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**CONCEPT SHEET: REGIONAL ANALYSES**

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| **Steering Group approval date:** | *N/A* |
| **Tracking number:** | *SA254* |
| **Title:** | Management of opioid use disorder in private sector care in South Africa: a cohort study |
| **Lead author:**  **Email:** | Mpho Tlali  mpho.tlali@uct.ac.za |
| **IeDEA senior investigator:**  **Email:** | Andreas Haas  andreas.haas@ispm.unibe.ch |
| **Type of c0ncept** | *Select as appropriate:*  New concept – no linked conference abstract  New concept – linked to conference abstract which **has not been** approved by SG  New concept – linked to conference abstract which **has been** approved by SG  Existing concept – major revisions requiring SG approval |
| **Type of study** | *Select as appropriate:*  Full research study – multiple sites  Full research study – single site  Study protocol  Fast track study using existing dataset  Mathematical or methodological modelling *(indicate if this will use IeDEA-SA data)*  Systematic review |
| **Statisticians:**  **Email:** | Mpho Tlali & Andreas Haas  mpho.tlali@uct.ac.za; andreas.haas@ispm.unibe.ch |
| **Data manager:**  **Email:** | Nicky Maxwell  nicky.maxwell@uct.ac.za |
| **Where will statistical analyses be done?** | University of Cape Town and University of Bern |
| **Required variables:** |  |
| **Target journal:** | *Epidemiology and Psychiatric Sciences, International Journal of Drug Policy, Harm Reduction Journal, PLOS Global Public Health* |
| **Ethics:** | *Select as appropriate:*  This concept uses only the IeDEA-SA standard dataset and is covered by the core IeDEA-SA ethics approvals.  This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA-SA standard dataset. Additional ethics approval is required.\* (Describe ethical considerations for any additional data collection here, including responsible IRBs.) |
| **Milestones:** | *Circulation of concept sheet: <date>*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background**  Opioid use disorder is a chronic, relapsing, but manageable medical condition. In 2018, the estimated global prevalence of opioid use was 1.2% in adults aged 15-64 years. South Africa is experiencing a rapid increase in opioid use. This study examines the management of opioid use disorder among beneficiaries of a private-sector medical aid scheme in South Africa.  **Methods**  For this cohort study, we will analyse insurance claims of beneficiaries aged 11 years or older of a South African medical aid scheme, covering the period from Jan 1, 2011, to Jul 1, 2020. We classify beneficiaries as having problematic opioid use if they received opioid agonists (buprenorphine or methadone), were diagnosed with an opioid use disorder, or had opioid poisoning. We will calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for factors associated with the incidence of problematic opioid use, opioid use disorders, and opioid agonist therapy initiation using Cox proportional hazards models. We will estimate the cumulative incidence of opioid agonist use for detoxification (no opioid agonist refill within 35 days), initiation of opioid agonist therapy initiation (opioid agonist refill within 35 days) and retention on opioid agonist therapy (refill at least every 35 days) using the Aalen-Johansen and Kaplan-Meier estimator.  **Objective**  1. To examine sociodemographic and clinical characteristics associated with problematic opioid use, opioid use disorder, opioid agonist use, and opioid agonist therapy  2. To estimate the cumulative incidence of opioid agonist, use for detoxification and initiation of opioid agonist therapy after opioid use disorder diagnosis  3. To examine retention on opioid agonist therapy  4. To quantify excess mortality in opioid use disorder |
| **Outline:** (about 1000 words) | Background  Opioid use disorder is a leading cause of the global burden of disease, accounting for 70% of the burden from drug-related causes (1). In 2018 the estimated global prevalence of opioid use was 1.2% in adults aged 15-64 years (1). In South Africa, data on opioid use is limited. In 2010, the prevalence of opioid use in adults was estimated at 0.5% (2). Data from drug treatment centres and health surveys in the country suggest a growing problem signified by a rapid increase in opioid use across many provinces (3–5). The emergence of cheaper “street” heroin derivates largely accounts for the surge in opioid use in the country and across sub-Saharan Africa (SSA) (6). Over-the-counter prescription opioids (OTC), such as codeine and tramadol, are also commonly misused in many SSA countries (7). In South Africa, 2% of adults report nonmedical use of codeine (8).  In South Africa, the average age of individuals treated for opioid use disorders is around 30 years (3–5). Men make up more than three-quarters of individuals treated for opioid use disorder in South Africa (3,5). However, opioids are also the most common illicit drug used by women (3,9). Over half of the individuals treated for opioid user disorder identify as Black or African, and just over a quarter (26%) have mixed ancestry. The Gauteng and the Western Cape provinces appear to be the opioid use hotspots in South Africa: 38.9% and 26.6% of the admissions for opioid use disorders occurred in these two provinces (5).  Opioid use disorder commonly co-occurs with other mental health and substance use disorders. Among people treated for opioid use disorder, the rate of mood disorders, posttraumatic stress disorders, and personality disorders has been reported as high as 52% (10,11) Co-morbid use of methamphetamine was reported in 52% of people treated for opioid use disorder (10).  Opioid agonist therapy is a safe and effective treatment for opioid use disorder (12–14). Retention on opioid agonist therapy is associated with optimum dosage of therapy, female gender, high education, older age (greater than 35 years of age) and access to free opioid agonist therapy (15,16). The benefits of treatment include reduced use of illicit opioids and other substances, reduced morbidity and mortality from infectious diseases, and improved social functioning (15,16). Opioid agonist therapy is not available in South Africa’s public health care sector, despite the strong evidence supporting its use and benefits. Most opioid users access their care from private sector medical insurance schemes (16,17). Self-funded care, government-supported civil societies and academic institutions make up the remainder (16,17).  Mortality rates for opioid users in South Africa are high (18). Drug overdose, violence, suicide, and infectious disease complications are important causes of mortality in opioid users (18).  This analysis aims to examine the management of opioid use disorder in private sector care in South Africa.  Objectives  1. To examine sociodemographic and clinical characteristics associated with problematic opioid use, opioid use disorder, opioid agonist use, and opioid agonist therapy  2. To estimate the cumulative incidence of opioid agonist, use for detoxification and initiation of opioid agonist therapy after opioid use disorder diagnosis  3. To examine retention on opioid agonist therapy  4. To quantify excess mortality in opioid use disorder  Study design  In this cohort study, we will analyse outpatient, hospital, and medication claims of beneficiaries of a South African medical aid scheme, covering the period from Jan 1, 2011, to Jul 1, 2020, and data of the vital status of beneficiaries from the National Population Register, covering the period from Jan 1, 2011, to Jan 26, 2021. Outpatient and hospital claims contain International Classification of Diseases, 10th Revision (ICD-10) diagnoses. Pharmacy claims contain drug names, drug classifications (Anatomical Therapeutic Chemical [ATC] code), drug strength, the dispensed amount, and the date of claim.  **Eligibility criteria**  • Individuals (≥ 11 years) enrolled in the private insurance program with health care coverage between 2011 and 2021.  **Key Variables**  • Sociodemographic characteristics: age, sex, population group (Indian/Asian, Black African, White, Mixed)  • ICD10 diagnoses from medication claims, outpatient claims and hospital claims  • Medication claims: table: treatment date, quantity, ATC code  • Mortality: Data on the vital status of beneficiaries collected by the medical aid scheme will be updated by the National Population Register data. The National Population Register classified the underlying cause of death as unnatural (ICD-10 codes V01–Y99), natural (death due to natural disease per the ICD-10), unknown, or under investigation.  **Definitions**  We define baseline as beneficiaries’ date of enrolment with the medical aid scheme, Jan 1, 2011, or their 11th birthday, whichever occurs last. We will classify beneficiaries as having opioid problems if they received opioid agonists used in drug dependence (buprenorphine [ATC code N07BC01], or methadone [ATC code N07BC02]), were diagnosed with an opioid use disorder (ICD10 code F11), or with opioid poisoning (ICD 10 code T40.0, T40.1, or T40.3). Substance use disorders (F10-F19) will be classified as alcohol use disorder (F10), opioid use disorder (F11), multiple drug use disorder (F19), or other substance use disorders (F12-F18). Mental health disorders (F00-F09, F20-F99) will be classified as serious mental disorders (F20-F29, F31), depression (F32, F33, F34.1, F54), anxiety disorders (F40-48), or other mental disorders (F00-F09, F50-F99). Infectious diseases and infections will be grouped into HIV (B20-24), hepatitis C virus (B17.1, B18.2), tuberculosis (A15-A19) and infective endocarditis (I33.0). Beneficiaries who refill opioid agonists within 35 days of their first claim will be considered as initiating opioid agonist therapy. Beneficiaries who refill opioid agonists at least every 35 days will be considered to be retained on opioid agonist therapy.  Statistical analysis:  We will follow beneficiaries from baseline to the end of their health care plan or the outcome of interest (whichever occurs first). We will estimate unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for factors associated with problematic opioid use, opioid use disorder diagnosis, opioid agonist use, and opioid agonist therapy initiation using Cox proportional hazards models. Variables considered in univariable, and multivariable analyses include year, sex, age group, population group, serious mental disorders, depression, anxiety, other mental disorders, alcohol use disorders, and other substance use disorders. Age group, year, and mental and substance use diagnoses will be modelled as time-varying covariates. To estimate the cumulative incidence of opioid agonist therapy initiation after opioid use disorder diagnoses, we will follow persons from opioid use disorder diagnosis to initiation of opioid agonist therapy, death or the end of follow-up. Mortality will be considered as a competing event (19,20). We will assess retention on opioid agonist therapy initiation using the Kaplan-Meier method. To quantify excess mortality, we will estimate the excess life years lost (ELYLs) in opioid use disorders (21–24). ELYLs in opioid use disorders measure the average reduction in life expectancy in people with opioid use disorders compared to the general population (21–24). ELYLs will be calculated for all causes of death, natural and unnatural causes of death, and stratified by sex. The analysis will be done in R using the package lillies (25), and 95% confidence intervals (CIs) will be estimated using parametric bootstrapping (24).  **Sample size calculations:**  Preliminary analysis of data from the private care medical scheme identified 1313 patients as having problematic opioid use.  **References:**  1. United Nations Office on Drugs and Crime. The world drug report [Internet]. United Nations publication. 2020. 1–4 p. 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\* If additional ethics approvals are required, a copy must be sent to the ISPM Program Manager before data collection can begin.