Opioid agonist maintenance treatment outcomes : the OPTIMUS international consensus towards evidence-based and patient-centred care, an interim report

Opioid agonist maintenance treatment outcomes - the OPTIMUS international consensus towards evidence-based and patient-centred care, an interim report

Authors: Lucas Wiessing*1, Prakashini Banka-Cullen2, M Gabriela Barbaglia3, Vendula Belackova4, Saed AS Belbaisi5, Peter Blanken6, Patrizia Carrieri7, Catherine Comiskey8, Daniel Dacosta-Sánchez9, Geert Dom10, Venus Fabricius11, Hugo Faria12, Liljana Ignjatova13, Nemanja Inić14, Britta Jacobsen15, Jana D. Javakhishvili16, Zuzana Kamendy17, Máté Kapitány-Fövény18, Anna Kiss19, Evi Kyprianou20, Kirsten Marchand21, Tim Millar22, Viktor Mravcik23, Naser J.Y Mustafa24, Carlos Nordt25, Markus Partanen26, Mads Uffe Pedersen27, Hanna Putkonen28, Mariam Razmadze29, Perrine Roux30, Bernd Schulte31, Paulo Seabra32, Luis Sordo33, Lisa Strada34, Emilis Subata35, Esmeralda Thoma36, Marta Torrens37, Alexander Y. Walley38, Ioanna Yiasemi39, for the OPTIMUS** study group.

Affiliations and contact details:

[1] Lucas Wiessing PhD, Public Health Unit, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal. <lucas.wiessing@emcdda.europa.eu> +351-969786080 ; [2] Prakashini Banka-Cullen PhD, Trinity College Dublin, School of Nursing and Midwifery, 24 D'Olier St., Trinity College, Dublin, Dublin 2, Ireland. <sonam.banka@tcd.ie> ; [3] María Gabriela Barbaglia MD, PhD, Public Health Agency of Barcelona, Drug dependence prevention and care service, Barcelona, Plaça Lesseps 1, CP: 08023, Barcelona, Spain. <mgbarbag@aspb.cat> ; [4] Vendula Belackova PhD, University of New South Wales, Arts, Design & Architecture, Social Policy and Research Centre, ; John Goodsell Building (F20), Library Rd, UNSW Sydney, Kensington NSW 2052, Australia. <vendulabelackova@gmail.com> ; [5] Saed A.S. Bilbeisi MSD, Palestinian Ministry of Health, Al Ersal Street, Ramallah, Palestine. <drsaed2005@gmail.com> ; [6] Peter Blanken PhD, Parnassia Addiction Research Centre (PARC), Brijder Addiction Treatment, Parnassia Academy, The Hague, The Netherlands. Zoutkeetsingel 40, 2512 HN The Hague, The Netherlands. <Peter.Blanken@brijder.nl> ; [7] Patrizia Carrieri, Aix Marseille Univ, Inserm, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de ; l'Information Médicale, ISSPAM, 27, Bld Jean Moulin, 13385, Marseille, France. <pmcarrieri@aol.com> ; [8] Catherine Comiskey PhD, Trinity College Dublin, School of Nursing and Midwifery, 24 D'Olier St., Trinity College, Dublin, Dublin 2, Ireland. <catherine.comiskey@tcd.ie> ; [9] Daniel Dacosta Sánchez PhD, Department of Clinical and Experimental Psychology. University of Huelva. Avda. Fuerzas Armadas s/n. Huelva. CP: 21071, Spain. <daniel.daco@dpces.uhu.es> ; [10] Geert Dom PhD, University of Antwerp, Universiteitsplein 1 2610, Wilrijk, Antwerp, Belgium. <geert.dom@uantwerpen.be> ; [11] Venus A. V. Fabricius MSc, Centre for Alcohol and Drug Research, Department of Psychology, University of Aarhus, Bartholin Allé 10, building 1322, DK 8000 Aarhus C, Denmark. <vavf.crf@psy.au.dk>; [12] Hugo JA Faria Lic., Ares do Pinhal, Rua José Inácio Andrade lt 2 lj 10 B, 1900-418 Lisboa, Portugal. <hugo.faria@aresdopinhal.pt> ; [13] Liljana Ignjatova PhD, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine-Skopje, North Macedonia, Professor, str. „50 Division" N. 6, 1000 Skopje, North Macedonia. <liljana.kiteva.ignjatova@medf.ukim.edu.mk> ; [14] Nemanja Inić, Special Prison Hospital, Belgrade, dept for drug and alcohol addictions, Bačvanska 14a, Belgrade, Serbia. <inic.nemanja@gmail.com> ; [15] Britta Jacobsen, Centre for Interdisciplinary Addiction Research (ZIS), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246, Hamburg, Germany. <Jacobsen@zis-hamburg.de> ; [16] Jana D. Javakhishvili PhD, Professor in Psychology, Institute of Addiction Studies, Ilia State University, Tbilisi, ⅗ Cholokashvili ave, 0162 Tbilisi, Georgia. <darejan.javakhishvili@iliauni.edu.ge> ; [17] Zuzana Kamendy, Centre for Treatment of Drug Dependencies, Bratislava, Slovakia; PAN-EUROPEAN University, Faculty of Psychology, Bratislava, Slovakia. <kamendy@cpldz.sk> ; [18] Máté Kapitány-Fövény, 1) National Institute of Mental Health, Neurology and Neurosurgery - Drug outpatient centre, Lehel utca 59., Budapest, H-1135. 2) Semmelweis University Faculty of Health Sciences, Budapest, Hungary, Vas utca 17., Budapest, H-1088, Hungary. <m.gabrilovics@gmail.com> ; [19] Anna Kiss, National Institute of Mental Health, Neurology and Neurosurgery - Drug outpatient centre ; Lehel utca 59., Budapest, H-1135, Hungary. <pszichologus@kiss-anna.hu> ; [20] Evi Kyprianou MSc, Monitoring Centre, Cyprus National Addictions Authority, 35 Iosif Hadjiosif and Andreas Avraamides, 1st floor, 2028 Strovolos, Nicosia, Cyprus. <evi.kyprianou@naac.org.cy> ; [21] Kirsten Marchand, Centre for Health Evaluation and Outcome Sciences, Providence Health Care and University of British Columbia, Vancouver Canada. 588-1081 Burrard Street, Vancouver, BC, Canada, V6Z 1Y6. <kmarchand@cheos.ubc.ca> ; [22] Tim Millar, Professor of Substance Use, Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester. Ellen Wilkinson Building, University of Manchester, Oxford Rd, Manchester, M139PL, UK. <tim.millar@manchester.ac.uk> ; [23] Viktor Mravcik MD, PhD. 1) Department of Addictology, 1st Medical Faculty and General University Hospital in Prague, Charles University. Apolinářská 447/4 120 00 Prague. 2) NGO Spolecnost Podane Ruce, Hilleho 1842/5, Cerna Pole, 602 00 Brno, Czech Republic. <viktor.mravcik@lf1.cuni.cz> ; [24] Naser JY Mustafa MSD, Palestinian Ministry of Health, Al Ersal Street, Ramallah, Palestine. <naltarifi@gmail.com> ; [25] Carlos Nordt PhD, Centre for Addictive Disorders,

Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, Postfach 1931, 8032 Zürich, Switzerland. <carlos.nordt@bli.uzh.ch>; [26] Markus Partanen, A-Clinic Ltd, Addiction services, Outpatient clinics, Ajurinkatu 2, 2nd floor, 20100 Turku, Finland. <markus.partanen@a-klinikka.fi>; [27] Mads U. Pedersen, PhD professor, Centre for Alcohol and Drug Research, Department of Psychology, University of Aarhus, Bartholin Allé 10, building 1322, room no 214, DK 8000 Aarhus C, Denmark. <mup@crf.au.dk> ; [28] Hanna Putkonen, Health Care Services for Prisoners (VTH), c/o National Institute for Health and Welfare (THL), P.O. Box 30, 00271 Helsinki, Finland. <hanna.putkonen@vth.fi> ; [29] Mariam Razmadze MA, Institute of Addiction Studies, Ilia State University, Tbilisi, ⅗ Cholokashvili ave, 0162 Tbilisi, Georgia. <mariam.razmadze.3@iliauni.edu.ge> ; [30] Perrine Roux, Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, ISSPAM, 27, Bld Jean Moulin, 13385, Marseille, France. ; [31] Bernd Schulte, Centre for Interdisciplinary Addiction Research (ZIS), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246, Hamburg, Germany. <b.schulte@uke.de> ; [32] Paulo R.C. Seabra PhD, Nursing School of Lisbon, ESEL, Av. Prof. Egaz Moniz, 1600-190 Lisboa, Portugal. <pauloseabra@esel.pt> ; [33] Luis Sordo. Public Health Department. Faculty of Medicine. Complutense University (Madrid). CIBER in epidemiology and Public Health (CIBERESP). Plaza Ramón y Cajal s/n, 28040 Madrid, Spain. <lsordo@ucm.es> ; [34] Lisa Strada PhD, Trimbos Institute, Department Drugs, Utrecht. Da Costakade 45, 3521 VS Utrecht, Netherlands. <LStrada@trimbos.nl> ; [35] Emilis Subata PhD, National Center for Addictive Disorders, Vilnius, Gerosios Vilties 3 LT-03147 Lithuania. <emilis.subata@rplc.lt> ; [36] Esmeralda Thoma PhD, University Hospital Center"Mother Teresa"/University of Medicine of Tirana/Tirane-Albania, Rruga e Dibres:1005 Tirane, Albania. <esmeraldahoxha@yahoo.com> ; [37] Marta Torrens PhD Professor, Addiction Program - Hospital del Mar, University of Vic-Central Catalonia, UAB Pg Maritim 25-29, 08003 Barcelona, Spain. <mtorrens@psmar.cat> ; [38] Alexander Y. Walley MD, MSc, Grayken Center for Addiction, Clinical Addiction Research and Education Unit, Boston Medical Center and Boston University Chobanian & Avedisian School of Medicine, 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02459, USA. <awalley@bu.edu> ; [39] Ioanna Yiasemi, Monitoring Centre, Cyprus National Addictions Authority, 35 Iosif Hadjiosif and Andreas Avraamides, 1st floor, 2028 Strovolos, Nicosia, Cyprus. <ioanna.yiasemi@naac.org.cy>

* **Corresponding Author**: Lucas Wiessing PhD, Principal Scientist
Public Health Unit, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Address: Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal.
Email: <lucas.wiessing@emcdda.europa.eu> Phone: +351-969786080

** **OPTIMUS**: OPioid Treatment outcomes Interview for Maintenance medication USers (See list of names of the full study group in Annex 1, Part A of the online appendix)

Running head: Assessing opioid maintenance treatment outcomes

Acknowledgements: See Annex 1 in online appendix

Conflict of Interest Statement: none declared

Funding Sources: none declared

Author Contributions: LW - coordination project, drafting consensus protocol, drafting manuscript. All authors - participation in live and online consensus meetings, comments on multiple draft versions of the consensus protocol, comments on multiple draft versions of this manuscript and approval of the final version.

Number of Tables: 1 (Box)

Number of Figures: 0

Word count: 3257 (abstract 170)

Number of references: 96

Opioid agonist maintenance treatment outcomes - the OPTIMUS international consensus towards evidence-based and patient-centred care, an interim report

Abstract

Non-medical opioid use is a major public health concern causing high mortality. While opioid agonist maintenance treatment (OMT) is a key life-saving intervention, there is a) no international consensus on opioid treatment outcomes, b) few opioid treatment outcome studies include key (public) health outcomes, such as overdose or HIV/hepatitis C. We report the rationale and study protocol for, and preliminary results of, an on-going international OMT outcomes consensus study that aims to address this double gap (n=110 collaborating experts from 32 countries, plus a n=477 Delphi evaluation panel from 26 of those countries: 58% male - 41% female; 47% OMT patients - 53% OMT professionals). We present a first draft of a patient interview guide (including a 'clinical form') to monitor OMT outcomes in six domains. The form appears to be well accepted and feasible in early testing. Through this we aim to enhance the quality of and access to OMT, and improve the survival, health and quality of life of people who use opioids, while promoting non-stigmatising patient-physician relationships.

Mortality due to non-medical opioid use is high and varies geographically

Non-medical opioid use and opioid use disorders continue to result in an unacceptably large number of deaths. Worldwide, about 600 000 deaths were attributable to drug use in 2019. Close to 80% of these deaths were related to opioids, with about 25% of those deaths caused by overdose (UNODC, 2022; World Health Organization, 2023; Vos et al., 2020). Mortality rates due to overdose (direct drug-related deaths) vary greatly between countries and regions, in part due to underlying variations in the prevalence of high-risk drug use and the toxicity of the drug supply (e.g. the integration /contamination of fentanyl into the heroin and counterfeit prescription pill supply) (Mattson et al., 2021; Degenhardt et al., 2019; Millar & McAuley, 2017). For example, while the European Union reported 14.8 deaths due to drug overdose per 1 million population aged 15–64 in 2019, the United States reported an age-adjusted mortality of 216 per 1 million population for the same age group in the same year (UNODC, 2022).

A higher uptake of evidence-based OMT could save lives and improve health

Many opioid-related deaths are preventable, and long-term uninterrupted opioid agonist maintenance treatment (OMT) would need to play a far greater role in this. There is compelling evidence that uninterrupted and adequately dosed OMT (such as with methadone, buprenorphine, slow-release morphine, etc.) strongly reduces (with up to 3-6 times) the risk of death in people who use opioids (PWUO) (McAuley et al., 2023; Santo et al., 2021; Bogdanowicz et al., 2018; Sordo et al., 2017; Pierce et al., 2016; Mathers et al., 2013; Mattick et al., 2009; Bao et al., 2009; Brugal et al., 2005). However, where data are available, they suggest that many countries still have low, or even near-zero, coverage of OMT among PWUO, over two decades since the EMCDDA developed harm reduction and OMT coverage metrics that are now widely used (Harm Reduction International, 2022; Larney et al., 2017; World Health Organization et al., 2012; Mathers et al., 2010; Wiessing et al., 2009; European Monitoring Centre for Drugs and Drug Addiction, 2006, 2007; Wiessing et al., 2000). In those countries, important reductions in opioid-related mortality may be achievable, by increasing OMT coverage to internationally recommended levels of 40-50% or higher (European Monitoring Centre for Drugs and Drug Addiction, 2023; The Global Fund, 2022; UNAIDS, 2021; World Health Organization et al., 2012). Further mortality reductions might be reached by strengthening additional health and social interventions (Levengood et al., 2021; Razaghizad et al., 2021; Wiessing et al., 2021; van Draanen et al., 2020; Katzman et al., 2020).

OMT not only prevents key causes of death, including overdose, suicide, HIV, hepatitis B and C virus infections, and injuries (Ferraro et al., 2021; Pitkänen et al., 2020; Degenhardt et al., 2019; Fraser et al., 2018; Platt et al., 2018; Sordo et al., 2017; Mattick et al., 2014; Gowing et al., 2013; Mathers et al.,

2013; Allen et al., 2012; Deacon et al., 2012; MacArthur et al., 2012; World Health Organization et al., 2009; Metzger et al., 1993), but also improves health-related quality of life and reduces illicit drug use and the severity of opioid use disorder (Feelemeyer et al., 2014; Mattick et al., 2014; Farré et al., 2002; Torrens et al., 1999). It may further reduce depression (Namchuk et al., 2022; Mohammadi et al., 2020) and decrease drug-related offences and incarceration rates (Carrieri et al., 2017; Sun et al., 2015; Marsch, 1998), while overall being cost-saving (Degenhardt et al., 2019; World Health Organization, 2005). OMT has been shown to be more effective in reducing adverse events in PWUO than short-term detoxification or psychological treatment (Nielsen et al., 2022; Wild et al., 2021; Rice, 2020; Friedmann & Schwartz, 2012). Also, combining syringe programs or antiretroviral treatment with OMT has been shown to be highly effective (Platt et al., 2018; Roux et al., 2009). However, in 2021 only four countries in Europe had met the WHO-recommended coverage of at least 200 syringes per injecting user per year and 40% of PWUO in OMT (European Monitoring Centre for Drugs and Drug Addiction, 2023). Thus, increasing OMT coverage to recommended levels, or higher, in countries where these are not yet being reached, would likely have a positive impact on PWUO reaching far beyond reducing mortality.

A lack of consensus and confusion in terminology limit OMT uptake

A good understanding of the full potential impact of high-coverage OMT on the morbidity and mortality of PWUO is essential for achieving recommended levels of coverage (World Health Organization et al., 2012), including in specific subgroups, such as women or migrants (Nordt et al., 2018). However, despite the abundance of evidence, this understanding is often still partial and lacks consensus on key issues, both in the scientific literature and in policy and practice, thereby seriously hampering wider implementation of OMT (Torrens et al., 2013; Schackmanm 2010).

There is surprisingly little agreement in the scientific literature on what constitutes successful treatment of opioid disorder and what are the key indicators to evaluate patients over time (Wiessing et al., 2018). Different studies use different outcome domains and indicators to assess patient outcomes, ranging from a narrow focus on abstinence-based recovery to a broader (public health or harm reduction-oriented) approach, including health and survival, social and quality of life outcomes (Rosenberg et al., 2020; Wiessing et al., 2018). Importantly, few published opioid use disorder treatment outcome studies have considered the key health outcomes that dominate the global burden of disease due to opioid use, such as non-fatal overdose and mortality, HIV/HCV infection and their associated risk behaviours (James et al., 2018; Wiessing et al., 2018).

There is no global consensus either on what constitutes successful drug policy or treatment practice. A decades-long emphasis on repression and supply reduction is only recently showing a possible first

pivot towards evidence-based public health outcomes, while national drug policies appear not always to be evidence-based either (Interlandi, 2023; Fordham, 2022; Hamilton et al., 2022; Burki, 2019; Global Commission on Drug Policy, 2019; American Hospital Association - Legislative Advisory, 2018; Radimecký, 2007; World Health Organization, 2005). In treatment practice, even when agonist medication such as methadone or buprenorphine is used, it is too often tapered and discontinued in detoxification or residential treatments (Friedmann & Schwartz, 2012). This, despite the evidence that treatment interruptions are a major risk factor for overdose and death, and, conversely, long-term uninterrupted OMT is life-saving (McAuley et al., 2023; Santo et al., 2021; O'Connor et al., 2020; Sordo et al., 2017; Mathers et al., 2013; Mattick et al., 2009). Moreover, there is evidence that clinical practices of OMT delivery (e.g., urine screening, dosage decision-making, daily dispensing, etc) and an emphasis on clinical outcomes (e.g. abstinence) rather than patients' preferences and perceptions, may not always constitute a patient-centred practice and may impose substantial barriers to OMT engagement (Frank, 2021; Woo et al., 2017; Harris & McElrath, 2012; Anstice et al., 2009), while mental health and quality of life domains are often not addressed (Javakhishvili et al., 2021; Eurasian Harm Reduction Association, 2020).

The lack of consensus extends to the terminology being used, creating confusion and undermining the ability to even discuss the issues at stake. Historically clear WHO-endorsed and evidence-based concepts such as OST (opioid substitution treatment) or OMT are now being replaced by concepts and acronyms that combine opposite treatment approaches within one and the same term, rendering them imprecise and meaningless with regard to their life-saving properties. For example, long-term maintenance or substitution treatments with agonist medication which are evidence-based lifesaving (e.g. Sordo et al., 2017) are now often combined with short-term agonist detoxification approaches in the term 'opioid agonist treatment' (OAT), apparently following abstinence-oriented and non-evidence based arguments (Samet & Fiellin, 2015; Bøg et al., 2017). Similarly, treatments with live-saving long-term agonist medication are put together with potentially ineffective or even life-threatening antagonist medication treatments (e.g. with naltrexone) in the terms 'medication for opioid disorder' (MOUD) or 'medication assisted treatment' (MAT) (Jarvis et al., 2018; Sordo et al., 2017; Minozzi et al., 2011). (For more detail and empirical evidence from our work regarding opioid disorder treatment terminology, see the Online appendix: "Document 1a. OMT guidance Part A", p21).

The OPTIMUS international consensus on OMT outcomes

Here we report the rationale and the need for, as well as the protocol and preliminary results of, an ongoing international consensus study to define key outcomes for the monitoring of patients on OMT (The OPTIMUS study: OPioid Treatment outcomes Interview for Maintenance medication USers). We aim to promote international consensus on evidence-based treatment policies and treatment outcome indicators for PWUO and OMT by bringing together experts (professionals and patients) from as many countries as possible, including from outside Europe. We focus on patient-

reported outcomes and present a tool that aims to directly support clinical practice, encouraging a non-stigmatising patient-centred approach within an enabling and positive patient–physician relationship (Marchand et al., 2020; Seabra et al., 2018; Lions et al., 2014). With this work we hope to contribute to a much-needed global paradigm shift towards evidence-based and patient-centred opioid treatment, non-abstinence based recovery and increased survival, health and quality of life of PWUO.

We present the early version ('version 1.0') of a clinical tool to monitor and evaluate OMT outcomes based on patient-reported results (see the Online appendix, Annex 1, part B). The tool centres on a set of 26 core questions for a patient interview, organised in 6 domains and 13 indicators (see Box 1), which we suggest taking once every three months, and depending on patient needs. It functions simultaneously as an interview guide and a patient questionnaire or clinical form. Our tool is being developed by an international group of 110 OMT experts from 32 - mostly European - countries (6 outside Europe: 2 from North-America, 3 from West Asia and 1 from Oceania), including people with lived OMT experience. It incorporates 1049 open comments from an international panel of an additional 477 OMT experts from 26 countries, received during the first round (out of 2) of an on-going Delphi-method consensus study.

Box 1. The consensus list of 6 domains and 13 indicators (totalling 26 core questions)*

Domain A 'Treatment'
1. 'Treatment continuity'
   (4 core questions)
2. 'Treatment satisfaction'
   (1 core question)

Domain B 'Physical health and risks'
3. 'Physical health'
   (1 core question)
4. 'Overdose'
   (2 core questions)
5. 'Injecting drugs'
   (2 core questions)
6. 'Sharing injection materials'
   (2 core questions)
7. 'Diseases screening'
   (4 core questions)

Domain C 'Mental health'
8. 'Mental health'
   (2 core questions)

Domain D 'Social functioning'
9. 'Social support'
   (2 core questions)
10. 'Social activities'
    (1 core question)
11. 'Legal problems'
    (1 core question)

Domain E 'Substance use'
12. 'Substance use'
    (2 core questions)

Domain F 'Quality of life'
13. 'Quality of life'
    (2 core questions)

** This is work in progress and the domains and indicators may still be subject to change. See full details of the core and optional questions in the Online appendix: "Document 1b. OMT guidance Part B".*

OPTIMUS Delphi study preparation and methods

The EMCDDA has a long-standing collaboration with, and organises an annual meeting of, country representative treatment experts from the EU and neighbouring countries, to discuss drug treatment patient monitoring. (The Treatment Demand Indicator - TDI, a descriptive monitoring of patients at treatment entry for substance use disorders (European Monitoring Centre for Drugs and Drug Addiction, 2012)). Prior to the Delphi study, an email survey was sent to all TDI collaborating country experts asking them to describe any existing substance disorder treatment outcomes monitoring in their country (Wiessing, 2018b). Out of 31 countries (EU-28, plus Norway, Turkey and Kazakhstan) only 7 responded with the requested information, suggesting a) limited existence of treatment outcomes monitoring systems in these countries and, based on the 7 responses, b) a wide variation in indicators and methods used (similar to the literature review findings (Wiessing et al., 2018) mentioned above). These results were ~~discussed and as far as possible~~ confirmed in a subsequent workshop with 17 countries participating (15 EU countries plus Kazakhstan and Uzbekistan) during the 2018 TDI expert meeting (Wiessing, 2018b). ~~None of the 17 countries participating in the workshop indicated that treatment outcomes monitoring existed but had not been reported in the email survey.~~ Workshop participants were asked to prioritise domains and indicators taking account of the need for international consensus treatment outcomes monitoring with a focus on (public) health outcomes. This resulted in a 'First priority OMT health impact indicators' list: 1) Overdose and mortality /causes (outcome indicator), 2) Infectious diseases (hepatitis C) test and treat (outcome /service indicator), 3) OMT waiting time and coverage /treatment participation (affordable and including prisons) (service indicator), and a list of 'Second priority OMT health impact indicators': 4) Treatment retention (outcome /service indicator), 5) NSP coverage of PWID population including in prisons (service indicator), 6) Quality of life /health (outcome indicator) (Wiessing, 2018b). To follow-up on and further develop the results of the TDI workshop, a two-day expert meeting was held at the EMCDDA in Lisbon in early 2019, with 13 treatment experts from ten countries participating (a further 8 experts from 4 more countries - one of them with lived OMT patient experience - could not attend but contributed by email) (Wiessing, 2019). During this meeting the results of the TDI workshop were discussed and further developed, and it was agreed that a Delphi study was needed with a wider panel, composed of both professionals and patients, to evaluate and increase the representativeness and legitimacy of the findings (Wiessing, 2019).

The expert group continued working during 2019-2020 in weekly online meetings and group emails to further define the domains and indicators and prepare the Delphi study (group emails and meeting minutes are available on request). It was decided that indicators would be limited to patient-reported outcomes to maximise their relevance for patients (e.g. dropping service-level indicators, which have been covered elsewhere (HRI, 2022; Larney et al., 2017; Wiessing et al., 2017)), and that the Delphi study surveys would be translated to the national languages. A first version of domains and indicators

was finished for evaluation in the Delphi study and a study protocol was developed covering the Delphi study methods and with additional detailed instructions regarding translations and panel recruitment (see Annex 2 in the Online appendix) and medical-ethical clearances were obtained. During this period the expert group expanded and eventually covered 27 countries (at round 1 of the Delphi study). The additional countries and experts were recruited via formal invitations to the TDI expert network and through professional contacts of the existing expert group.

During 2020-2021 the Delphi panel members were invited to fill out the round 1 survey following the protocol (see Annex 2 in the Online appendix). Each country strived to invite (8-)10 professionals and (8-)10 OMT patients. Each of these two groups was to be as much as possible balanced by gender. As far as possible, professionals included at least 3 OMT medical professionals (e.g. psychiatrist, addiction doctor, general practitioner), 3 OMT health professionals (e.g. social [care] worker, councillor, nurse, outreach worker, psychologist, pharmacist), 1 public health specialist, 1 prison health professional. Professionals would also, as far as possible, be working in their field at least 5 years, cover different sectors if applicable in the country (e.g. public and private), preferably working directly with clients (with some exceptions, e.g. public health specialist), and not just in the management of the OMT organisation. Patients included were those currently in OMT, at least 18 years old, and were balanced with regard to time in OMT (about half of them less than 2 years in OMT and half of them 2 years or more in OMT). We comply with guidance on conducting and reporting Delphi studies in palliative care (Jünger et al., 2017) (see Annex 3 in the Online appendix).

Interim results and discussion

The final list of 26 countries participating in round 1 of the survey was: Albania, Belgium, Bosnia and Herzegovina, Canada, Cyprus, Czechia, Denmark, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Netherlands, North Macedonia, Palestine, Poland, Portugal, Slovakia, Spain, Switzerland, UK, Ukraine. In total the expert group recruited 477 panel members in round 1, with about half of those being patients (n=224, 47%) while 193 professionals (40.5%) indicated working directly with OMT patients and 60 (12.6%) working in an area related to OMT. Support for the domains and indicators was strong (average score across all 13 indicators 5.06 out of 6 (range 4.90-5.26), average SD 1.04 (range 0.93-1.31), alpha coefficient 0.90). However, based on the 1049 open comments received, the indicators were further revised, and optional questions were added (see Box 1 and Annex 1). The indicators are currently being re-evaluated in round 2 of the Delphi study (indicator questions were extensively revised but domains remained unchanged between round 1 and round 2).

Initial feasibility testing on a limited number (n=20) of patients in four countries suggests the tool is well accepted by both clinician and patient and is deemed balanced, feasible and very useful (interview time: without optional questions: median 14 min., interquartile range (IQR) 11.5-17.5 min.; with optional questions: median 27 min., IQR 22-31 min.). In some cases patients found the interview a bit too long, in other cases the clinician said a longer interview was actually helpful, allowing for more discussion on interventions (Sharma, 2022).

Other studies have proposed indicators to evaluate outcomes of drug treatment (Stirling et al., 2023; Karnik et al., 2022; World Health Organization, 2020; Marsden et al., 2008). However, these have been developed for specific national contexts and are not based on an international consensus process. Also, most of these studies are not focused on PWUO /OMT (Stirling et al., 2023; World Health Organization, 2020; Marsden et al., 2008), in some cases resulting in relatively generic and unspecific indicators for this key group of patients. Some studies combine patient-level and system-level indicators, or indicators that require additional complex methodology (e.g. mortality), making them difficult to apply in, or even irrelevant for, clinical practice (Stirling et al., 2023; Karnik et al., 2022). To the best of our knowledge, we present the first international consensus protocol for treating opioid use disorders that is evidence-based (i.e. focused on OMT as the evidence-based treatment of choice), fully patient-centred (i.e. based on patient-reported data) and directly aimed at supporting clinical practice in monitoring OMT outcomes in PWUO, while including key (public) health outcomes that have so far scarcely been covered in treatment outcome studies (Wiessing et al., 2018). Although we here present a patient-centred set of treatment outcome indicators for use in clinical practice, we strongly support additional system- or aggregate-level monitoring to be carried out in parallel, using both patient-reported outcome measures, service data and observational studies, and combining these using formalised implementation science methods (Wiessing et al., 2017; Lambdin et al., 2015; Schackman, 2010; Silverman, 2009).

An important limitation of the present report is that it presents preliminary results of ongoing, unfinished work. Our draft consensus guidance has only been evaluated in one survey round with the Delphi panel, however, we found a very high level of agreement already and received mostly very supportive open comments. These resulted in the addition of optional questions, which may be a strength (adding depth) but also made the tool seem larger - although it should be noted that the optional questions will usually be partly or mostly omitted as they are only recommended for domains where the core questions suggest a problem exists. A further limitation is that the draft tool has so far been feasibility-tested on only a small number of patients (n=20). However, these first feasibility testing results are highly encouraging, with very positive feedback from both clinicians and patients, and suggesting that the time investment (about 15 mins for core questions only and about 30 mins when including also optional questions) is feasible in clinical practice, if only done once every three months or, depending on the patient, even less frequently. Based on responses received so far in round

2 of the Delphi study (n=171 by 6 November 2023), levels of agreement are as high as in round 1 (data not shown) and we do not foresee important further changes to the tool, until after doing more extensive feasibility and validity testing studies with patients.

With this preliminary interim report, we aim to make the first version of our tool available in the scientific domain, to potentially already start influencing treatment policies for saving and improving the lives of PWUO. Readers of this interim report are welcome to translate the tool into their own language for their own use, preferably after contacting us and following our agreed translation protocol, to test it together with OMT patients in their own local or national context, and to join our study group and/or let us know their experiences.

References

American Hospital Association - Legislative Advisory. (2018). The support for patients and communities Act of 2018. *Public Law*, 115-271. https://www.aha.org/system/files/2018-10/181024-legislative-adv-patients-and-communities-act.pdf

Allen, E. J., Palmateer, N. E., Hutchinson, S. J., Cameron, S., Goldberg, D. J., & Taylor, A. (2012). Association between harm reduction intervention uptake and recent hepatitis C infection among people who inject drugs attending sites that provide sterile injecting equipment in Scotland. *International Journal of Drug Policy*, *23*(5), 346-352.

Anstice, S., Strike, C. J., & Brands, B. (2009). Supervised methadone consumption: client issues and stigma. *Substance use & misuse*, *44*(6), 794-808.

Bao, Y. P., Liu, Z. M., Epstein, D. H., Du, C., Shi, J., & Lu, L. (2009). A meta-analysis of retention in methadone maintenance by dose and dosing strategy. *The American journal of drug and alcohol abuse*, *35*(1), 28-33.

Bøg, M., Filges, T., Brännström, L., Jørgensen, A. M. K., & Fredrikksson, M. K. (2017). 12-step programs for reducing illicit drug use. *Campbell Systematic Reviews*, *13*(1), 1-149.

Bogdanowicz, K. M., Stewart, R., Chang, C. K., Shetty, H., Khondoker, M., Day, E., ... & Strang, J. (2018). Excess overdose mortality immediately following transfer of patients and their care as well as after cessation of opioid substitution therapy. *Addiction*, *113*(5), 946-951.

Brugal, M. T., Domingo-Salvany, A., Puig, R., Barrio, G., Garcia de Olalla, P., & De La Fuente, L. (2005). Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction*, *100*(7), 981-989.

Burki, T. (2019). Inquiry says that "UK drugs policy is failing". *The Lancet*, *394*(10209), 1605.

Carrieri, P., Vilotitch, A., Nordmann, S., Lions, C., Michel, L., Mora, M., ... & Methaville Study Group. (2017). Decrease in self-reported offences and incarceration rates during methadone treatment: A comparison between patients switching from buprenorphine to methadone and maintenance treatment incident users (ANRS-Methaville trial). *International Journal of Drug Policy*, *39*, 86-91.

Deacon, R. M., Topp, L., Wand, H., Day, C. A., Rodgers, C., Haber, P. S., ... & Maher, L. (2012). Correlates of susceptibility to hepatitis B among people who inject drugs in Sydney, Australia. *Journal of Urban Health*, *89*, 769-778.

Degenhardt, L., Grebely, J., Stone, J., Hickman, M., Vickerman, P., Marshall, B. D., ... & Larney, S. (2019). Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *The Lancet*, *394*(10208), 1560-1579.

Eurasian Harm Reduction Association. (2020). Survey of client satisfaction with opioid maintenance therapy (OMT) services among patients of OMT programmes in Kyiv and the Kyiv Oblast region. Pilot study report. Vilnius: EHRA. https://harmreductioneurasia.org/wp-content/uploads/2020/06/Report-Eng06.03-1.pdf

European Monitoring Centre for Drugs and Drug Addiction. (2023). *European Drug Report 2023: Trends and Developments*. Publications Office of the European Union. https://www.emcdda.europa.eu/publications/european-drug-report/2023_en

European Monitoring Centre for Drugs and Drug Addiction. (2012). *Treatment demand indicator (TDI) standard protocol 3.0: Guidelines for reporting data on people entering drug treatment in European countries*. Publications Office of the European Union. https://www.emcdda.europa.eu/system/files/media/publications/documents/675/EMCDDA-TDI-Protocol-3.0_392671.pdf

European Monitoring Centre for Drugs and Drug Addiction. (2006). *Annual Report 2006 - The state of the drugs problem in Europe* (p 80). Publications Office of the European Union. https://www.emcdda.europa.eu/system/files/media/publications/documents/924/ar2006-en_69466.pdf

European Monitoring Centre for Drugs and Drug Addiction. (2007). *Annual Report 2007. The state of the drugs problem in Europe* (p 70). Publications Office of the European Union. https://www.emcdda.europa.eu/system/files/media/publications/documents/446/TDAC07001ENC_84793.pdf

Farré, M., Mas, A., Torrens, M., Moreno, V., & Camí, J. (2002). Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug and alcohol dependence*, *65*(3), 283-290.

Feelemyer, J. P., Des Jarlais, D. C., Arasteh, K., Phillips, B. W., & Hagan, H. (2014). Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: an international systematic review. *Drug and alcohol dependence*, *134*, 251-258.

Ferraro, C. F., Stewart, D. E., Grebely, J., Tran, L. T., Zhou, S., Puca, C., ... & French, C. E. (2021). Association between opioid agonist therapy use and HIV testing uptake among people who have recently injected drugs: a systematic review and meta-analysis. *Addiction*, *116*(7), 1664-1676.

Fordham A. (2022). *'Drug-free world' no more! Historic resolution at the UN spells end of consensus on drugs*. International Drug Policy Consortium (IDCP). https://idpc.net/blog/2022/12/drug-free-world-no-more-historic-resolution-at-the-un-spells-end-of-consensus-on-drugs

Frank, D. (2021). "That's No Longer Tolerated": policing patients' use of non-opioid substances in methadone maintenance treatment. *Journal of psychoactive drugs*, *53*(1), 10-17.

Fraser, H., Martin, N. K., Brummer-Korvenkontio, H., Carrieri, P., Dalgard, O., Dillon, J., ... & Hickman, M. (2018). Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *Journal of hepatology*, *68*(3), 402-411.

Friedmann, P. D., & Schwartz, R. P. (2012). Just call it "treatment". *Addiction Science & Clinical Practice*, *7*, 1-3.

Global Commission on Drug Policy. (2019). Classification of psychoactive substances: When science was left behind. http://www.globalcommissionondrugs.org/wp-content/uploads/2019/06/2019Report_EN_web.pdf

Gowing, L. R., Hickman, M., & Degenhardt, L. (2013). Mitigating the risk of HIV infection with opioid substitution treatment. *Bulletin of the World Health Organization*, *91*, 148-149.

Hamilton, L. K., Wheeler-Martin, K., Davis, C. S., Martins, S. S., Samples, H., & Cerdá, M. (2022). A modified Delphi process to identify experts' perceptions of the most beneficial and harmful laws to reduce opioid-related harm. *International Journal of Drug Policy*, *108*, 103809.

Harm Reduction International. (2022). *Global State of Harm Reduction 2022*. Harm Reduction International. https://hri.global/wp-content/uploads/2022/11/HRI_GSHR-2022_Full-Report_Final-1.pdf

Harris, J., & McElrath, K. (2012). Methadone as social control: Institutionalized stigma and the prospect of recovery. *Qualitative health research*, *22*(6), 810-824.

Interlandi J. (2023, February 22). One Year Inside a Radical New Approach to America's Overdose Crisis. *The New York Times*. https://www.nytimes.com/2023/02/22/opinion/drug-crisis-addiction-harm-reduction.html

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Briggs, A. M. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789-1858.

Jarvis, B. P., Holtyn, A. F., Subramaniam, S., Tompkins, D. A., Oga, E. A., Bigelow, G. E., & Silverman, K. (2018). Extended-release injectable naltrexone for opioid use disorder: a systematic review. *Addiction*, *113*(7), 1188-1209.

Javakhishvili, J.D., Razmadze, M., Kutelia, L., Shengelia, N., Lejava, L. (2021). *Survey of Client Satisfaction with Opioid Substitution Program in Western Georgia (online)*. Eurasian Harm Reduction Association. Ilia State University. Vilnius, Lithuania, 2021. file:///Users/janajavakhishvili/Downloads/OST-Clients-Satisfaction-Survey-Report-EHAR-and-ILiauni-2021.pdf

Jünger, S., Payne, S. A., Brine, J., Radbruch, L., & Brearley, S. G. (2017). Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliative medicine*, *31*(8), 684-706.

Karnik, N. S., Marsden, J., McCluskey, C., Boley, R. A., Bradley, K. A., Campbell, C. I., ... & Wu, L. T. (2022). The opioid use disorder core outcomes set (OUD–COS) for treatment research: findings from a Delphi consensus study. *Addiction*, *117*(9), 2438-2447.

Katzman, J. G., Takeda, M. Y., Greenberg, N., Balasch, M. M., Alchbli, A., Katzman, W. G., ... & Bhatt, S. R. (2020). Association of take-home naloxone and opioid overdose reversals performed by patients in an opioid treatment program. *JAMA network open*, *3*(2), e200117-e200117.

Lambdin, B., Cheng, B., Peter, T., Mbwambo, J., Apollo, T., Dunbar, M., ... & Volberding, P. (2015). Implementing implementation science: an approach for HIV prevention, care and treatment programs. *Current HIV research*, *13*(3), 244-246.

Larney, S., Peacock, A., Leung, J., Colledge, S., Hickman, M., Vickerman, P., ... & Degenhardt, L. (2017). Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *The Lancet Global Health*, *5*(12), e1208-e1220.

Levengood, T. W., Yoon, G. H., Davoust, M. J., Ogden, S. N., Marshall, B. D., Cahill, S. R., & Bazzi, A. R. (2021). Supervised injection facilities as harm reduction: a systematic review. *American journal of preventive medicine*, *61*(5), 738-749.

Lions, C., Carrieri, M. P., Michel, L., Mora, M., Marcellin, F., Morel, A., ... & Methaville Study Group. (2014). Predictors of non-prescribed opioid use after one year of

methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug and alcohol dependence*, *135*, 1-8.
MacArthur, G. J., Minozzi, S., Martin, N., Vickerman, P., Deren, S., Bruneau, J., ... & Hickman, M. (2012). Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *Bmj*, *345*.
Marchand, K., Foreman, J., MacDonald, S., Harrison, S., Schechter, M. T., & Oviedo-Joekes, E. (2020). Building healthcare provider relationships for patient-centered care: a qualitative study of the experiences of people receiving injectable opioid agonist treatment. *Substance abuse treatment, prevention, and policy*, *15*, 1-9.
Marsch, L. A. (1998). The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*, *93*(4), 515-532.
Marsden, J., Farrell, M., Bradbury, C., Dale-Perera, A., Eastwood, B., Roxburgh, M., & Taylor, S. (2008). Development of the treatment outcomes profile. *Addiction*, *103*(9), 1450-1460.
Mathers, B. M., Degenhardt, L., Ali, H., Wiessing, L., Hickman, M., Mattick, R. P., ... & Strathdee, S. A. (2010). HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *The Lancet*, *375*(9719), 1014-1028.
Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: a systematic review and meta-analysis. *Bulletin of the World Health Organization*, *91*, 102-123.
Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database of systematic reviews*, (2). https://doi.org/10.1002/14651858.CD002207.pub4
Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane database of systematic reviews*, (3). https://doi.org/10.1002/14651858.CD002209.pub2
~~Mattick RP, Kimber J, Breen C, Davoli M. (2003). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews, (4). doi: 10.1002/14651858.CD002207.~~
Mattson, C. L., Tanz, L. J., Quinn, K., Kariisa, M., Patel, P., & Davis, N. L. (2021). Trends and geographic patterns in drug and synthetic opioid overdose deaths—United States, 2013–2019. *Morbidity and Mortality Weekly Report*, *70*(6), 202.
McAuley, A., Fraser, R., Glancy, M., Yeung, A., Jones, H. E., Vickerman, P., ... & Hutchinson, S. J. (2023). Mortality among individuals prescribed opioid-agonist therapy in Scotland, UK, 2011–20: a national retrospective cohort study. *The Lancet Public Health*.
Metzger, D. S., Woody, G. E., McLellan, A. T., O'Brien, C. P., Druley, P., Navaline, H., ... & Abrutyn, E. (1993). Human immunodeficiency virus seroconversion among intravenous drug users in-and out-of-treatment: an 18-month prospective follow-up. *Journal of acquired immune deficiency syndromes*, *6*, 1049-1049.
Millar, T., & McAuley, A. (2017). EMCDDA assessment of drug-induced death data and contextual information in selected countries. https://www.emcdda.europa.eu/system/files/publications/4667/Assessment%20of%20drug-induced%20death%20data.pdf
Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., & Verster, A. (2011). Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews*, (4). https://doi.org/10.1002/14651858.CD001333.pub4
Mohammadi, M., Kazeminia, M., Abdoli, N., Khaledipaveh, B., Shohaimi, S., Salari, N., & Hosseinian-Far, M. (2020). The effect of methadone on depression among addicts: a systematic review and meta-analysis. *Health and quality of life outcomes*, *18*(1), 1-12.

Namchuk, A. B., Lucki, I., & Browne, C. A. (2022). Buprenorphine as a treatment for major depression and opioid use disorder. *Advances in drug and alcohol research*, *2*, 10254.
Nielsen, S., Tse, W. C., & Larance, B. (2022). Opioid agonist treatment for people who are dependent on pharmaceutical opioids. *Cochrane Database of Systematic Reviews*, (9). https://doi.org/10.1002/14651858.CD011117.pub3
Nordt, C., Wiessing, L., Kuijpers, W., Wisselink, J., Espelt, A., Brugal, M. T., ... & Herdener, M. (2018). Long-term opioid agonist treatment participation after first treatment entry is similar across 4 European regions but lower in Non-Nationals. *European addiction research*, *24*(4), 173-183.
O'Connor, A. M., Cousins, G., Durand, L., Barry, J., & Boland, F. (2020). Retention of patients in opioid substitution treatment: a systematic review. *PloS one*, *15*(5), e0232086.
Pierce, M., Bird, S. M., Hickman, M., Marsden, J., Dunn, G., Jones, A., & Millar, T. (2016). Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction*, *111*(2), 298-308.
Pitkänen, T., Kaskela, T., & Levola, J. (2020). Mortality of treatment-seeking men and women with alcohol, opioid or other substance use disorders–A register-based follow-up study. *Addictive Behaviors*, *105*, 106330.
Platt, L., Minozzi, S., Reed, J., Vickerman, P., Hagan, H., French, C., ... & Hickman, M. (2018). Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. *Addiction*, *113*(3), 545-563.
Radimecký, J. (2007). Rhetoric versus practice in Czech drug policy. *Journal of drug issues*, *37*(1), 11-44.
Razaghizad, A., Windle, S. B., Filion, K. B., Gore, G., Kudrina, I., Paraskevopoulos, E., ... & Eisenberg, M. J. (2021). The effect of overdose education and naloxone distribution: an umbrella review of systematic reviews. *American journal of public health*, *111*(8), e1-e12.
Rice, D., Corace, K., Wolfe, D., Esmaeilisaraji, L., Michaud, A., Grima, A., ... & Hutton, B. (2020). Evaluating comparative effectiveness of psychosocial interventions adjunctive to opioid agonist therapy for opioid use disorder: A systematic review with network meta-analyses. *PLoS One*, *15*(12), e0244401.
Rosenberg, H., Grant, J., & Davis, A. K. (2020). Acceptance of non-abstinence as an outcome goal for individuals diagnosed with substance use disorders: A narrative review of published research. *Journal of Studies on Alcohol and Drugs*, *81*(4), 405-415.
Roux, P., Carrieri, M. P., Cohen, J., Ravaux, I., Poizot-Martin, I., Dellamonica, P., & Spire, B. (2009). Retention in opioid substitution treatment: a major predictor of long-term virological success for HIV-infected injection drug users receiving antiretroviral treatment. *Clinical infectious diseases*, *49*(9), 1433-1440.
Samet, J. H., & Fiellin, D. A. (2015). Opioid substitution therapy—time to replace the term. *The Lancet*, *385*(9977), 1508-1509.
Santo, T., Clark, B., Hickman, M., Grebely, J., Campbell, G., Sordo, L., ... & Degenhardt, L. (2021). Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: a systematic review and meta-analysis. *JAMA psychiatry*, *78*(9), 979-993.
Schackman, B. R. (2010). Implementation science for the prevention and treatment of HIV/AIDS. *Journal of acquired immune deficiency syndromes (1999)*, *55*(Suppl 1), S27.
Seabra, P. R. C., Amendoeira, J. J. P., & Sá, L. O. (2018). Testing nursing sensitive outcomes in out-patient drug addicts, with "Nursing Role Effectiveness Model". *Issues in Mental Health Nursing*, *39*(3), 200-207.

Sharma, H. (2022). How short or long should be a questionnaire for any research? Researchers dilemma in deciding the appropriate questionnaire length. Saudi journal of anaesthesia, 16(1), 65.

Silverman, S. L. (2009). From randomized controlled trials to observational studies. *The American journal of medicine*, *122*(2), 114-120.

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., ... & Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *bmj*, *357*.

Stirling, R., Nathan, S., & Ritter, A. (2023). Prioritizing measures to assess performance of drug treatment services: a Delphi process with funders, treatment providers and service-users. Addiction, 118(1), 119-127.

Sun, H. M., Li, X. Y., Chow, E. P., Li, T., Xian, Y., Lu, Y. H., ... & Zhang, L. (2015). Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: a systematic review and meta-analysis. *BMJ open*, *5*(1), e005997.

The Global Fund. (2022). *Technical Brief. Harm reduction for people who use drugs: priorities for investment and increased impact in HIV programming allocation period 2023-2025*. The Global Fund. https://www.theglobalfund.org/media/1279/core_harmreduction_infonote_en.pdf?u=636850056300000000

Torrens, M., Domingo-Salvany, A., Alonso, J., Castillo, C., & San, L. (1999). Methadone and quality of life. *The Lancet*, *353*(9158), 1101.

Torrens, M., Fonseca, F., Castillo, C., & Domingo-Salvany, A. (2013). Methadone maintenance treatment in Spain: the success of a harm reduction approach. *Bulletin of the World Health Organization*, *91*, 136-141.

UNAIDS. (2021). Global AIDS strategy 2021–2026. End inequalities. End AIDS. [2022– 01– 03]. UNAIDS. https://www.unaids.org/en/Global-AIDS-Strategy-2021-2026

UNODC. (2022). World drug report. *United Nations New York, NY, 2*. https://www.unodc.org/res/wdr2022/MS/WDR22_Booklet_2.pdf

Van Draanen, J., Tsang, C., Mitra, S., Karamouzian, M., & Richardson, L. (2020). Socioeconomic marginalization and opioid-related overdose: a systematic review. *Drug and alcohol dependence*, *214*, 108127.

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., ... & Bhutta, Z. A. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1204-1222.

Wiessing, L. (2018b). Report on Workshop 4 Monitoring treatment outcomes – a challenge worth the effort. TDI meeting / Treatment expert meeting, 3-4 October 2018. EMCDDA: Lisbon, 2018. https://drive.google.com/file/d/1rn8rPMB4EnFz18Y2c7Kxm2nLE6xPdb0W/view?usp=drive_link

Wiessing, L. (2019). Expert meeting to start developing EMCDDA guidance for monitoring opioid substitution treatment outcomes in Europe. EMCDDA: Lisbon, 2019. https://drive.google.com/file/d/1vYaLJoLD2VoF2SHikL6x43wNodT33jMX/view?usp=drive_link

Wiessing, L. G., Seguin-Devaux, C., & Merendeiro, C. S. (2021). Could the COVID-19 Crisis Help Eradicate Chronic Homelessness?. *American Journal of Public Health*, *111*(1), 25.

Wiessing, L., Denis, B., & Guttormsson, U. et al., (2000). Estimating coverage of harm-reduction measures for injection drug users in Europe. *Global Research Network on HIV Prevention in Drug-Using Populations- Third Annual Meeting Report.*

https://www.emcdda.europa.eu/system/files/attachments/14922/Wiessing_article_final.pdf
Wiessing, L., Ferri, M., Běláčková, V., Carrieri, P., Friedman, S. R., Folch, C., ... & Griffiths, P. (2017). Monitoring quality and coverage of harm reduction services for people who use drugs: a consensus study. *Harm reduction journal*, *14*, 1-14.
Wiessing, L., Ferri, M., Darke, S., Simon, R., & Griffiths, P. (2018). Large variation in measures used to assess outcomes of opioid dependence treatment: A systematic review of longitudinal observational studies. *Drug and Alcohol Review*, *37*, S323-S338.
Wiessing, L., Likatavičius, G., Klempová, D., Hedrich, D., Nardone, A., & Griffiths, P. (2009). Associations between availability and coverage of HIV-prevention measures and subsequent incidence of diagnosed HIV infection among injection drug users. *American Journal of Public Health*, *99*(6), 1049-1052. https://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.2008.141846
Wild, T. C., Hammal, F., Hancock, M., Bartlett, N. T., Gladwin, K. K., Adams, D., ... & Hodgins, D. C. (2021). Forty-eight years of research on psychosocial interventions in the treatment of opioid use disorder: a scoping review. *Drug and alcohol dependence*, *218*, 108434.
Woo, J., Bhalerao, A., Bawor, M., Bhatt, M., Dennis, B., Mouravska, N., ... & Samaan, Z. (2017). "Don't judge a book by its cover": A qualitative study of methadone patients' experiences of stigma. *Substance abuse: research and treatment*, *11*, 1178221816685087.
World Health Organization, UNODC, UNAIDS. (2012). Technical Guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users- 2012 revision. https://www.who.int/publications/i/item/978924150437
World Health Organization. (2005). Effectiveness of drug dependence treatment in prevention of HIV among injecting drug users. Evidence for action technical papers. https://apps.who.int/iris/bitstream/handle/10665/43259/9241593362-eng.pdf?sequence=1&isAllowed=y
World Health Organization. (2020). International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing. https://www.ichom.org/portfolio/addiction/
World Health Organization. (2023). Opioid overdose factsheet. https://www.who.int/news-room/fact-sheets/detail/opioid-overdose
World Health Organization. Department of Mental Health, Substance Abuse, World Health Organization, International Narcotics Control Board, & United Nations Office on Drugs. (2009). *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence.* World Health Organization. https://www.who.int/publications/i/item/9789241547543