on average (median) 218 visits during their first year in LARO treatment ranging from over 20 visits during the first four months to around 11 during the last three months of a 12-month period. This indicated a decrease in treatment contact and a shift to a rehabilitation phase.

In the study we showed that among those who were possible to follow up until two years after LARO entrance, 92 percent remained in treatment after 18 months and 72 percent remained in treatment after 24 months (Figure 19). An important outcome measure for LARO success is retention measured as the percentage of people who remain in treatment compared to the number who started LARO. This is an important quality measure when evaluating LARO and comparing activities between different clinics (3). A previously report on LARO showed an increased retention after the introduction of Choice of healthcare provider – "Vårdval LARO", particular among people in LARO with comorbidities and lateral abuse. For this group of LARO people the retention after one year was 80 percent in 2014 and 83 percent in 2015 (5).

Our data showed that persons included in Group 1 also visited non-LARO healthcare during their first year of LARO. More than 40 percent in both the stable and the irregular populations used non-LARO psychiatric care during this period, and those who did had on average 5.6 and 4.6 visits respectively. This result indicates a psychiatric comorbidity in the LARO population that is handled outside the LARO clinic. Other reports on people in LARO treatment confirm this presence of comorbidities, both psychiatric problems, such as depression, psychoses, neuropsychiatric disabilities, but also somatic problems (3, 9). One report emphasizes the need for dental care in this group as poor dental status can be an obstacle to full rehabilitation (9).

In conclusion, this report shows that LARO has increased in volume over time with more people gaining access to treatment and with more visits per individual. However, the increasing level of central purchases of LARO treatment medications may counteract the third phase (pharmacy phase) intentions in LARO treatment. In addition, the report also indicates a quality improvement in the provision of LARO treatments as more types of healthcare personnel seems to be involved in treatment.

6. References

1. World Health Organization (WHO). Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. https://www.who.int/substance_abuse/publications/drugs/en/: 2009.

2. Centers for Disease Control and Prevention (CDC). Module 5: Assessing and Addressing Opioid Use Disorder (OUD). https://www.cdc.gov/: Centers for Disease Control and Prevention (CDC), [cited 2020 2020-01-28]. Available from: https://www.cdc.gov/drugoverdose/training/oud/accessible/index.html.

3. Andersson L, Johnson B. Vårdval LARO, en målorienterad intresseutvärdering ["Patient Choice LARO" in Region Skåne: an Evaluation from the Perspective of Different Stakeholders]. Malmö University, 2017.

4. Socialstyrelsen [The National Board of Health and Welfare]. Kartläggning av verksamheter som bedriver läkemedelsassisterad behandling vid opiatberoende [Mapping of units offering drug assisted treatment for opioid dependency]. www.socialstyrelsen.se: Socialstyrelsen, 2015.

5. KEFU [Radet för Kommunalekonomisk Forskning och Utbildning]. Vårdvalets och ersättningsmodellens effekter för Läkemedelsassisterad rehabilitering vid opiatberoende (LARO) [The reimbursement effects for Pharmaceutically Assisted Treatment or Rehabilitation for Opioid Dependence in Region Skåne]. KEFU Skåne, 2015.

6. Socialstyrelsen [The National Board of Health and Welfare]. Uppföljning av föreskrifter och allmänn råd om läkemedelsassisterad behandling vid opioidbereonde (LARO) [Evaluation of regulations concering Pharmaceutically Assisted Treatment or Rehabilitation for Opioid Dependence]. www.socialstyrelsen.se: Socialstyrelsen, 2017.

7. Socialstyrelsen [The National Board of Health and Welfare]. Nationella riktlinjer för vård och stöd vid missbruk och beorende [National gudielines for care and support in the treatment of drug abuse and dependency]. www.socialstyrelsen.se: Socialstyrelsen, 2017.

8. Socialstyrelsen [The National Board of Health and Welfare]. Nationella riktlinjer för vård och stöd vid missbruk och beroende. Stöd för styrning och ledning [National guidelines for health care and support for abuse and dependence]. www.socialstyrelsen.se: 2019.

9. Nilsson LH. Medecinsk utvärderingen Vårdval LARO, Region Skåne [Medical Evaluation of LARO in Region Skåne]. Region Skåne, 2017.

10. Kakko J, Gronbladh L, Svanborg KD, von Wachenfeldt J, Ruck C, Rawlings B, et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. The American journal of psychiatry. 2007;164(5):797-803.

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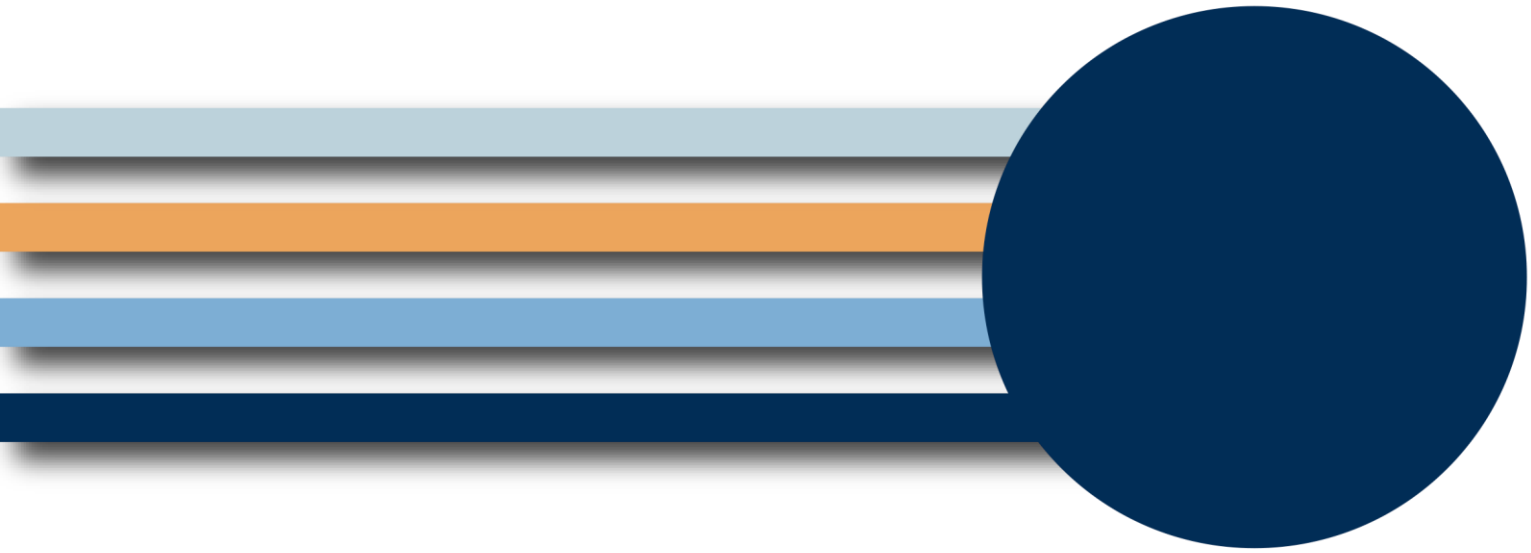

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