



Guidance for

Injectable Opioid Agonist Treatment for Opioid Use Disorder

About the BC Centre on Substance Use

The [BC Centre on Substance Use \(BCCSU\)](#) is a provincially networked resource with a mandate to develop, implement, and evaluate evidence-based approaches to addiction and substance use. Building on the extensive efforts of the BC Centre for Excellence in HIV/AIDS and the Urban Health Research Initiative, the BCCSU's vision is to transform treatment of substance use in BC by translating research into education and evidence-based care guidance. By supporting the collaborative development of evidence-based treatment policy, guidelines, and standards, BCCSU will improve the integration of care across the continuum of substance use programming and policy, thereby serving all British Columbians.

The BCCSU is founded on the values of: advancing, seeking and sharing of knowledge; collaboration at all levels across the continuum of care; empowerment of individuals, families, and communities; excellence and quality through innovation and evidence; advocacy for positive policy change, reduction of stigma and support for patients and families; and mutual respect and equity for all members of the community and their contributions.

In order to provide leadership in treatment system for addiction and substance use and to help reach all British Columbians who need these services, the BCCSU will integrate activities of its three core functions:

1. **Research and Evaluation** – Lead an innovative multidisciplinary program of research and evaluation activities to guide health system improvements in treatment and care for addiction and substance use.
2. **Education and Training** – Strengthen education activities that address addiction and substance use across disciplines, academic institutions, and health authorities, and train the next generation of leaders in the field.
3. **Clinical Care Guidance** – Develop and implement evidence-based clinical practice guidelines and treatment pathways.

Authors and Contributors

Supervised Injectable Opioid Agonist Treatment Guidance Committee

Dr. Keith Ahamad, MD, CCFP, Dip. ABAM, CISAM; Division Lead - Addiction, Department of Family and Community Medicine, Providence Health Care; Clinical Assistant Professor, University of British Columbia; Clinician Scientist, British Columbia Centre on Substance Use

Miranda Compton, MSW; Regional Director – Prevention, Vancouver Coastal Health

Corrine Dolman, MSW; Practice Lead, Mental Health and Substance Use, Interior Health

Dr. Nadia Fairbairn, MD, FRCPC; Assistant Professor, Department of Medicine, University of British Columbia; Research Scientist, British Columbia Centre on Substance Use

Julie Foreman, RN, BSN; Clinic Coordinator, Providence Crosstown Clinic

Dr. Reka Gustafson, MD; Medical Health Officer, Vancouver Coastal Health

Scott Harrison RN(C), BScN, MA, CCHN(C), (Committee Co-Chair); Director of Strategy & Transformation, Urban Health, Aboriginal Health, Mental Health and Substance Use, Providence Health Care

Dr. Ramm Hering, MD, CCFP, MSc, Dip PH, Dip ABAM; Physician Lead, Victoria Rapid Access Addiction Clinic, Island Health; Physician Lead, Victoria Inpatient Addiction Medicine Consult Service, Island Health; Physician Lead, Primary Care Substance Use, Island Health

Amin Janmohamed, BSc Pharm, MSc; Research Scientist, Centre for Health Evaluation and Outcome Sciences; Pharmacy Director, Providence Crosstown Clinic

Cheyenne Johnson, RN, MPH, CCRP; Director, Clinical Activities and Development, BC Centre on Substance Use

Dr. Ronald Joe, MD; Medical Director, Vancouver Community Substance Use Services, Vancouver Coastal Health

Dr. Venu Karapareddy MBBS, MSc, MRCPsych, FRCPC, MBA; Concurrent Disorder Lead, Vancouver Coastal Health Acute and Tertiary

Dr. Piotr Klakowicz, MD, MPH, MSc, CCFP; Primary Care & Addiction Medicine Physician, St. Paul's Hospital Urban Health Program; Primary Care & Addiction Medicine Physician, Providence Crosstown Clinic; Primary Care & Addiction Medicine Physician, Vancouver Native Health Medical Clinic

Mona Kwong, BSc(Pharm), PharmD, MSc; Clinical Pharmacist

Marcus Lem, MD, MHSc, FRCPC; Senior Medical Advisor, Public Health Addiction and Overdose Prevention and Treatment Policy, BC Centre for Disease Control

Kurt Lock, BA; MPP Candidate, School of Public Policy, Simon Fraser University; Outreach Coordinator, SALOME; Centre for Health Evaluation and Outcome Sciences

Dr. Scott MacDonald, MD; Physician Lead, Providence Crosstown Clinic

Keith McDonald; Director, Lower Mainland Pharmacy Services

Dr. Nick Mathew, MD, MSc, ABPN, FRCPC, Dip. ABAM; Addiction Division Lead, Surrey Memorial Hospital; Clinical Assistant Professor, University of British Columbia

Ministry of Health staff

Ministry of Mental Health and Addictions staff

Garth Mullins, BC Association of People on Methadone

Dr. Seonaid Nolan MD, FRCPC; Clinician Scientist, BC Centre on Substance Use

Dr. Eugenia Oviedo-Joekes, PhD; Associate Professor, School of Population and Public Health, University of British Columbia; Research Scientist, Centre for Health Evaluation and Outcome Sciences

Heather Palis, MSc, PhD Candidate; School of Population and Public Health, University of British Columbia; Trainee, Centre for Health Evaluation and Outcome Sciences

Dr. Daniel Paré, MD, CCFP, DABAM, CCSAM; Vancouver Coastal Health, University of British Columbia
Department of Family Practice

Dr. Gerrard Prigmore, MB BCh MRCGP DFSRH CCFP DABAM FASAM, Medical Lead, Addiction and Harm Reduction, Northern Health

Kelly Reid; Director, Operations, Mental Health & Substance Use, Island Health

Dr. Christy Sutherland (Committee Co-Chair), MD, CCFP, Dip. ABAM; Medical Director, PHS Community Services Society; Clinical Assistant Professor, University of British Columbia; Education Physician Lead, BC Centre on Substance Use

Meaghan Thumath, RN, BSN, MScPH; Trudeau Scholar, Department of Social Policy and Intervention, University of Oxford; Senior Practice Leader, BC Centre for Disease Control

Dr. Mark Tyndall, MD, ScD; Executive Director, BC Centre for Disease Control; Professor, School of Population and Public Health, University of British Columbia

Dr. Karen Urbanoski, PhD; Centre for Addictions Research of BC, University of Victoria

Jordan Westfall; President, Canadian Association of People Who Use Drugs

External Reviewers

Leslie McBain, Family Engagement Lead, BC Centre on Substance Use; Co-Founder, Moms Stop The Harm
Community members of the Downtown Eastside

Scientific Reviewers

Dr. Peter Blanken, PhD; Senior Researcher at Parnassia Addiction Research Centre (PARC), Brijder Addiction Treatment, Parnassia Group

Dr. Hans-Guenter Meyer-Thompson, Physician, ASKLEPIOS Hamburg Nord, Dept. for Substance Abuse; Editor (www.forum-substitutionspraxis.de), Hamburg, Germany

Dr. Uwe Verthein, PhD; Centre for Interdisciplinary Addiction Research of Hamburg University (ZIS) University Medical Centre Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy

Acknowledgements

The guidance committee wishes to thank the study participants in NAOMI, SALOME, and RUTH, as well as the staff and patients at Providence Health Care's Crosstown Clinic. The guidance committee also gratefully acknowledges the expert contributions of Dr. Eugenia Oviedo-Joekes, Dr. Scott MacDonald, Julie Foreman, Heather Palis, and Dr. Evan Wood. Additionally, the guidance committee gratefully acknowledges the Ministry of Health and Ministry of Mental Health and Addictions. The guidance committee would also like to thank Dr. Uwe Verthein, Dr. Hans-Guenter Meyers-Thompson, Dr. Peter Blanken, Leslie McBain, community members from the Downtown Eastside, and an anonymous reviewer from the recovery community for their thorough review.

Finally, the guidance committee wishes to thank the following individuals for their contributions to the development and completion of the guidance document: Josey Ross and Emily Wagner for primary research and writing assistance; Maryam Babaei, Dr. Brit Cooper-Jones, and Jessica Jun for editorial and administrative support. Additionally, we wish to thank Lindsay Farrell, Jennifer Navin, and Yuko Endo for their administrative support, and Kevin Hollett for design and graphic support.

Table of Contents

Executive Summary	9
Part I: Evidence and Implementation of Injectable Opioid Agonist Treatment	10
Introduction	10
British Columbia Opioid Addiction Treatment Support Program & BCCSU Guideline	10
Development Process	11
Content Development	11
Review Process	11
Intended Audience	12
Purpose and Scope	12
British Columbia Opioid Overdose Epidemiology	13
The Continuum of Care for Opioid Use Disorder	14
Role of Injectable Opioid Agonist Treatments in the Continuum of Care	14
Supervised Injectable Opioid Agonist Treatment	16
Overview	16
Injectable Opioid Agonist Treatment in Other Jurisdictions	16
Evidence Summary	16
Summary of Cochrane Review and Recent Evidence	16
SALOME & Hydromorphone	16
Safety	17
Models of Care	19
Continuum of Care	19
Family Involvement in Care	20
Patient-Centred Care	20
Recovery-Oriented Care	21
Models of Care for BC	21
1. A Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program	22
2. Integrated or Embedded Supervised Injectable Opioid Agonist Treatment Program	22
3. Emerging Model: Pharmacy-Based Supervised Injectable Opioid Agonist Treatment Program	22
Community Context	25
Suggested Budgetary and Operational Considerations	26
Section II: Recommendations for Clinical Practice	27
Summary of Clinical Practice Recommendations	27
General Considerations	28
Patient Population and Eligibility	28
Youth	30
Obtaining and Preparing Hydromorphone	30
Prescribing Injectable Hydromorphone	31
Selection of Dose	31
Supervision of Injections	31
Pre- and Post-Injection Assessment	32

Administration of Injectable Medications	32
Titration Process	32
Co-Prescription of Oral Opioid Agonist Treatments	33
Dosage Equivalence with Oral Methadone and Slow-Release Oral Morphine	33
Conversion of Oral Methadone and Slow-Release Oral Morphine for Travel	33
Missed Doses	33
Managing Ongoing Substance Use	33
De-Intensifying Treatment	34
Indications for Transitioning to Oral Treatment	35
Prescriber Competencies	35
Appendices	36
Appendix 1: Pre-and Post-Injection Assessment	36
Pre-Injection Assessment	36
Post-Injection Assessment	36
Pasero Opioid-induced Sedation Scale (POSS)	38
Appendix 2: Health Care Provider Administration of Intra-muscular Injection	39
Appendix 3: Operational and Budgetary Considerations	40
Operational Requirements	40
Budgetary Considerations	41
1. A Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program	42
2. Community Clinic with an Integrated Supervised Injectable Opioid Agonist Treatment Program	42
3. Pharmacy-Based Supervised Injectable Opioid Agonist Treatment Program	42
Appendix 4: Titration Process	43
Hydromorphone Titration Protocol	43
Co-Prescription of Oral OAT	45
Appendix 5: Conversion Table	46
Appendix 6: Strategies for De-intensifying Treatment	48
1. Transition from Hydromorphone to Methadone	48
2. Transition from Hydromorphone to Slow-Release Oral Morphine	48
3. Transition from Hydromorphone to Buprenorphine/Naloxone	49
Provider-Initiated De-Intensification of Treatment	49
Appendix 7: Urine Drug Testing	51
Appendix 8: Sample Treatment Agreement	52
Appendix 9: Diacetylmorphine	54
Obtaining and Preparing Diacetylmorphine	54
Injectable Diacetylmorphine	55
Prescribing Injectable Diacetylmorphine	55
Selection of Dose	55
Dosage Equivalence with Oral Methadone and Slow-Release Oral Morphine	55
Diacetylmorphine Titration Protocol	56
Co-Prescription of Oral OAT	57
Appendix 10: Frequently Asked Questions	58
References	62

Executive Summary

Opioid use disorder is one of the most challenging forms of substance use disorder facing the health care system in British Columbia and a major driver of the recent surge in overdose deaths in the province. More than 500 people died of overdose in 2015. By April 2016, nearly 300 people had already died, prompting the province to declare a public health emergency in response to the rapid and unprecedented increase in accidental overdose deaths. By the end of 2016, over 930 people had died as a result of drug overdose.

The introduction of fentanyl and other synthetic analogues into the drug supply is a major contributing factor to the overdose emergency. In 2016, fentanyl was detected, either alone or in combination with other drugs, in 61.8% of overdose deaths. The number of deaths excluding fentanyl has remained relatively stable since 2011. This toxicity of the drug supply adds urgency to addressing the significant gaps in treatment options currently available for opioid use disorder (OUD) in British Columbia — gaps which have become more apparent during this public health emergency. However, the primary purpose of this document is not to suggest that the expansion of treatment options alone, including injectable agonist treatment (iOAT), are a panacea for the opioid overdose crisis. Rather, the crisis has identified a profound need to improve the overall OUD system of care, including expanding treatment options for those patients with opioid use disorder who have not benefited from other treatments.

In the context of the current public health emergency, there is an urgent need to expand and offer the full continuum of care for the treatment of opioid use disorder in order to optimize treatment of adults and youth. Injectable opioid agonist treatment is an evidence-based, high intensity treatment option for OUD for those patients who have not benefited from other treatments.

When OUD is treated effectively, the benefits are not only to the individual (e.g., reduction in morbidity and mortality) but also to the community (e.g., reduced activity in the criminal justice system). Along these lines, the primary aim of iOAT is to improve the health of the individual, by reducing overdose risk and other imminent health and social harms associated with ongoing injection drug use. The second aim of iOAT is to engage individuals in addiction treatment who have not benefited from less-intensive treatments or who have been otherwise unable to access other forms of treatment. Patients may not benefit from oral medications such as buprenorphine/naloxone, methadone, and slow-release oral morphine for a variety of reasons, including side effects, cravings persisting despite optimal OAT dosing or being unable to reach a therapeutic dose. Repeated oral treatment attempts without significant benefit for these patients may result in increased risk of poor health and social outcomes, including fatal and non-fatal overdose(s).

This guidance document was created to provide an overview of the evidence on iOAT, potential models of care, recommendations for clinical practice, and operational requirements. It describes three potential models of care, two established and one emerging. These models include a comprehensive and dedicated supervised iOAT program in which clients can access a full complement of care in one setting; an integrated or embedded supervised iOAT program for clients in a less intensive setting within pre-established services; and an emerging model, which is a pharmacy-based supervised iOAT program, allowing for improved access to care in communities where other, more intensive models may not be appropriate or feasible.

The BC Centre on Substance Use (BCCSU) assembled an expert interdisciplinary committee composed of over 40 individuals, including representation from each regional health authority, the Provincial Health Services Authority, people who use drugs, the BC Ministry of Health, and the BC Ministry of Mental Health and Addictions, to develop this guidance document. Key health systems partners, community and family advocacy groups, and international experts have subsequently reviewed the document. The guidance document was developed with guidance from the expert committee, which established three smaller working groups to expedite the writing process. Recommendations are based on a structured literature review and clinical expertise.

This unprecedented public health emergency underscores the importance of developing comprehensive, collaborative, compassionate, and evidence-based health services to address the harms related to untreated OUD.

a. This guidance document provides recommendations on best practice, rather than a set of practice standards.

Part I: Evidence and Implementation of Injectable Opioid Agonist Treatment

Introduction

This document comprises two sections: I) Evidence and Implementation of Injectable Opioid Agonist Treatment and II) Recommendations for Clinical Practice. The first section, providing an overview of the evidence and suggested models of care, offers policy guidance for policy makers and health authorities interested in implementing and expanding injectable opioid agonist treatment. The second section offers basic clinical guidance. General considerations from clinical experience and the literature are provided, offering a framework for how to build a clinical practice of injectable opioid agonist treatment (iOAT). However, the unique nature of each patient's situation requires clinical judgment in order to determine the best course of treatment.

The purpose of this document is to provide a framework for injectable opioid agonist treatment in BC including models of care and basic clinical guidance. It does not represent a clinical guideline nor the setting of provincial standards, both of which are out of scope for this document.

British Columbia Opioid Addiction Treatment Support Program & BCCSU Guideline

The BC Centre on Substance Use (BCCSU) is a provincially networked organization with a mandate to develop, help implement, and evaluate evidence-based approaches to substance use and substance use disorders. In partnership with the Ministry of Health, the BCCSU developed [A Guideline for the Clinical Management of Opioid Use Disorder](#)¹ to guide clinical care and treatment of opioid use disorder (OUD) in British Columbia using oral opioid agonist treatment (OAT). The Guideline makes eleven recommendations, including the use of buprenorphine/naloxone as the preferred first-line treatment for opioid agonist treatment, with methadone as an additional first-line treatment when contraindications to buprenorphine/naloxone exist, and slow-release oral morphine as an alternative, specialist-led oral OAT option for patients who have not benefited from buprenorphine/naloxone or methadone.

In addition to its other work, in June 2017, the BCCSU took on stewardship of the Provincial Opioid Addiction Treatment Support Program (formerly the Methadone Maintenance Program) from the College of Physicians and Surgeons of British Columbia. To build health system capacity and increase the number of OAT providers across the province, the BCCSU is significantly expanding the educational component of the Provincial Opioid Addiction Treatment Support Program in volume and scope. The Provincial Opioid Addiction Treatment Support Program will offer interactive, online educational opportunities to increase the capacity of prescribers in rural and remote areas, as well as training on the full range of OUD treatments available and managing transitions between treatment modalities.

As part of its provincial mandate and its role in the coordination of the Provincial Opioid Addiction Treatment Support Program, the BCCSU will conduct real-time monitoring and evaluation of treatment, health, and social outcomes of patients engaged in treatment for opioid use disorder in the province, with the aim of optimizing patient outcomes, ensuring public safety, and improving quality of care. A range of metrics will be assessed, including optimal dosing, retention, mortality, and adherence to therapeutic guidelines, for the full spectrum of medications available to treat opioid use disorder, including injectable opioid agonist treatments. For iOAT specifically, as programs are implemented provincially, the BCCSU plans to launch a comprehensive research component to closely monitor patient safety and long-term treatment outcomes. All individuals engaged in iOAT will be eligible to participate. This research component will involve completion of a questionnaire at intake and at regular follow-up intervals, and, with consent of individual patients, the use of administrative data linkages to confidentially assess health and social outcomes for up to five years following treatment initiation. A subset of participants will also be invited to participate in in-depth qualitative interviews about their experiences with iOAT.

a. This guidance document provides recommendations on best practice, rather than a set of practice standards.

Development Process

This guidance document was developed at the request of and to be delivered to the Ministry of Health. The BCCSU assembled an expert committee composed of over 40 individuals, including representation from each regional Health Authority, the Provincial Health Services Authority, and the BC Ministry of Health, led by committee co-chairs Dr. Christy Sutherland (Medical Director, PHS Community Services Society; Education Physician Lead, BCCSU) and Scott Harrison (Director of Strategy and Transformation, Urban Health, Aboriginal Health, Mental Health and Substance Use, Providence Health Care). Cheyenne Johnson (Director of Clinical Activities and Development, BCCSU) worked closely with the co-chairs and BCCSU medical writing team throughout the development process as a representative of BCCSU leadership.

A proposed outline for the guidance document was circulated to the committee for initial review. In the first committee teleconference, committee members provided feedback and suggestions for the outline, contents, and overall scope of the document.

In the initial teleconference, the committee approved a tentative work plan involving the establishment of three working groups, each assigned a core section of the document: 1) Evidence Review and Environmental Scan; 2) General Program Considerations and Proposed Models of Care; and 3) Obtaining, Preparing and Delivering Injectable Medication. Committee members were asked to volunteer and nominate others in the field to participate; final group sizes were five, nine and three individuals, respectively. The committee co-chairs, BCCSU leadership (C. Johnson), and two members of the BCCSU medical writing team also participated in all working group meetings.

Content Development

With input from the committee chairs, the BCCSU medical writing team drafted sections for initial review and feedback. For Section 1, the evidence review was based on a structured review of the literature, and used a traditional hierarchy to identify relevant research evidence, with meta-analyses of randomized clinical trials given the most weight, followed by individual clinical trials, observational reports, and expert opinion. The writing team started from high quality meta-analyses (Cochrane Collaboration) and reviewed all included and excluded studies, then looked at any articles that cited the review subsequently and searched for meta-analyses, RCTs, observational studies, and other studies published after the review. Additional literature searches were conducted at the request of the committee when new topics or issues were considered for inclusion in the guidance document.

For Section 2, clinical recommendations and operational considerations were derived through discussion with members of the guidance committee, and informed by opinion and experience of local experts, personal communication with study authors and Crosstown clinic staff, and review of existing national and international evidence-based clinical practice guidelines, position papers and practice bulletins issued by recognized addiction medicine professional organizations and authorities. In addition, where appropriate, product monographs approved by Health Canada or the equivalent international regulatory body, and guidelines and standards of the College of Physicians and Surgeons of BC (CPSBC), the College of Registered Nurses of BC (CRNBC), and the College of Pharmacists of BC (CPBC), were consulted so as to comply with provincial safety regulations and standards for practice. Considerations for obtaining, preparing, and delivering injectable medications, were completed in close consultation with experienced pharmacy professionals and Crosstown Clinic staff.

Review Process

Once complete, section drafts were sent to each working group for initial review and feedback. Working groups were provided with full text of articles or documents referenced in their assigned section, as well as the full master document for context. Working group members were asked to return their feedback in advance of meetings, so that the medical writing team could incorporate suggested revisions and circulate a revised draft

for discussion in the meeting. Major themes and issues were also highlighted for discussion, where applicable. Work Group 2 required two rounds of revision and group discussion prior to approval of the final draft section.

Following the working group process, a complete draft was assembled and circulated to the full committee for written feedback (via email). An updated draft incorporating this feedback was circulated in advance of a committee teleconference. In the teleconference, the committee reviewed the draft and provided feedback as a group. The group agreed that the document would be rapidly revised per teleconference discussions and then sent for external review.

Input from peer and other stakeholders was sought through active participation of three prominent community leaders in the committee membership and as participants in Working Group 2. In addition, a facilitated discussion was held with community members (4 members attended) to review the guidance document and provide an opportunity to give feedback on scope, contents, and recommendations.

Following committee review and revisions, the draft guidance document was circulated to several external reviewer groups simultaneously. These groups included an expert scientific review panel, expert clinician group, and recovery and family advocacy stakeholder partners.

Intended Audience

The two sections of this document have different target audiences. The target audience of Part I: Evidence and Implementation of Injectable Opioid Agonist Treatment is policy makers, clinical and operational leads in the health authorities, and funders. The target audience of Part II: Recommendations for Clinical Practice is physicians and other healthcare providers and organizations that provide substance use disorder treatment and care. Clinical and operational leads in the health authorities may find the Recommendations for Clinical Practice useful in informing the implementation of iOAT. It should be noted that the Recommendations for Clinical Practice represent recommendations extrapolated from clinical judgment and the literature, and should be understood as a framework for implementing an iOAT program rather than provincial guidelines or standards, which are outside the scope of this document.

Purpose and Scope

This guidance document was created to provide an overview of the evidence on injectable opioid agonist treatment, potential models of care for this treatment, recommendations for clinical practice, and the necessary operational requirements. Injectable opioid agonist treatment is an evidence-based high intensity treatment option for opioid use disorder for patients who have not benefited from other treatments. The opioid overdose crisis detailed in the following section revealed significant gaps in the treatment options for opioid use disorder in British Columbia. The primary purpose of this document is not to suggest the expansion of iOAT as a panacea for the opioid overdose crisis. Rather, the crisis has identified a profound need to improve the overall OUD system of care, including expanding treatment for those patients with opioid use disorder who have not benefited from other treatments.

Based on local research and clinical experience, where iOAT patients have significantly decreased illegal and non-medical opioid use—thus decreasing their exposure to fentanyl and carfentanil-laced street opioids—and where no patients retained in care at Crosstown have died of an overdose from iOAT, it is hypothesized that expanding access to iOAT may be one effective tool in addressing the public health crisis. It is important to note that expansion of iOAT should be considered an integral component of the continuum of care for opioid use disorder rather than a response to the opioid overdose emergency, and that expansion of iOAT must be implemented in such a way that ensures ongoing access, including adequate funding to support long-term sustainability.

As the evidence review of this document outlines, the bulk of the literature on iOAT to date focuses on injectable diacetylmorphine. However, due to regulatory barriers in Canada, diacetylmorphine is currently only available to a small number of patients through the [Special Access Programme](#),^b and inclusion in Health Canada's [List of Drugs for an Urgent Public Health Need](#) in British Columbia.²

The SALOME (Study to Assess Longer-term Opioid Medication Effectiveness) trial, conducted at Providence Health Care's Crosstown Clinic, compared hydromorphone to diacetylmorphine, and found to be non-inferior to diacetylmorphine for the treatment of opioid use disorder.³ This study was a non-inferiority trial, which is a study design that is based on the assumption that a finding of non-inferiority indicates that the trial medication would prove superior to placebo in a placebo-controlled trial. Given that the results of the trial showed non-inferiority to diacetylmorphine, the assumption is made that hydromorphone would show the same (that is, non-inferior) effectiveness as diacetylmorphine,³ which has been shown to be superior to oral methadone for a small number of long-term opioid users who have not benefited from oral treatments.⁴ Much of the evidence review below concerns diacetylmorphine and, given the finding of non-inferiority paired with clinical experience, is extrapolated, when appropriate, to hydromorphone. Additionally, hydromorphone does not face the same regulatory challenges as diacetylmorphine and faces few barriers to rapidly scaling up treatment. Thus, **this document provides clinical guidance for iOAT treatment with hydromorphone** as it currently faces fewer regulatory barriers to expansion. Clinical guidance for the provision of diacetylmorphine can be found in **Appendix 9**.

This document should be understood as a living document, which will be updated regularly to reflect changes in evidence, policy, and practice. As the implementation and expansion of iOAT progresses, regulatory and training frameworks will emerge and be added to this document.

British Columbia Opioid Overdose Epidemiology

Opioid use disorder is one of the most challenging forms of substance use disorder facing the health care system in British Columbia and a major driver of the recent surge in overdose deaths in the province. People with OUD who inject opioids face significant risks to their health, including fatal overdoses, endocarditis, human immunodeficiency virus (HIV) and hepatitis C, and violence.^{5,6} The burden on communities includes medical care, public health and criminal justice costs, public disorder, and crimes against people and property. While current Canadian estimates are lacking, OUD is estimated to affect approximately 1.4% of Americans.⁷ A state of public health emergency was declared on April 14, 2016 in response to a sharp increase in overdose deaths in British Columbia. Between January 1 and Dec 31, 2016, British Columbia saw 935 overdose deaths, representing an 80.5% increase over 2015.⁸ The total number of confirmed and suspected overdose deaths in British Columbia from January 1, 2016 to July 31, 2017 is 1853.⁸ The recent emergence of street fentanyl, carfentanyl, and other highly potent synthetic opioids increasingly cut into heroin and other street drugs, including cocaine and methamphetamine, is a pressing public health concern that has contributed significantly to the overdose emergency. Provincial surveillance data indicate that the proportion of illegal drug overdose deaths involving fentanyl has rapidly increased from 5% in 2012 to approximately 62% in 2016.^{9,10} From January 1 to December 31 2016, there were 657 overdose deaths where fentanyl was detected, which translates to a 283% increase in overdose deaths involving fentanyl compared to the corresponding period in 2015 (151 deaths).^{8,11}

This unprecedented public health emergency underscores the importance of developing comprehensive, collaborative, compassionate, and evidence-based health services to address the harms related to untreated OUD. Opioid agonist treatment has proven to be the most effective approach to supporting abstinence from illegal or non-medical opioid use, while also reducing morbidity and mortality.¹²⁻¹⁶ In British Columbia oral OAT in the form of buprenorphine/naloxone and methadone is considered the first- and second-line

b. As of June 28, 2017 diacetylmorphine has been included in Health Canada's "[List of Drugs for an Urgent Public Health Need](#)," which will simplify the process for importing diacetylmorphine. This document will be updated as soon as possible to provide more clarity on the process for prescribing diacetylmorphine.

pharmacological treatment for OUD. While oral OAT represents a vital and foundational component of the provincial strategy, there are known limitations. Thus, the purpose of this document is to provide guidance for health authorities and physicians and other health care providers in British Columbia in making decisions regarding implementing and expanding injectable opioid agonist treatment (iOAT) provision in their region, in order to expand treatment options for those who have not benefited from oral OAT.

The Continuum of Care for Opioid Use Disorder

The continuum of care for OUD includes pharmacological (oral and injectable OAT) and non-pharmacological (e.g., psychosocial) treatment interventions and supports in order to meet individual and population needs. The BCCSU's [A Guideline for the Clinical Management of Opioid Use Disorder](#)¹ provides an overview of the spectrum of care available for OUD and guidance on oral OAT, while this document focuses specifically on the role of iOAT.

Opioid agonist treatments have proven to be the most effective approach to supporting abstinence from illegal or non-medical opioid use, while also reducing morbidity and mortality.¹²⁻¹⁶ In British Columbia, buprenorphine/naloxone (i.e., Suboxone[®]), methadone, and, increasingly, slow-release oral morphine (SROM) are used to treat opioid use disorder. Buprenorphine and methadone are supported by a large body of evidence for the treatment of OUD,¹⁶ and are included on the World Health Organization's list of essential medicines.^{13,17} However, there are known limitations, including intolerance, side effects, and long-term retention in treatment. While Canadian statistics are lacking, one 2012 study of Medicaid-enrolled individuals in the United States found that 63% of new OUD treatment episodes did not include OAT.¹³ Of those who are started on OAT, long-term retention on OAT and relapse prevention remains an ongoing challenge. For example, between 46-65% of patients who initiate methadone-based OAT discontinue treatment in the first year and relapse to opioid use.^{12,18,19} In British Columbia in 2014/15 (the most recent statistics available), 6-month retention for methadone-based OAT was 42%, with retention declining to 32% at 12 months.²⁰ Additionally, studies have found that less than 30-60% of individuals who are initiated on buprenorphine/naloxone-based OAT are retained in treatment at the 6-month mark.^{21,22}

Role of Injectable Opioid Agonist Treatments in the Continuum of Care

Patients may not benefit from first-line medications for a variety of reasons, including cravings persisting despite optimal OAT dosing; patients being unable to reach a therapeutic dose; or opting not to initiate oral OAT (e.g., previous experience with oral OAT including side effects, intolerance, or insufficient reduction in craving and illegal drug use). Individuals who do not benefit from first-line medications, like other individuals using illegal and non-medical opioids, face significant risks, including premature death, non-fatal overdose, blood-borne infectious diseases (e.g., HIV and hepatitis C), violence, and arrest.^{5,6} Research has shown that, among patients who are treatment refractory to methadone, prescription diacetylmorphine—administered under the supervision of trained health professionals in a clinic setting—is beneficial in terms of reducing illegal or non-medical opioid use, treatment drop-out, criminal activity, incarceration, and mortality.^{3,4,23,24} A 2011 Cochrane review reported that prescription diacetylmorphine appears to be associated with slightly superior outcomes related to social functioning, in comparison with methadone treatment at established therapeutic doses in individuals previously unsuccessfully treated with methadone.⁴ Overall, diacetylmorphine was found to be favourable compared to other treatments, when all of the studies included in the Cochrane review were pooled.⁴

While iOAT is still considered an off-label treatment in Canada, this treatment is an established standard of care in other jurisdictions where, typically, diacetylmorphine is supplemented with flexible doses of oral OAT at the patient's and physician's discretion.²⁵ In almost all countries where it is available, prescription diacetylmorphine is provided within supervised clinic settings (which ensures compliance and allows monitoring for safety and to prevent diversion), and to specific patients with severe, treatment-refractory opioid use disorder.²³ Some

jurisdictions have expanded their eligibility criteria beyond those with treatment-refractory opioid use disorder. For example, between 2005 and 2010 in Switzerland, over 90% of patients had been on oral OAT, leaving a small but notable minority of patients who had not previously received oral OAT.^{4,25} Retention rates for diacetylmorphine treatment have consistently been found to be quite high, with an 87.8% 12-month retention rate found in the NAOMI trial,²⁴ and a range of 12-month retention rates between 67-88% found overall.^{24,26,27} Retention rates for diacetylmorphine and hydromorphone were similar in the SALOME trial, with 6 month retention rates of 80% for diacetylmorphine and 77% for hydromorphone.³ These retention rates are notably more than double the retention rate for methadone-based OAT in BC (32%).²⁰

Health care utilization data from Europe indicate that the average length of prescription diacetylmorphine treatment is approximately three years.²⁵

Summary

- 46-65% of patients discontinue methadone treatment in the first year^{12,18,19}
- 40-70% of patients discontinue buprenorphine/naloxone treatment in the first six months^{21,28}
- Diacetylmorphine treatment is beneficial in terms of reducing illegal or non-medical opioid use, treatment drop-out, criminal activity, incarceration, and mortality^{3,4,23}
- 67-88% of patients retained on diacetylmorphine in the first year^{24,26,27}
- 77% of patients retained on hydromorphone in the first six months³
- Average length of diacetylmorphine treatment is approximately three years²⁵

Supervised Injectable Opioid Agonist Treatment

Overview

Several randomized trials and cohort studies have shown that injectable opioid agonist treatment provided in dedicated clinics is feasible, safe, and effective when treating long-term, chronic injecting opioid users for whom the available treatments have not been effective.^{26,27,29-32} In these studies, patients treated with diacetylmorphine and hydromorphone showed improvements in a number of dimensions, including reductions in non-medical heroin (and, in the SALOME trial, other non-medical opioids³) and cocaine use, decreased criminal activity, and improvements in physical and mental health.

Injectable Opioid Agonist Treatment in Other Jurisdictions

The United Kingdom has provided prescription diacetylmorphine for the treatment of opioid use disorder for over a century.³³ Prescription diacetylmorphine treatment has been available in Switzerland starting with a national clinical study in 1994,³⁴ and as a standard drug treatment since 1999. In 2008, as part of a national referendum, 68% of Swiss voters supported the permanent institution of a legalized prescription diacetylmorphine program funded by national health insurance.³⁵ More recently, Germany, Denmark and the Netherlands also adopted supervised prescription diacetylmorphine treatment for those with severe, treatment-refractory opioid use disorder.³³ In these countries, diacetylmorphine is used for <1% to 8% of all patients engaged in treatment for OUD.^{33,36} The Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program model (see Models of Care for BC in this document) has been widely applied in European jurisdictions, wherein patients receive comprehensive addictions care, with the aim of meeting as many of the patient's health and psychosocial needs as possible on-site. There are both stand-alone clinics and clinics co-located with (or very close to) other addictions and psychosocial services.³⁷

Evidence Summary

Summary of Cochrane Review and Recent Evidence

Meta-analyses of clinical trials involving patients with long-term refractory heroin addiction have demonstrated the efficacy of diacetylmorphine in comparison to methadone in terms of reducing non-medical heroin use, criminal activity, and involvement in sex work, as well as improving overall health and social functioning.^{4,23} These meta-analyses include a 2011 Cochrane Review which examined eight randomized controlled trials and found that supervised injection of diacetylmorphine, paired with flexible doses of methadone, was superior to oral methadone alone in retaining treatment refractory patients in treatment while helping reduce the use of illegal or non-medical drugs.⁴ The authors of the Cochrane review concluded that there is value in co-prescribing diacetylmorphine with flexible doses of methadone and that, due to the higher risk of adverse events, treatment with diacetylmorphine should be considered for those who have not benefited from oral agonist treatment.⁴ In 2015, the lead investigators of iOAT treatment trials conducted a systematic review and meta-analysis on the efficacy of injectable diacetylmorphine, to complement the Cochrane Review.²³ Six randomized controlled trials (in Switzerland, the Netherlands, Spain, Germany, Canada, and England) were identified and included in the analysis, which found greater reductions in non-medical heroin use among individuals who received supervised injectable diacetylmorphine compared to those who received oral methadone treatment only.²³ Supervised injectable diacetylmorphine was noted as a “low-volume, high-intensity” treatment (i.e., a low total number of patients engaged in highly-structured treatment requiring multiple clinic visits per day) with the potential to improve the impact of comprehensive health care provision. A loss of treatment benefit—that is, an increase in street heroin use post-treatment to levels comparable to that of the control group—when prescription diacetylmorphine treatment was discontinued at a predetermined end date has been found repeatedly.^{27,38} Thus, the authors of the Treatment Assisted by DAM study in Belgium, in

line with World Health Organization recommendations for other opioid agonist treatments, recommend that supervised injection of diacetylmorphine be provided as an open-ended treatment.^{32,38}

The majority of clinical trials evaluating injectable OAT have restricted participation to individuals who have previously undergone oral OAT treatment, thus, the evidence base is generally viewed as supportive of injectable OAT for the treatment of patients who have not benefited from oral OAT. However, one large randomized trial comparing injectable diacetylmorphine with oral methadone included a subset of participants (n=107 of 1,015 total) with severe OUD but no previous experience with oral OAT.^{26,39} Study authors found that outcomes of diacetylmorphine treatment were similar whether individuals had prior oral OAT experience or not, and within the subset of participants with no prior OAT experience, diacetylmorphine was superior to methadone in reducing nonmedical heroin use and criminal involvement, and as effective as methadone in improving overall health and retaining individuals in treatment.³⁹ The authors conclude that while these results may support re-evaluation of mandating prior oral OAT attempt(s) as a prerequisite to accessing iOAT, additional controlled trials that include prior OAT experience as a factor in trial design are needed to confirm these findings, as they have important implications for development and implementation of evidence-based health policy and services.³⁹ It should be noted that in this study, individuals who had no prior OAT experience had severe, chronic opioid use disorder – on average, people had injected drugs for 10 years, and at baseline, were injecting illicit heroin daily or more frequently.³⁹ As described above (p. 15), some European jurisdictions have expanded their eligibility criteria beyond those with treatment-refractory opioid use disorder.

SALOME & Hydromorphone

Though treatment with diacetylmorphine is a standard of care in a number of countries,²⁵ it is considered an emerging treatment in Canada and can only currently be accessed through Health Canada's Special Access Programme.^c In view of the restrictions on accessing diacetylmorphine, the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME), a phase 3, double-blind randomized controlled trial conducted in Vancouver, BC, compared diacetylmorphine with injectable hydromorphone in a population of patients with long-term, treatment-refractory opioid use disorder.³ After six months of treatment, researchers found that injectable hydromorphone was not inferior to injectable diacetylmorphine for long-term injection street opioid users not currently benefitting from available treatments. Both medications, delivered in identical conditions, have been shown to have positive outcomes such as high retention rates (over 85%), reduction of street opioid use (from daily to a few days per month) and illegal activities.³ Thus, in jurisdictions where diacetylmorphine is currently not available, or in patients where it is contraindicated or unsuccessful, hydromorphone provides an off-label, licensed alternative.³ The SALOME trial was run out of Providence Health Care's Crosstown Clinic in Vancouver, which now provides diacetylmorphine and hydromorphone treatment to a small number of patients with chronic, severe opioid use disorder who have not benefited from oral OAT despite multiple treatment attempts. Treatment is provided alongside life-skills counselling, housing referrals, and other psychosocial supports provided by on-site nurses, substance use counsellors, psychiatrists, addiction medicine physicians, nurse practitioners, and social workers.³

Safety

Optimizing patient safety has been an important factor in the designation of iOAT as a second-line intervention when oral OAT has not been successful (in jurisdictions where iOAT is available), and requiring doses to be administered in structured, supervised clinical settings. Any frequently administered injectable treatment is associated with higher risks of cutaneous and infectious complications compared to its equivalent oral formulation. In the context of injectable OAT, the more rapid onset of action and shorter duration to reach peak effects (including respiratory depression) that is achieved with intravenous or intramuscular injection rather than oral ingestion of high dose, full agonist opioid medications must also be considered. For this reason, and as

c. Access may improve in the near future upon implementation of the federal government's regulation to facilitate medications needed to address urgent public health issues.

emphasized throughout this document, iOAT should only be administered in designated clinical settings, with sterile supplies and in clean and safe conditions, and under supervision of qualified staff trained to intervene in the event of an adverse event or emergency. Further, while injectable treatment may confer higher risks of adverse effects than oral treatment, it is important to note that risks of injecting street drugs are considered to be significantly higher than injecting prescribed iOAT.

Studies in Europe and Canada have reported instances of significant respiratory depression events in people receiving injectable opioids, at an overall rate of about 1 in every 6000 injections, which is significantly lower than the risk present when injecting street heroin.²³ Each of these incidents were safely managed with appropriate resuscitation measures, which speaks to the necessity of injection being supervised by trained staff.²³ Prescription diacetylmorphine may pose an increased risk of other adverse events (e.g., histamine reactions, seizures, and overdose) compared to injectable hydromorphone³ and oral methadone.^{4,23} It is important to note that the majority of serious adverse events (SAEs) occur within a few minutes of receiving an injection;²⁶ therefore, the recommended post-injection supervision period of 15-20 minutes, which would be required regardless of program type or treatment setting (see Models of Care in this document), would be sufficient to recognize and resolve the majority of SAEs. Additionally, the combination of prescription diacetylmorphine and flexible doses of oral methadone may have a protective effect against overdose, as demonstrated by a non-statistically significant reduced mortality risk compared to oral methadone alone.^{4,23}

An additional concern with ongoing injection-based opioid agonist treatment is heightened risk of infectious complications such as sepsis, osteomyelitis, cellulitis, and abscesses. When the skin is punctured (even with a clean needle in a sterile setting), it provides a potential port of entry for bacteria or other microorganisms, particularly when the injections are being given multiple times per day (as is the case with diacetylmorphine and hydromorphone). With that said, the risk of infection and infectious sequelae in a sterile and supervised setting is only a fraction of the risk for those injecting street heroin. For example, in the 12-month NAOMI trial, two SAEs involving sepsis or other infections were reported, while three SAEs involving abscesses or cellulitis were reported, across a total of 89,924 injections.²⁹ In the SALOME trial, over the 180-day treatment period, 18 adverse events involving infectious complications were reported (14 cellulitis, 4 subcutaneous abscesses) over a total of 85,451 injections, which translates to 3.4% and 4.8% of all adverse events deemed related to injectable hydromorphone and diacetylmorphine treatment, respectively.⁴⁰ Additionally, the risk of contracting a blood-borne illness through equipment sharing (e.g., HIV or hepatitis C) is eliminated with the use of sterile equipment in a supervised setting.

In the majority of the studies on prescribed diacetylmorphine, nurses supervised patients' self-administration of medication and closely monitored patients to ensure their safety both before (e.g., no signs of intoxication) and after (e.g., no signs of over-sedation, respiratory depression) treatment was administered. If an overdose occurred after injection of the medication, supervision allowed for immediate onsite treatment, ensuring the safety of the patient; it is for this reason that supervised administration of iOAT is recommended rather than take-home dosing.^{4,23,40} Provision of injectable opioids under supervision also ensures the safety of the community by, for example, preventing diversion of a prescribed injectable opioid into the street for non-medical use. While concern has been expressed over security, public safety, and potential for diversion from sites offering prescribed injectable opioids, findings thus far suggest no negative effects for public safety.²³

As with other types of ongoing chronic opioid therapy, there is potential for opioid-induced hyperalgesia, which may require tapering the iOAT dose, introducing an opioid-sparing adjuvant for analgesia, or rotating to an alternative treatment.⁴¹ For this reason, it is suggested that only one or two dose escalations be made in the years after initial stabilization. If the patient continues to build tolerance or develops hyperalgesia, consultation with the RACE line or an addictions physician or community pharmacist with experience with iOAT is recommended.

Models of Care

Continuum of Care

Injectable opioid agonist treatment should be understood as one part of a continuum of care in the treatment of opioid use disorder. Similar to other chronic conditions (such as diabetes or hypertension), people with opioid use disorder may need to try multiple approaches of varying intensities along the care continuum. As part of their practice, iOAT service providers should establish fully functioning referral pathways to addiction, recovery, and substance use treatment programs in their local area, to ensure access to a variety of related services. These referral pathways may include outpatient, inpatient, and residential treatment programs; recovery-oriented services including peer-support programs; supportive recovery housing; psychosocial treatment interventions and supports; chronic pain management; primary care; addiction medicine specialist consultation; trauma therapy; and specialized services for women, youth, and Indigenous peoples. Beyond addiction care needs (including treatment for comorbid substance use disorders, e.g., stimulant use disorders), iOAT provision should also integrate mechanisms to support appropriate movement along the continuum of care. This guidance document uses the Substance Abuse & Mental Health Services Administration definition of recovery,^d which is:

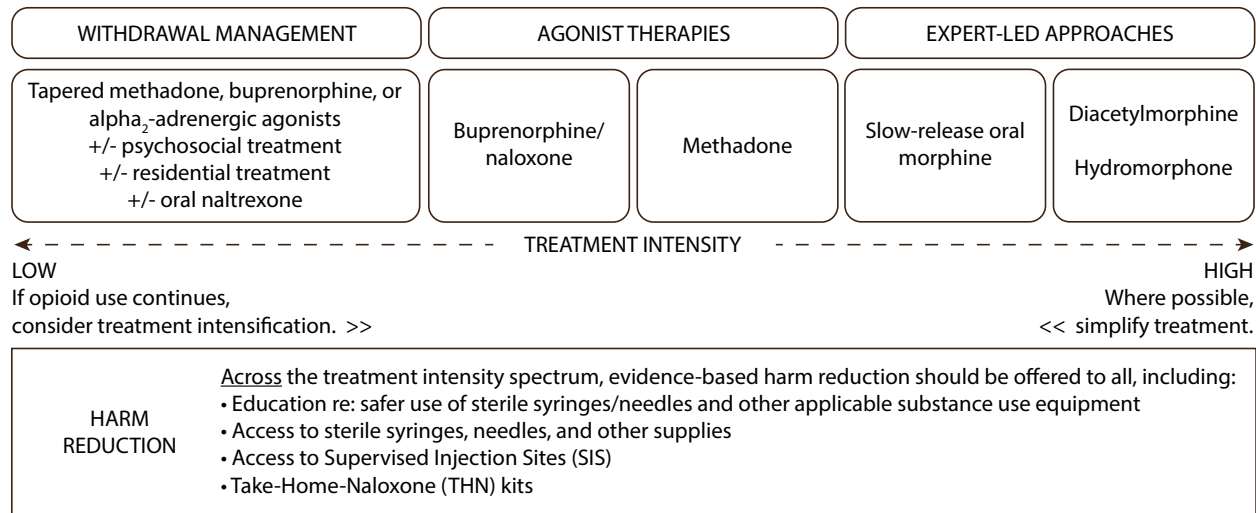
A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential.⁴²

To achieve these goals, health care practitioners providing iOAT should ensure patients are aware of the range of available opioid use disorder treatment services and continuously assess patients for readiness to access additional treatment programs for substance use disorders. Providers should also discuss the type of program that is most suitable to their patient's evolving goals, needs and interests. In addition, patients should be linked to a primary care provider or integrated primary care team. An integral component of expanding and improving the continuum of care involves decreasing the barriers to existing oral OAT and increasing access to psychosocial treatment interventions and supports available to patients. These expanded supports and increased access to oral OAT may assist the patient in succeeding with oral treatment.

Injectable OAT should be understood by both patients and prescribers as the highest intensity treatment option available for people with severe opioid use disorder who have been unsuccessful at reducing or ceasing their non-medical use of opioids with the assistance of adequately dosed lower-intensity treatment options (i.e., oral treatments). Patients must be prepared to attend for supervised injection at least daily. Supervised injection will include limited options for injection sites (e.g., not injecting in jugular or femoral vein) in order to reduce the risks associated with any intravenous access. Once patients are stable on iOAT and have been engaged in substance use treatment and primary health care they should be assessed for readiness to transition to less intensive and invasive treatment regimens at regular intervals. When patient and prescriber determine that transition is appropriate, patients should be supported and encouraged to move from this higher intensity treatment option to oral OAT (i.e., methadone, buprenorphine/naloxone, or slow-release oral morphine). Benefits of this transition include reduced risk from ongoing injection, reduced frequency of medication administration, decreased treatment intensity in terms of clinic attendance, and decreased risk of adverse events from oral OAT compared to iOAT.⁴ The continuum of care and ability to intensify and de-intensify treatment (as appropriate) is represented in Figure 1 below.

d. Note: the definition of recovery used in this document may be updated in order to provide consistency across all BCCSU guidance documents.

Figure 1: Continuum of Care



Family Involvement in Care

This document emphasizes the important role of families as partners in patient care when appropriate, and recommends the inclusion of family members in decision-making processes and care at all levels when deemed appropriate by the adult patient and their care team. Patients should not be pressured to include family members and should be given full discretion on the decision to include family, if at all.

If the patient determines family involvement would be a positive element in their treatment plan, care providers are encouraged to educate family members about available options and resources and provide as much patient-specific information as possible within the boundaries set by BC's privacy legislations.⁴³ The care team must have current and complete knowledge of consent protocols for releasing information. In the context of this document, the term 'family' encompasses all relations that are important to the patient, including significant others who are not legally recognized as family.

Patient-Centred Care

Research suggests that incorporating patient-centred approaches in clinical management of substance use disorders can improve retention in care, treatment satisfaction, and health outcomes.⁴⁴⁻⁴⁶ In addition to recognizing the unique needs, values, and preferences of each patient, patient-centred care aims to engage and empower patients as experts in their own care, including acting as the primary agent for reducing harms related to substance use, setting individualized treatment goals that are realistic and meaningful, and selecting treatment options or interventions that will best support achieving their individual goals.⁴⁷ From this foundation of inclusion and encouraging personal agency, providers can build on the therapeutic relationship, while keeping patients safe from the harms associated with street opioid use and reducing the risks associated with iOAT.

As is the standard of care for management of any complex or chronic medical condition, all iOAT prescribers should provide patient-centred medical management including general support and unstructured counselling to patients receiving iOAT, and regardless of the model of iOAT care employed. In this context, medical management is defined as medically-focused, informal counselling that includes, but is not limited to, health and mental wellness checks, offering non-judgmental support and advice, assessing motivation and exploring barriers to change, developing a holistic treatment plan, promoting alternative strategies for managing stress,

and providing referrals to health and social services when requested or appropriate. Establishing a trusting, respectful, and collaborative therapeutic relationship with patients remains a cornerstone of treating substance use disorders in clinical practice.

Due to the higher prevalence of histories of trauma and comorbid post-traumatic stress disorder among individuals with substance use disorders compared to the general population,⁴⁸ physicians should be familiar with the principles of trauma-informed practice (e.g., trauma awareness; safety and trustworthiness; choice, collaboration, and connection; strengths-based approaches and skill building). The provincial trauma-informed practice guide may be a useful resource when working with this patient population.⁴⁹ The trauma-informed practice guide can be accessed on the [Centre of Excellence in Women's Health's website](#).

In addition, physicians and staff should consider undertaking cultural safety and humility training to improve ability to establish positive partnerships with Indigenous clients seeking care for substance use and related harms. The San'yas Indigenous Cultural Safety Training Program, developed by the Provincial Health Services Authority (PHSA) Aboriginal Health Program, is an online training program designed to increase knowledge, enhance self-awareness, and strengthen the skills of those who work both directly and indirectly with Aboriginal people, and is an excellent resource for health care providers seeking to build their cultural competency. Please refer to the [San'yas program website](#) for more information. In addition, the First Nations Health Authority (FNHA) and BC Patient Safety & Quality Council offer a cultural safety and cultural humility webinar series that can be accessed on the [FNHA website](#).

Recovery-Oriented Care

The continuum of care for opioid use disorder should be understood as inclusive of recovery, with an understanding that recovery looks different for each person, with many different possible paths. Those seeking recovery require understanding, support, and referral to appropriate services to achieve their goals. iOAT care teams are encouraged to incorporate and use language that promotes recovery in their practice. These include ensuring respect of the patient's autonomy and individuality, emphasizing skills and strengths, and avoiding reinforcement of paternalistic models of care provision.⁵⁰ Additionally, and as appropriate, iOAT prescribers and care teams are encouraged to work with patients to develop long-term, personalized, strengths based recovery plans regardless of the severity, complexity, and duration of their substance use. The importance of peer navigators and peer support should also be recognized across the continuum of care for opioid use disorders. For recovery planning iOAT providers should consider incorporating peer navigators to support long term, patient-centered treatment goals.

Models of Care for BC

This document describes three potential models of care, two established and one emerging, in more detail below. These models are based on the following aims of iOAT:

- Preventing premature death from overdose and other imminent harms (such as HIV/hep C, abscesses, and systemic infections) associated with ongoing injection drug use, especially in the context of the overdose emergency in BC and the highly unpredictable potency of street opioids due to the emergence of fentanyl and other synthetic opioids entering the illegal drug market.
- Engaging individuals in addiction treatment who have been otherwise unable to access other forms of treatment. Regular contact with physicians, nurses, pharmacists, and other healthcare and service providers allows a variety of patient needs to be met. The supervised models of care of iOAT may increase safety for the patients and the community, and provide an opportunity to build relationships and offer ancillary services.

The provision of iOAT requires a multidisciplinary care approach in which individuals receive, as needed and appropriate, addictions care; primary care; mental health care; chronic pain management; and psychosocial services including housing, employment services, trauma therapy, and specialized services for women, youth, and Indigenous peoples.

Two established models and an emerging model have been proposed for implementation of iOAT programs in British Columbia, and are briefly described below.

1. A Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program

In regions with the capacity and demand, a comprehensive model of care dedicated specifically to the delivery of supervised injectable opioid agonist treatment for people with severe, long-term opioid use disorder can be instituted. This may be a stand-alone facility or located at a hospital or other acute care centre. In addition to attending the clinic up to three times per day to self-administer injectable hydromorphone under the supervision of qualified health professionals or trained staff supervised by qualified health professionals (physicians, Registered Nurses, Licensed Practical Nurses, Registered Psychiatric Nurses, Registered Social Workers, Registered Clinical Social Workers, pharmacists), patients can be linked with ancillary services co-located at the clinic or referred to community services. These services may include addictions care; primary care; mental health care; chronic pain management; and psychosocial services including housing, employment services, trauma therapy, and specialized services for women, youth, and Indigenous peoples. The Providence Health Care Crosstown Clinic in Vancouver is an example of a comprehensive and dedicated supervised iOAT model. The majority of European jurisdictions that offer iOAT also use the comprehensive and dedicated supervised model, with a combination of stand-alone clinics and clinics co-located with other addictions and psychosocial services.

2. Integrated or Embedded Supervised Injectable Opioid Agonist Treatment Program

In this model of care, existing community health clinics (CHC) and harm reduction programs across the province could integrate an iOAT program within their range of treatments and programs offered. Similar to the comprehensive and dedicated iOAT program presented above, the integrated-CHC model will also foster client and health care provider relationships, continuity, and comprehensiveness of care. As patients may already be familiar with the staff and services in the CHC, the integration of an iOAT program would represent an extension of the range of programs already offered to clients. Additional services, which may not be available on site, should be referred out. These may include addictions care; primary care; mental health care; chronic pain management; and psychosocial services including housing, employment services, trauma therapy, and specialized services for women, youth, and Indigenous peoples. This model, which is currently being piloted by the PHS Community Services Society (PHS) in the Downtown Eastside neighbourhood of Vancouver, could also be integrated into acute care settings, or supportive housing with nursing and/or other health care provider services already embedded, by opening a dedicated space for an iOAT program.

3. Emerging Model: Pharmacy-Based Supervised Injectable Opioid Agonist Treatment Program

In this model of care, which is currently being piloted by the PHS in Vancouver, primary care and addiction services are provided in existing clinics with supervision of iOAT provided by appropriately trained pharmacists at select pharmacy locations. This allows for a lower intensity of treatment than the comprehensive and dedicated model, and for access to iOAT in communities where the CHC model may not be appropriate or feasible. This option may be appropriate for patients who are already well connected to other services and/or for patients where the more intensive options are not possible due to infrastructure or operational funding. Patients who are not connected to adequate services should be referred, as needed. These services may include mental health care; chronic pain management; and psychosocial services including housing, employment services, trauma therapy, and specialized services for women, youth, and Indigenous peoples. Similar to daily pharmacy-witnessed methadone ingestion, prescribed hydromorphone syringes would be prepared, dispensed, self-administered, and witnessed by trained pharmacists. Once patients have given consent to and

fully understand the goals of treatment, intensity of treatment, risks of iOAT, requirements of inclusion in the program, and the requirements of supervised self-administration, patients are titrated onto a stable dose at their prescriber's office or clinic, with injection supervised by their physician, a Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, Registered Social Worker, or Registered Clinical Social Worker, and then transferred to the pharmacy for supervised injection, with ongoing regular prescriber visits to ensure appropriate dosing and provision of other addiction care. This model requires that pharmacies develop processes to ensure the safe delivery of iOAT (e.g., prevent diversion, ensure overdose risk is addressed) and pharmacy staff to undergo additional training (e.g., overdose response, education on preventing diversion, first aid). In this pharmacy-based supervised iOAT model, it would be the responsibility of the pharmacy to complete the pre- and post-intake evaluations (see **Appendix 1**), including intoxication and referral to ongoing treatment of needle-site wounds. Onsite supervision allows for immediate intervention and treatment in case of an adverse event or overdose, ensuring the safety of the patient. In this model, the pharmacist and prescriber would work closely together to ensure adequate dosing, make any changes to dosing as needed, and provide ongoing addiction care to ensure patients' basic health and psychosocial needs are met. Ongoing coordination of care and regular communication between pharmacist and prescriber would also ensure that any emerging care issues outside the scope of practice for pharmacy professionals (e.g., wound care) can be quickly referred to the prescribing physician for follow-up.

As the pharmacy-based supervised iOAT program is currently an emerging model being piloted, best practices and any requirements beyond those outlined in this document for iOAT provision, will be developed by the BCCSU, PHS, and participating pharmacies. It should be noted that regulatory colleges will need to be involved in a regulatory capacity as the pharmacy models are explored, to ensure that pharmacists are appropriately trained and all necessary procedures including documentation are being followed.

As noted previously, as part of its provincial mandate, the BCCSU plans to conduct rigorous monitoring and evaluation of iOAT program expansion and implementation across the province, including pharmacy-based supervised models, with the goal of optimizing treatment outcomes, patient and public safety, and quality of care.

Table 1—Benefits and Drawbacks of Each Proposed Model

Model	Benefits	Drawbacks
A Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program	<ul style="list-style-type: none"> • Comprehensive, multi-disciplinary care provided in one location; “one-stop shop” • Established model used at Providence Health Care’s Crosstown Clinic and in European jurisdictions • Few or no barriers to receiving additional services • Continuity and comprehensiveness of care • Preferred option for patients lacking clinical and social stability • Currently the only model for diacetylmorphine as per Health Canada regulations 	<ul style="list-style-type: none"> • Resource-intensive, including on-site pharmacy • Not appropriate for communities with low demand or capacity for iOAT services • May create challenges moving patients down the continuum of care (i.e., de-intensifying treatment) when applicable
Integrated or Embedded Supervised Injectable Opioid Agonist Treatment Program	<ul style="list-style-type: none"> • iOAT integrated into existing services • Lower resource requirements • Continuity and comprehensiveness of care • Currently being piloted by PHS Community Services Society in Vancouver • Low barriers to additional services • Appropriate for communities with lower demand for iOAT • Currently being piloted by PHS Community Services Society in Vancouver 	<ul style="list-style-type: none"> • Requires more resources than programs offered at existing site • Requires dedicated space in sites that may already have limited space • Requires on-site pharmacy or pharmacy delivery
Emerging Model: Pharmacy-Based Supervised Injectable Opioid Agonist Treatment Program	<ul style="list-style-type: none"> • Appropriate for communities with low demand for iOAT • Appropriate for patients on a stable dose • Low resource requirements • Less intensive treatment requirements for patients • Currently being piloted by PHS Community Services Society in Vancouver 	<ul style="list-style-type: none"> • Higher barriers may exist to receiving additional services • Emerging model will require evaluation and refinement as model trialled

Community Context

There are different ways to plan, design, and implement iOAT services and, accordingly, many issues to consider with respect to the target client population, existing network of services for people who use drugs, and resources available, including funding, space, and staff. Need should be determined through relevant environmental scans, needs assessments, and, if appropriate, feasibility studies. This can involve reviewing local health data and/or conducting surveys or qualitative research with local people who use drugs and other relevant stakeholders to assess need, potential uptake, and design preferences. Importantly, such work can be instrumental in determining the model or models of iOAT needed and the most appropriate location of these services. Local people who use drugs should be involved in the planning and execution of such feasibility work and service planning.

In addition to feasibility and planning work for iOAT services, each health authority should strive to create a community context in which there is robust addiction treatment available across the continuum of care. As such, it is recommended that health authorities also prioritize the scaling-up of oral OAT to ensure that same-day initiation (i.e., low barrier treatment) of methadone, buprenorphine/naloxone, and SROM is available in addition to a full range of addiction treatment and supports, including iOAT. This increased capacity should not be understood as a pre-requisite to offering iOAT but, rather, the necessary expansion of all evidence-based treatments across the province, to ensure patients and their families have access to a full continuum of care for the treatment of opioid use disorder in each region.

As iOAT is a high intensity treatment regimen with associated risks that require ongoing management and oversight, there are recommended criteria that need to be met to ensure safe provision of this treatment. These criteria should be achievable in a variety of settings and overall programming can be tailored to the needs and capacities of the community.

Minimum Recommended Criteria

- Dedicated space for supervised self-administration;
- Trained health professionals (i.e., physician, Registered Nurse, or Registered Psychiatric Nurse) to provide intramuscular injection when clinically appropriate, see Appendix 2;
- At least one Registered Nurse, Registered Psychiatric Nurse, or pharmacist who has the authority and experience to manage opioids under the Controlled Drugs and Substances Act to oversee the program;
- A plan for patient safety in case of overdose and appropriate equipment to manage an overdose prior to transfer to a higher level of care;
- A plan to prevent diversion and manage attempts at diversion which may include suspension from the program to a less intensive method of treatment;
- Provision for access to medication up to 12 hours per day (minimum 3 hours required between doses, most patients require 3 doses per day), seven days per week;
- Secure, locked storage for medication;
- A staff-to-patient ratio that is appropriate to the space and number of patients;
- Ability to provide individually titrated, patient-specific doses;
- Ongoing and consistent access to prescriber to allow medication adjustment;
- Capacity to observe patients before, during, and after administration; and
- Ability to link patients to ancillary services.

Suggested Budgetary and Operational Considerations

Budgetary and operational considerations, including space needs, pharmacy requirements, staffing models, security considerations, and programmatic limitations can be found in **Appendix 3**.

Part II: Recommendations for Clinical Practice

The section offers clinical guidance, which each health authority or service provider may tailor to meet the needs of their health service delivery area. General considerations from existing clinical programs and the scientific literature are provided, offering a framework for how to expand iOAT services in BC. Physicians are encouraged to consult with addiction medicine experts with iOAT experience as needed.

Summary of Clinical Practice Recommendations

The clinical practice recommendations are summarized in Table 2 below.

Table 2: Summary of Clinical Practice Recommendations

General Considerations	Patients with severe and/or refractory opioid use disorder who have not benefited from oral OAT or are assessed as being at severe risk of overdose death	P. 28
Eligibility	Recommended considerations for eligibility in concert with clinical judgment and precautions	P. 28-29
Obtaining the injectable medications	Hydromorphone may be dispensed by NAPRA-compliant pharmacies through advanced compounding. Alternatively, single-use doses can be delivered and/or drawn prior to administration	P. 30-31
Selection of Dose	Follow the titration protocol and note maximum recommended daily doses	Appendix 4 (P. 43-45)
Pre-Intake Assessment	Performed by health professional or trained staff supervised by health professional to ensure the patient is not intoxicated or in any other contraindicated acute clinical condition	P. 32, Appendix 1 (P. 36-38)
Administration of Injectable Medications	Up to 3 visits per day Patients self-administer under supervision of a Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, pharmacist, Registered Social Worker, or Registered Clinical Social Worker Intravenous injection allowed only in upper extremities (excluding neck or chest veins) Intramuscular injections allowed in the thighs, deltoid, and gluteal muscles. IM sites should be identified by a physician, Registered Nurse, or Registered Psychiatric Nurse, and rotated	P. 32
Titration Process	Follow titration protocol	Appendix 4 (P. 43-45)
Co-Prescription of Oral OAT	Can be added to care at any time, per physician. SROM is preferred over methadone due to improved safety profile	P. 33
Dosage Equivalence w/ Oral Methadone and SROM	See conversion table	Appendix 5 (P. 46-47)

General Considerations

Supervised injectable opioid agonist treatment is generally considered for those patients with severe and refractory opioid use disorder who have not benefited from oral opioid agonist treatments (buprenorphine/naloxone and/or methadone and/or slow-release oral morphine) as evidenced by multiple unsuccessful attempts, or who have been assessed as being at severe risk of overdose death from injection opioid use as evidenced through documentation/reports of repeated overdoses requiring naloxone or transfer to higher level of care. It is important that all healthcare providers maintain thorough documentation of treatment offers, treatment attempts, overdoses, and patient outcomes in order to ensure that patients are appropriately transitioned through the continuum of addiction treatment and care.

The following eligibility considerations are based on research literature and existing clinical programs. However, it should be noted that these clinical programs were developed under different circumstances, not during an opioid overdose crisis driven by street opioids adulterated with highly potent synthetic opioids such as fentanyl and carfentanil. Thus, the following eligibility considerations were compiled with the assumption, based on decades of clinical and research experience with opioid agonist treatment, that safe pharmaceutical grade opioids prescribed under supervision with clean injection supplies is much safer than illegal and non-medical opioids, especially in the context of the fentanyl crisis in British Columbia.

Patient Population and Eligibility

As individual situations vary, the below is presented as considerations for eligibility, with the recognition that individual patients may not meet all of the listed criteria, while other criteria, not listed, could make a compelling case for program admission. Physicians are advised to use their discretion in determining which treatments have the highest likelihood of ensuring the goals of care, which should continue to be survival, reduction in the use of non-medical opioids, and the least intensive level of care possible.

Eligibility considerations for injectable opioid agonist treatment include:

- Capacity to consent to and fully understand the goals of treatment, including:
 - Level of intensity of treatment (i.e., multiple clinical visits per day)
 - Risks of iOAT
 - Requirements of inclusion in the program
 - Requirements of supervised self-administration;
- Well-established history of injection drug use with opioids and severe opioid use disorder (DSM-V);
- Current opioid injection drug use confirmed by patient report, signs of injection drug use (e.g., fresh puncture wounds or “track” marks), and documented opioid-positive urine drug tests (at least two recommended but clinical judgment may supersede this recommendation);
- Able to attend clinic or pharmacy up to three times daily (physically able and reside in proximity);
- Able to self-administer (i.e., inject via intravenous or intramuscular route) medication under supervision;
- Past experience with appropriately dosed oral agonist therapies (per [A Guideline for the Clinical Management of Opioid Use Disorder](#)¹) in the form of methadone, buprenorphine/naloxone, or slow-release oral morphine^e and evidence of regular and ongoing injection opioid use while trialed on these therapies

d. With the June 5, 2017 provincial adoption of the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder, slow-release oral morphine (24-hour formulation, brand name Kadian[®]) is, for the first time in British Columbia, recommended for higher intensity oral treatment for OUD. Prescribers should connect with the RACE line for assistance as needed when assessing this eligibility consideration and treatment with slow-release oral morphine.

(confirmed via consultation with previous OAT prescribers and review of medical records including urine drug testing, PharmaNet history, dosing, treatment intensification, and adherence). If a patient has had multiple attempts at oral agonist therapies but has never been able to achieve a therapeutic dose or has not been able to successfully reduce or discontinue their use of illicit opioids and continue to experience health and social consequences related to their opioid use disorder they may be considered for iOAT at the discretion of the treating physician;

- Significant risk of medical consequences of injection drug use that would likely benefit from increased health system involvement and engagement in care, or existing significant medical and/or psychiatric comorbidities (e.g., HIV positive and antiretroviral non-adherence, acute hepatitis, cardiopulmonary disease, severe mental health challenges, history of multiple overdoses);
- At least 18 years old;
- No co-prescribed benzodiazepines and/or z-drugs; and
- Does not fit the criteria for active moderate or severe alcohol use disorder or sedative use disorder (see the College of Physicians and Surgeons of British Columbia's [Safe Prescribing of Medications with Potential for Misuse/Diversion⁵¹](#)).

In addition to the above considerations, it is suggested that the iOAT prescriber, with their patient's consent, consult members of that patient's extended care network (e.g., addictions counsellor, outreach worker, supervised consumption site staff, mental health worker) in order to gain a robust understanding of each patient's individual situation and risks. For example, an outreach worker may have important information about the level of risk an individual is facing that the prescriber may otherwise be unaware of, such as a recent history of multiple overdoses where naloxone was administered. Those same health and service providers should, in partnership with the patient, formulate biopsychosocial treatment goals in the same manner as for oral OAT. Prior to admission, individuals identified as likely to benefit from iOAT should go through an admission process that involves full informed consent and a recommended peer orientation, to ensure program regulations, time commitments, and other requirements are fully understood.

The appropriateness of iOAT should be determined by the patient in concert with their primary care provider and the iOAT prescriber (if different from their primary care provider). As such, the decision of starting treatment with iOAT relies not simply on a list of criteria, but on the prescriber-patient relationship, input from the patient's network of care providers (who may have relevant information, for example knowledge of recent overdoses), and clinical judgement. If the patient is currently receiving oral OAT, the iOAT prescriber should consult with the oral OAT prescriber as part of the assessment process. While the above criteria are not exhaustive, they reflect current best practices in multiple jurisdictions with a focus on ensuring patient and community safety without making entrance requirements overly restrictive for patients who are at high risk of fatal overdose and other significant harms from ongoing injection opioid use.

Precautions

- Caution should be exercised in prescribing iOAT to patients with chronic medical conditions such as respiratory, hepatic or renal disease, acute conditions, or a history of recent head injury. Caution is also required for youth and older adults, in whom oral OAT or other forms of treatment may be more appropriate;
- The greater inherent risk of overdose with injectable treatments should be individually considered in each case;
- Extreme caution should be exercised in prescribing iOAT to patients with existing injection-related infections (e.g., septicemia, endocarditis, pneumonia, infective osteomyelitis), and in individuals with coagulation disorders (e.g., patients prescribed anticoagulants, severe hepatic disease, deep vein thrombosis). Oral treatment options should be preferentially prescribed for such patients;

- Physicians should carefully consider drug-drug interactions⁶
- Caution should be exercised with pregnant women or women who become pregnant while receiving iOAT. This caution should be balanced against the potential harms of denying access to iOAT for a pregnant woman who otherwise meets eligibility criteria; and
- Caution should be exercised in prescribing iOAT to patients who cannot safely self-administer their medications, due to either inadequate venous access in ‘low-risk’ sites (with consequent injecting in neck or groin veins), or persistently poor injecting technique not remedied by education about intramuscular injection.

Youth

Although the research evidence presented here has been extrapolated from studies conducted in adult populations, it is recognized that prescribers may encounter adolescent (aged 12–17 years) and young adult (aged 18–25 years) populations with severe opioid use disorder who do meet some or all of the considerations for eligibility for injectable opioid agonist treatment in their practice. While it is outside the scope of this guidance document to make specific recommendations for treatment of adolescents and young adults, it is emphasized that physicians should use all available information and their best judgment when considering treatment options for any individual who is at high risk of overdose death, including use of available and evidence-based pharmacotherapy where indicated and appropriate and with the support of appropriate agencies such as local health authorities and the Ministry of Child and Family Development. If administration of pharmacotherapy to this patient population is beyond scope of practice or expertise, care providers should refer such patients to a health care professional with experience in treatment of adolescents and young adults with substance use disorders.

Obtaining and Preparing Hydromorphone

Hydromorphone must be compounded in a facility that complies with the National Association of Pharmacy Regulatory Authorities (NAPRA) sterile compounding standards⁵² and the College of Pharmacists of British Columbia Bylaws.⁵³ Please see the College’s website for more information on bylaws: www.bcpharmacists.org. Health authorities should be involved in providing the service or contracting for pharmacy services within their area.

Hydromorphone may be dispensed by pharmacies in two ways – either through advanced compounding and preparation of doses in a NAPRA-compliant pharmacy or via delivery of single-use vials by a local pharmacy, which are drawn into a syringe prior to administration. The decision of which format is utilized will vary based on the number of patients for whom the medication is needed in a particular setting as well as available infrastructure and resources. Advanced compounding is recommended when possible to prevent drug wastage and potential for diversion, however, the lack of an embedded pharmacy to provide this service should not preclude consideration of offering this treatment to patients who would benefit.

Advanced Compounding: Advanced preparation of doses by a NAPRA-compliant licensed pharmacy allows for a beyond-use date of up to nine (9) days if the compounded syringes are refrigerated and up to thirty (30) hours at room temperature.

Single-use Vials: High potency hydromorphone (50 mg/mL) is commercially available in single-use vials. Any unused portion of the vial must be discarded unless the hydromorphone is drawn up into a syringe in a laminar

f. Prescribers are encouraged to consult the Canadian Pharmacist’s Association’s RxTx tool, available as a subscription both [online](#) and in a [mobile app](#), or other subscription-based drug interaction tools. Prescribers may also consult with a pharmacist.

air flow hood (i.e., NAPRA compliant). Unused hydromorphone has 6-hour stability if it has been produced in a laminar flow hood. If drawn up outside of a laminar flow hood, hydromorphone has 1-hour stability. Single-use vials require preparation of the syringe while the patient is in attendance for their dose and does not allow advance syringe preparation. Best practices and established standards for preparing and handling injections must be followed.

All pharmacies must follow the College of Pharmacists of British Columbia’s *Pharmacy Operations and Drug Scheduling Act—Bylaws*,⁵³ including requirements for security, disposal of drugs, proper documentation, and inventory management. In addition, those pharmacies providing pharmacy-based supervision of iOAT must provide reports to doctors, report on adverse events, and (where applicable) manage injection space including management of supplies, disinfection of tourniquets and equipment, attending to and reporting of overdoses.

Prescribing Injectable Hydromorphone

Selection of Dose

Due to high inter-individual variability, each individual’s dose must be carefully determined. There are no fixed doses for optimal stable dosing of hydromorphone for persons with an opioid use disorder. The upward titration at the start of therapy should begin with a safe dose and follow the protocol outlined in Appendix 4. Maximum hydromorphone dosages are based on a 2:1 potency ratio of hydromorphone to diacetylmorphine observed in the SALOME study and the clinical experience at Providence Health Care’s Crosstown Clinic.⁵⁴

Maximum recommended daily doses of hydromorphone can be found in Table 3 below.

Table 3—Maximum Recommended Daily Doses

Medication	Hydromorphone
Maximum Number Doses Per Day	3
Maximum Daily Dose	500mg
Maximum Per Dose	200mg

Dose increases need to be tolerated in order to continue at that dose. Doses that are not tolerated, as per assessment during either the pre- or post-injection assessment periods, should be reduced. Doses should be titrated to clinical effect (i.e., cessation of illegal and non-medical opioid use and opioid cravings) and avoidance of side effects (e.g., sedation, narcotic bowel, opioid-induced hyperalgesia).

Supervision of Injections

Patients self-administer under supervision of a qualified health professional.^g Training involves orientation to an existing supervised injection program, along with training on conducting pre- and post-injection assessments (see **Appendix 1**), responding to overdose, and aftercare.

Supervision of self-administered injection involves completing a pre-injection assessment, direct observation of the injection, and a post-injection assessment (see following section for more information on pre- and post-assessments).

It should be noted that in the emerging pharmacy-based model, a pharmacist must supervise injection.

g. Physician, Registered Nurse, Registered Psychiatric Nurse, Licensed Practical Nurse, Registered Social Worker, Registered Clinical Social Worker, or pharmacist. Hereafter referred to as “qualified health professional.”

Pre- and Post-Injection Assessment

The purpose of the pre-injection assessment, completed by a health professional or other trained staff if supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist), is to ensure that the patient is not intoxicated, including by centrally-acting sedatives and/or stimulants or in any other acute clinical condition that would increase the risk of an adverse event with the use of the injectable hydromorphone. Cautions could include intoxication due to the use of stimulants resulting in the participant being actively psychotic or agitated in a way that would pose an immediate safety risk to themselves, staff, or other patients. Appropriate actions in response to these cautions may include holding the dose, reducing the dose, and/or delaying the dose.

Any qualified health professional or other trained staff supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) that has been trained to complete post-injection assessments can conduct the post-injection assessments, however, any doubts or uncertainties must be reported to a regulated health professional (e.g., physician, Registered Nurse or pharmacist) who will complete the post-injection assessment. The post-injection assessment time period should be extended if any of the following are present and are not part of the patient's usual disposition: drowsiness, slow response, slurring, or dyskinesia. Patients can leave the premises when they are deemed fit to do so after the minimum 15-20-minute observation period post-dose.

The pre- and post-injection assessment can be found in **Appendix 1**.

Administration of Injectable Medications

It is recommended that patients have access to the iOAT program up to three times per day. Patients are to self-administer their prepared dose under the supervision of a qualified health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, Registered Social Worker, Registered Clinical Social Worker, or pharmacist). Patients may inject intravenously, intramuscularly, or subcutaneously. For safety reasons, it is recommended that intravenous injection only be allowed in the upper extremities (hands or arms, no jugular use is permitted), while intramuscular injections can be allowed in the deltoid, thighs, and gluteal muscles.

Intramuscular (IM) injection sites should be identified in consultation with a physician, Registered Nurse, or Registered Psychiatric Nurse, and rotated, with the total volume of medication for injection taken into consideration for the most appropriate site (i.e., a large volume should be injected into a large muscle). When clinically indicated, a physician, Registered Nurse, or Registered Psychiatric Nurse can administer the medication intramuscularly. See **Appendix 2** for more information on healthcare provider administered IM injection.

Titration Process

The initial adjustment of the medication dose should be done over a three to five-day titration period. At any time during the titration period, physicians can lower a patient's dose or suggest a more gradual titration based on the patient's response and safety concerns. Doses must be titrated specifically for each patient in order to achieve a safe and effective dose for each patient. A lower starting dose or a slower titration process can be followed, per the patient's medical history or clinical experience, under the direction of the prescribing physician. Patients, in consultation with and under the guidance of their prescribing physician, can adjust the dose and frequency of daily injection sessions (up to three). Such adjustments can be considered after a visit between the physician and the patient, upon reviewing the dose received history and, if appropriate, consulting with at least one nurse (or other health care provider) who has been directly involved in pre- and post-assessment and supervision of current dosing schedule for that patient. This guideline supplement's recommended titration process can be found in **Appendix 4**.

Co-Prescription of Oral Opioid Agonist Treatments

It is recommended that, in consultation with their prescribing physician, patients can add oral OAT (i.e., methadone or slow release oral morphine) to their care at any time in order to avoid withdrawal symptoms between opioid injections (such as overnight) or to reduce the number of daily visits to the clinic. Methadone and slow-release oral morphine prescribing should follow the recommendations in [Guideline for the Clinical Management of Opioid Use Disorder](#).¹ It should be noted that the decision of whether to co-prescribe methadone or slow-release oral morphine should be based on patient choice and clinical judgment, however, this guidance document recommends slow-release oral morphine over methadone due to its improved safety profile.

Dosage Equivalence with Oral Methadone and Slow-Release Oral Morphine

In order to maintain an average degree of saturation of the opiate receptors by opioids to prevent withdrawal symptoms and avoid over-dosage, for those receiving an evening dose of oral methadone or slow-release oral morphine, it is critical to establish a conversion factor for switching between methadone or slow-release oral morphine and hydromorphone.

The opioid bioavailability of the individual pharmaceutical agents must be considered when converting dosages. A 100% bioavailability of hydromorphone injectable solution is assumed, irrespective of whether it is administered intravenously, subcutaneously, or intramuscularly. The calculation is always based on the intended effective opioid dose.

The conversion should be based on doses received, not prescribed. See the conversion table in **Appendix 5**.⁵⁵

Conversion of Oral Methadone and Slow-Release Oral Morphine for Travel

If patients receiving iOAT need to travel, for example to visit family or attend a funeral, they may receive prescriptions for methadone or slow-release oral morphine. Generally, for a single-day trip, patients would be provided with a prescription for witnessed ingestion of SROM, due to its superior safety profile compared to methadone. For longer absences, a slow transition (over 7 to 14 days) to methadone is possible, or witnessed ingestion of SROM at a community pharmacy is recommended. If the pharmacy is located outside of British Columbia the prescriber will have to call the pharmacy to ensure witnessed ingestion of SROM or methadone is possible. Note: Prescriptions filled outside of British Columbia will not be reimbursed by PharmaCare.

For conversions to SROM for travel standard opioid conversions should be used in concert with clinical judgment. All SROM doses must be witnessed ingestion. See **Appendix 5** for more details on conversion.

Missed Doses

A missed-dose protocol should be instituted which lowers the dose immediately and requires re-titration in the following circumstances:

- If a new, not-yet stabilized patient misses 3 consecutive sessions or 1 day (whichever is first); or
- If a stabilized patient misses 9 consecutive sessions or 3 days (whichever is first).

If a client misses a dose or a day they should have a social worker or other outreach worker follow up with them to ensure their safety.

Managing Ongoing Substance Use

Continued use of non-medical opioids (ascertained by self-report or urine drug test) while on iOAT should be considered an indication to intensify treatment. Clinical judgment should be used in determining what intensification is appropriate. Intensification of treatment may include adding an evening dose of oral OAT (e.g., slow-release oral morphine), increasing an existing evening dose of oral OAT, increasing the dose of injectable medication, transferring to a more intensive model of care (for example, moving from a community health

clinic to a comprehensive and dedicated iOAT model), or increasing evidence-based psychosocial treatment interventions and supports. If a patient is continuing to use non-medical opioids despite intensification of treatment, clinical judgment should be used to determine appropriate follow up. If the patient is receiving significant psychosocial, physical, or mental health benefits from the intervention, ongoing non-medical opioid or ongoing injection drug use should not be considered an absolute indication to stop or transition to another treatment. If the patient is continuing to use non-medical opioids or continuing to inject other substances and receiving no benefits from iOAT after intensification and optimization of treatment, treatment cessation may be considered. Treatment decisions should be made with the recognition that connection to healthcare and community are important outcomes of treatment engagement and access to services.

If a patient is found to be intoxicated during the pre-assessment, their dose should be postponed or withheld to ensure safety (see **Appendix 1**). Repeated findings of intoxication in the pre-assessment should be discussed with the patient and may be treated as an indication for intensification of treatment, as outlined above.

If patients are using stimulants (e.g., injecting cocaine or methamphetamines) while receiving iOAT, the risks and benefits of iOAT should be evaluated to ensure that the person is benefitting from the treatment. Clinical judgment should be used in determining if intensification of treatment is appropriate. Intensification of treatment may include increasing psychosocial and other supports, such as implementing Contingency Management.

De-Intensifying Treatment

This document recommends the use of a stepped and integrated continuum of care model for treatment of opioid use disorder (see Figure 1), where treatment intensity is continually adjusted to match individual patient needs and circumstances over time and recognizes that many individuals may benefit from the ability to move between treatments. This includes intensification (e.g., initiating iOAT when oral OAT approaches have not been met with success) as well as routine strategies to de-intensify treatment (e.g., transitioning from iOAT to oral opioid agonist treatments) when patients achieve successful outcomes and wish to transition to low intensity treatments. It is further recommended that iOAT prescribers support appropriate movement along the continuum of care for patients by routinely discussing treatment goals with patients and families (when appropriate), including plans for medically supported transition to oral OAT. Discussion of de-intensification of treatment should not involve pressuring patients into moving to other treatment options, but rather outline treatment options and their potential risks and benefits.

As patients stabilize they may be ready to move to lower intensity treatments, including oral OAT or move from an acute care setting to a community- or pharmacy-based iOAT service (see Models of Care, above). Any decisions to de-intensify care from iOAT to oral OAT should be made between patients and their families (if included in their care), iOAT prescriber, and any other relevant healthcare providers. This decision should be made with the understanding that treatment modalities across the continuum of care for OUD (see Figure 1) that were previously insufficient may be appropriate and effective at different times in a person's life, depending upon health and general life circumstances.

Patients should not be cut off from treatment. If, for example, a patient's prescribing doctor retires or moves, the patient should have the choice to be transferred to another iOAT prescriber, be slowly titrated off of iOAT, or transitioned to oral OAT.

De-intensification of treatment should not be understood as necessarily a permanent change. If a patient is not benefitting sufficiently from oral OAT, they should be offered the opportunity to reinstate iOAT.

More information on strategies for de-intensifying treatment can be found in **Appendix 6**.

Indications for Transitioning to Oral Treatment

Some patients, once they have reached stability, may request to transition to a less intensive treatment. In other situations, the care team may identify one or more of the following signs that transitioning to oral treatment may be appropriate or necessary and should be discussed with the patient.

- Patient request to transition to less intensive treatment;
- Patient not attending for all doses (Note, this may indicate a need for adjustment of the treatment schedule or dose);
- Ongoing or escalating alcohol and/or benzodiazepine use that causes sedation or other danger (Note, this may also indicate a need for treatment intensification);
- Cognitive and/or physical health decline resulting in inability to self-administer medication or consent to treatment; or
- New or evolving physical health conditions that exclude use of high dose opioid treatment or could be worsened by high-dose opioid treatment (e.g., severe respiratory disease requiring long-term oxygen, renal failure, hepatic failure).

If a patient has been stable and meeting their goals on iOAT they should be offered the opportunity to transition to oral OAT in a non-coercive manner that respects the long-term goals of the patient.

Prescriber Competencies

Due to the intensity of this model of care and highly supervised nature of this medical intervention, it is important that prescribers have experience with OAT prescription and an up-to-date understanding of the evidence and best practices with regard to iOAT provision. As such, the following minimum criteria for prescribers are recommended:

- Hold a methadone exemption;
- Have completed the online iOAT module of the Provincial Opioid Addiction Treatment Support Program offered through the BCCSU (available July 2017, however alternative training can be offered in the interim); and
- Consult the RACE line for at least the first five patients.

Please note: As of June 5, 2017 the education, training, and clinical care guidance aspects of the College of Physicians and Surgeons of BC Methadone Maintenance Program have been transferred to the BCCSU (including increased scope of practice for nurse practitioners to prescribe OAT). More information can be found on the [BCCSU website](#).

Appendices

Appendix 1: Pre-and Post-Injection Assessment

The pre- and post-injection assessments^h are completed by a qualified health professional or other trained staff if supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, Registered Social Worker, Registered Clinical Social Worker, or pharmacist) to ensure the safety of patients. The pre-injection assessment ensures that the patient is not intoxicated, including by centrally-acting sedatives or stimulants, or in any other acute condition that would increase the risk of an adverse event with the use of injectable hydromorphone. The post-injection assessment is performed to inform dosing (e.g., lowering dose if sedation occurs) and ensure safety (e.g., respond to respiratory depression). Patients may leave the premises when they are deemed fit to do so after the minimum 15- to 20-minute observation period post dose.

Pre-Injection Assessment

A qualified health professional or other trained staff if supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) will complete the following, in order to assess the safety of providing each patient's dose:

Assess for signs of intoxication, including severe agitation, dyskinesia, sedation, slurred speech, or smelling of alcohol.

A sample pre-injection assessment form appears in Table 4 below.

Table 4: Pre-Injection Assessment

Patient Name:			Assessment Date and Time:	
Yes	No	Unknown		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Severely anxious or agitated	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dyskinectic	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Overly sedated	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Slurred speech	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Smells of alcohol	
Baseline respiration rate: _____ breaths / minute				
Pasero Opioid-induced Sedation Scale ⁵⁶ (POSS) level:				
Breathalyzer required: Yes <input type="checkbox"/> No <input type="checkbox"/>				
If yes, breathalyzer reading:				
Notes:				
Assessment completed by:				

If initial assessment results in suspicion of recent use of psychoactive substances, the staff member will discuss with patient if they have consumed illegal or non-medical drugs (including any non-prescribed pharmaceutical drug) or alcohol. Where observation warrants further assessment (e.g., slurred speech, unsteady gait, smells of alcohol), a qualified health professional or other staff if supervised by a health professional (physician,

h. The pre- and post-intake assessment protocol has been adapted from the protocol used at Providence Health Care's Crosstown Clinic.

Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) trained to administer breathalyzer testing will check that the patient's blood alcohol level does not exceed 0.05%.

If the patient is judged to be intoxicated (whether through observation or results of pre-injection assessment, including breathalyzer results if applicable), the dose should be postponed or withheld. If the patient is judged safe to receive their dose, their patient chart and medication administration record should be checked to ensure that intoxication did not occur at the last dose, and that no prolonged absence (greater than 3 days or 9 appointments) has occurred.

If a prolonged absence has occurred, the patient should be given 1/3 of their prescribed dose and increased by 15% of the prescribed dose each session until their previously prescribed dose is reached.

If intoxication did occur at the last dose, the prescribing physician should be consulted to establish a safe dose. Special attention should be paid to any other psychoactive substances that the patient may have ingested, including benzodiazepines or other sedatives.

If intoxication did not occur at the last dose and no prolonged absence has occurred, the dose should be given as prescribed.

Post-Injection Assessment

Patients should be asked to stay in the clinic for a minimum of 15-20 minutes after they inject their medication. Qualified health professionals or other trained staff if supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, Registered Social Worker, Registered Clinical Social Worker, or pharmacist) can use this period to observe and engage with patients.

After 15-20 minutes has elapsed, a qualified health professional or other trained staff if supervised by a health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, or pharmacist) will conduct the post-injection assessment, observing any signs of intoxication including dyskinesia, sedation, slurred speech, agitation, or decreased respiration rate.

A sample post-injection assessment form appears in Table 5 below.

Table 5: Post-Injection Assessment

Patient Name:			Assessment Date and Time:		
Yes	No	Unknown			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Severely anxious or agitated		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dyskinectic		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Overly sedated		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Slurred speech		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Smells of alcohol		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Decreased respiration rate		
Respiration rate: _____					
Pasero Opioid-induced Sedation Scale ⁵⁶ (POSS) level:					
Notes:					
Assessment completed by:					

After a minimum of 15-20 minutes, once a patient is deemed fit to leave the clinic (that is, is showing no signs of intoxication), they may do so.

If a patient seems to be intoxicated, a pulse oximeter should be used and/or a vital sign assessment should be completed and documented in the patient’s chart.

If a patient must be kept for more than the initial twenty-minute period post-injection, this should be documented in their patient chart and medication administration record. In this case, the post-injection assessment should be administered at 15-minute intervals until the patient meets all criteria or other medical intervention is required. The patient’s prescriber should be advised, and a reduction in subsequent doses should be considered.

Pasero Opioid-induced Sedation Scale (POSS)

The Pasero Opioid-induced Sedation Scale (POSS) is used to assess level of sedation in patients receiving opioids. Because sedation level predicts opioid-induced respiratory depression and precedes other clinically significant events,⁵⁶ using the POSS scale provides a consistent way to measure sedation and provide follow-up when needed.

Table 6 provides an adapted version of the Pasero Opioid-induced Sedation Scale (POSS) with appropriate actions for each level of sedation.

Table 6: Modified Pasero Opioid-induced Sedation Scale (POSS)

Level of Sedation	Appropriate Action
1. Awake and alert	Acceptable; no action necessary; may continue with opioid dose
2. Slightly drowsy, easily aroused	Acceptable; no action necessary; may continue with opioid dose
3. Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; notify prescriber for orders.
4. Somnolent, minimal or no response to verbal or physical stimulation	Unacceptable; hold opioid; consider administering naloxone; notify prescriber; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

Appendix 2: Healthcare Provider Administration of Intra-muscular Injection

While the ability to self-administer medication is one of the considerations for eligibility, it is recognized that there may be time-limited, discrete events such as injury that require assistance from healthcare providers to ensure continuity of care. In some circumstances there may be other clinical or psycho-social indications for healthcare provider intra-muscular (IM) injection, in order to enable a client with specific needs to access iOAT. In these cases, physicians, Registered Nurses, and Registered Psychiatric Nurses may provide intra-muscular injections in the thighs, deltoid, and gluteal muscles. Standard protocols for IM injection including rotating sites and matching site to volume of medication should be followed.

Indications that iOAT may be appropriate despite inability to inject on an ongoing basis may include lacking the skills (e.g., a patient whose partner administered street drugs intravenously for them) or the ability to self-inject (e.g., mobility issues). It is recommended that clinical judgment be used in these situations to determine if iOAT with healthcare professional IM administration (physician, Registered Nurse, Registered Psychiatric Nurse) is the most appropriate treatment.

Appendix 3: Operational and Budgetary Considerations

Each of the three proposed models of care have operational and budgetary requirements which include the physical space; storage and preparation; safety; compounding pharmacy; staffing; and security requirements. Many of these requirements are similar, while some vary with the specific infrastructure and setting of each. The requirements for each of the three models is laid out below.

Operational Requirements

Table 7: Operational Requirements

Comprehensive and Dedicated iOAT Model	Community Health Clinic with Integrated iOAT Model	Pharmacy-Based Model	Requirements
			Injection Area
x	x	x	Private room with space for supervised injection.
x	x	x	Table/bench space with surface that is fully cleanable (i.e., not wood)
x	x	x	Seating that is easily moved and cleaned
x	x		Model 1—Round table
x	x		Model 2—Injection booths (If more than one injection booth, adequate lateral space between each patient)
			Mirrored tile or mirror in front of each injection space to enable supervision
x	x	x	Storage area for patient's belongings to prevent diversion
			Storage and Preparation
x	x	x	Storage area for tourniquets, Steri-Wipes, and needles of various gauges
x	x	x	Secure area for storage and preparation of the medication that is not accessible to patients or outsiders
x	x	x	Drug log tracking vials in and out, batch numbers, dose used, and disposal of any unused medication.
			Safety
x	x	x	Syringe disposal that enables syringes to be examined and counted prior to being placed in a destruction container
x	x	x	Access to electronic recordkeeping method to record each prescription, dose, time, and variances such as pre-waste
x	x	x	Monitoring system to ensure minimum of 3 hours between doses
x	x	x	A system that enables 2 staff members to check inventory and witness any destruction of doses, as a safeguard against diversion.
x	x	x	Resuscitation equipment
			Compounding Pharmacy Requirements
x	x	x	Pharmacies wishing to compound hydromorphone must comply with the National Association of Pharmacy Regulatory Authorities' (NAPRA) <i>Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations</i> . ⁵¹

			<i>Staffing Model</i>
x	x	x	Qualified health professionals or supervised trained staff for pre- and post-assessment, administration of correct dose, and supervision of self-administered injections
		x	All pharmacy staff must be trained to follow the policies and procedures put in place, including clinical procedures if pharmacy is acting as a clinic
		x	A minimum of two pharmacy staff must be available at all times, to ensure an adequate response in the event of an overdose
x	x	x	Access to qualified health professionals and trained staff 7 days per week, 365 days per year
x	x	x	Hours of operation must allow a minimum of 3 hours between dosing (i.e., up to a 12-hour shift)
x	x		Peer workers and/or allied health worker for support and connection to community agencies and services
x	x	x	Prescriber for regular assessments, dose adjustments, and transition to other medications
			<i>Security Considerations</i>
x	x	x	Supervision of self-administered injections to observe for diversion
x	x	x	Narcotic security tailored to setting and capacity (e.g., safe for storage in community, locked narcotic cupboard or closed loop medication system in hospital setting) Bolted down time-lock safes Maintenance of Daily Perpetual Inventory accounting for every milligram produced, wasted, lost in production, dispensed, pre-wasted, unused, waiting for destruction, and destroyed. Monthly reports accounting for daily count of above to ensure proper reconciliation.
		x	
		x	
		x	
x	x	x	Controlled entry to the injection room (can be simple accompaniment from staff member)
x	x	x	Syringes must be accounted for post-injection and prior to client leaving facility
x	x	x	Syringe labelling requirements of relevant regulatory bodies should be followed
x	x	x	Optional: Syringes may be marked (for example, with a coloured sticker) to prevent program syringes being switched with externally sourced syringes for the purpose of diversion

Budgetary Considerations

The delivery of iOAT requires a prescriber, medication, pharmacy support, a room where patients can self-administer the medication, and a qualified health professional or trained staff member supervised by a qualified health professional (physician, Registered Nurse, Licensed Practical Nurse, Registered Psychiatric Nurse, Registered Social Worker, Registered Clinical Social Worker, or pharmacist) to supervise self-administration, additional psychosocial services or referral to such, and necessary supplies. Budgetary considerations will depend on the model of care, the number of patients served per day, and labour costs for any ancillary services delivered on-site. Because of the possible variation in costs due to number of patients, labour costs, and community contexts, the following provides budgetary considerations rather than projected costs.

The medication costs vary per dose. Currently, injectable hydromorphone is covered by PharmaCare based on its indication for analgesia. Injectable hydromorphone is also covered by the Non-Insured Health Benefits program for registered First Nations and Inuit people.

Operational considerations for each of the three models of care are outlined below.

1. A Comprehensive and Dedicated Supervised Injectable Opioid Agonist Treatment Program

Based on the operations of Crosstown Clinic, it is estimated that the comprehensive and dedicated supervised iOAT model of care would require 4.5 nurses for the clinic to operate for 12 hours a day, serving up to approximately 150 patients per day who attend at different, scheduled times. Those clinics licensed to provide diacetylmorphine in addition to hydromorphone will require certain logistical and security features that would need to be built into the overall budget (see **Appendix 9**).

Additional costs would include wages for clinic coordinator, physicians, social workers, counsellors, peer-workers and other required staff, as well as non-labour costs. Non-labour costs include clinic security, equipment repair and maintenance, and medical and office supplies.

For those comprehensive and dedicated supervised iOAT programs located in hospitals or other acute settings, labour costs can be significantly reduced through referral to ancillary services located in the hospital or other acute setting.

2. Community Clinic with an Integrated Supervised Injectable Opioid Agonist Treatment Program

In the community clinic or other community outpatient setting, costs include dedicated injecting space, qualified health professionals or trained staff supervised by qualified health professionals for supervising self-administration, physician and nursing care in a primary care setting until the patient has been stabilized. Some of the costs associated with the comprehensive and dedicated model of care can be offset through the co-location of this service with existing services, for example, clinic coordinator, non-labour costs, and any other service providers already located at that site.

3. Pharmacy-Based Supervised Injectable Opioid Agonist Treatment Program

In the pharmacy-based supervised iOAT model, costs include dedicated injecting space, qualified health professionals or trained staff supervised by qualified health professionals for supervising self-administration, physician and nursing care in a primary care setting until the patient has been stabilized, medication costs, and pharmacy related costs.

Appendix 4: Titration Process

The following outlines the titration process recommended for patients not receiving oral OAT at the time of treatment initiation.

For patients transitioning from oral OAT to iOAT, the titration process is the same as the initial titration procedure described below, but special considerations should be made on a case-by-case basis to avoid withdrawal (e.g., target dose based on approximate conversion), while ensuring a cautious, safe, and patient-centered transition.

As with the general process for iOAT, doses are self-administered intravenously or intra-muscularly under supervision, with physicians, Registered Nurses, and Registered Psychiatric Nurses able to administer intra-muscular doses when clinically indicated (see Appendix 2).

At any time during the titration period, a physician or nurse may order a lower dose or a more gradual titration based on patient response and safety concerns. In order to allow flexibility, the patient can also request a lower dose or a more gradual titration process, such as only increasing the dose by 5mg, or not taking a second dose, etc.

The titration protocol for hydromorphone is based on doses expressed as diacetylmorphine-equivalents (diacetylmorphine to hydromorphone ratio 2:1).

It is recommended that the titration process be started between Monday and Wednesday to avoid dose increases on the weekend.

Hydromorphone Titration Protocolⁱ

Day 1

Dose 1: Give 10mg, wait 15 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 2: If earlier doses were well tolerated, give 20mg. Wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 3: If earlier doses were well tolerated, give 30mg. Wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Consider co-prescription of oral OAT (see below).

Day 2

Dose 1: Administer 40mg, wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 2: Administer 50mg, wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

i. This protocol can be adjusted per clinical judgment. The starting dose can range between 5-15mg, as can each supplementary dose given after the observation period. If renal or hepatic impairments are present, the above dose should be halved. This protocol is based on three doses per day.

Minimum 3 hours between injections.

Dose 3: Administer 60 mg, wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Consider co-prescription of oral OAT (see below).

Day 3

Dose 1: Administer 70mg, wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient.

Minimum 3 hours between injections.

Dose 2: Administer 80mg, wait 30 minutes. If no intoxication, give 10mg more based on clinical judgment and discussion with patient.

Minimum 3 hours between injections.

Dose 3: Administer 90mg.

Consider co-prescription of oral OAT (see below).

Table 8 below summarizes the dosages used during the induction process for quick reference.

Table 8: Hydromorphone Induction Dosage Chart

Dose #	Dose Administered	Additional Dose (if appropriate)
Day 1		
1	10	10
2	20	10
3	30	10
Day 2		
1	40	10
2	50	10
3	60	10
Day 3		
1	70	10
2	80	10
3	90	10

After consulting with the physician, adjust the dosage once a week, or as needed, until the patient feels comfortable (i.e., reduced cravings and withdrawal symptoms) and does not show any excessive intoxication or respiratory depression or until the maximum dose is reached (200mg/dose and/or 500mg/day). Dose increases are discouraged on weekends and holidays.

It should be noted that some patients may miss titration sessions due to unstable housing and other issues, and thus the initiation may require a modified protocol over multiple days.

Note: For the pharmacy-based model, where titration occurs at the prescriber's office or clinic, it is recommended that initiation of treatment be scheduled such that the first pharmacy-witnessed dose does not fall on a weekend or other day in which the prescriber is unavailable.

The titration process for diacetylmorphine can be found in **Appendix 9**.



Co-Prescription of Oral OAT

A small dose of oral OAT (i.e., slow-release oral morphine) may be taken under supervision with the last dose of the day to bridge until the first dose the following morning. Caution and safety should guide co-prescription, while working to ensure patient comfort. Nurses should assess the patient each day during the titration period to ensure the co-prescribed oral OAT is appropriately dosed.

Appendix 5: Conversion Table

The following conversion table can be used to determine an equivalent dosage for the purpose of travel (for example, converting to witnessed ingestion of SROM for travel to a funeral) or longer term (for example, if someone is entering the corrections system or hospitalized in a facility where iOAT is not feasible or clinically contraindicated). Ideally, travel is planned in advance, allowing for a slow titration from iOAT to oral OAT following the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder. It is recognized, however, that emergency travel (e.g., a funeral or family emergency) is at times required. In these cases, the below table can be used along with patient education to minimize safety risks. Although there is more evidence supporting the use of methadone for travel, the authors of this document favour the use of slow-release oral morphine for its improved safety profile, including significantly less variability in required dosage.

IMPORTANT SAFETY NOTE: All doses must be **reduced by 25%** from the figure given in the table due to incomplete cross-tolerance. Patient safety must be prioritized in converting from iOAT to oral OAT. If a patient has been injecting intramuscularly the bioavailable dose may be less, requiring a larger dose reduction.

Patients should be provided with take-home naloxone kits, training on how to administer naloxone, and be advised to make sure family or friends can observe them for sedation or respiratory depression.

Dose conversion should be calculated cautiously, and multiple-day prescriptions of oral OAT should be prescribed with recognition of the cumulative effects of dosing.

Maximum doses of 1200mg slow-release oral morphine and 100mg methadone are recommended to ensure patient safety.

Table 9: Conversion Table^j

Diacetylmorphine (mg)	Hydromorphone (mg)	SROM (mg)	Methadone (mg)
20	10	50	20
21-40	11-20	55-100	20
41-60	21-30	105-150	20
61-80	31-40	155-200	25
81-100	41-50	205-250	30
101-120	51-60	255-300	35
121-140	61-70	305-350	40
141-160	71-80	355-400	50
161-180	81-90	405-450	60
181-200	91-100	455-500	65
201-220	101-110	505-550	70
221-240	111-120	555-600	75
241-260	121-130	605-650	80
261-280	131-140	655-700	80
281-300	141-150	705-750	85
301-320	151-160	755-800	90
321-340	161-170	805-850	95
341-360	171-180	855-900	100
361-380	181-190	905-950	100
381-400	191-200	955-1000	100
401-420	201-210	1005-1050	100
421-440	211-220	1055-1100	100
441-460	221-230	1105-1150	100
461-480	231-240	1155-1200	100
481-500	241-250	1200	100
501-520	251-260	1200	100
521-540	261-270	1200	100
541-560	271-280	1200	100
561-580	281-290	1200	100
581-600	291-300	1200	100
601-620	301-310	1200	100
621-640	311-320	1200	100
641-660	321-330	1200	100
661-680	331-340	1200	100
681-700	341-350	1200	100
701-720	351-360	1200	100
721-740	361-370	1200	100
741-760	371-380	1200	100
761-780	381-390	1200	100
781-800	391-400	1200	100
801-820	401-410	1200	100
821-840	411-420	1200	100
841-860	421-430	1200	100
861-880	431-440	1200	100
881-900	441-450	1200	100
901-920	451-460	1200	100
921-940	461-470	1200	100
941-960	471-480	1200	100
961-980	481-490	1200	100
981-1000	491-500	1200	100

j. The DAM-methadone conversion was established by two DAM treatment centres in Switzerland, which has been refined and used in other settings, including the NAOMI trial. The HDM doses were calculated using the DAM:HDM ratio of 2:1. The SROM doses were calculated using the HDM:SROM ratio of 1:5. Doses reflect total daily dose

Appendix 6: Strategies for De-intensifying Treatment

De-intensification of treatment may be appropriate and/or required for one of three reasons. The first is when a patient has stabilized on iOAT and decides, with their prescriber, that a lower-intensity iOAT model is appropriate (for example, moving from the Comprehensive and Dedicated Model of Care to the Integrated or Embedded Model). When switching models of care, the prescriber should ensure that existing psychosocial supports will remain in place. The second is patient-initiated transition to oral OAT which is covered in more detail below. The third situation in which de-intensification would occur is when a patient is discontinued from iOAT as a consequence of behaviour such as violence or diversion (attempted or successful).

This guidance document should be understood as a living document, which will be refined as more evidence and clinical experience emerges from expanded iOAT provision. The following sections on de-intensifying treatment to oral OAT are based on the best evidence currently available. Clinical judgment, close monitoring, and, when appropriate, consultation with addiction specialists with experience in iOAT provision should further guide the process of de-intensifying treatment in order to ensure the safety of patients transitioning from iOAT to a less intensive treatment.

1. Transition from Hydromorphone to Methadone

Transition from injectable hydromorphone to methadone (see Conversion Table in **Appendix 5**) may be patient-initiated due to a desire to de-intensify treatment, in which case gradual transition is appropriate. The pace of transition and approach used should follow the same approach used for transitioning patients from any high dose short-acting opioid onto methadone while gradually lowering the dose of hydromorphone. Induction guidelines for methadone can be found in BCCSU's [A Guideline for the Clinical Management of Opioid Use Disorder](#). Due to inter-individual differences, which can vary widely among patients, clinical judgement should be used in the transition process.

2. Transition from Hydromorphone to Slow-Release Oral Morphine

It is important to note that due to the preliminary nature of research on using SROM to de-intensify iOAT, there is no existing clinical protocol to follow. It is recommended that clinical judgment be used in gradually decreasing the hydromorphone dose while simultaneously up-titrating the SROM dose, starting with a 10% dose decrease per week. General induction and dosing recommendations for SROM can be found in BCCSU's [A Guideline for the Clinical Management of Opioid Use Disorder](#). Patients should be under closer clinical review during this transition time and expert physicians should be consulted.

Although the evidence base for SROM is less robust than for other oral OAT medications (methadone and buprenorphine/naloxone), research has demonstrated that it is a safe and effective alternative to first-line treatment options, particularly in patients who have not benefited from first-line treatment options in the past.^{57,58} SROM may also confer specific advantages for patients engaged in iOAT who wish to transition to lower-intensity treatment, as the majority of these patients have not previously demonstrated benefit from oral methadone or buprenorphine/naloxone prior to iOAT initiation, and may wish to try an alternative treatment. Further, there is some evidence that supplemental SROM may help to reduce iOAT dose and frequency of daily injections among those individuals interested in doing so. A brief overview of the literature regarding use of slow-release oral morphine in the treatment of opioid use disorder, including as a supplement to ongoing injectable opioid agonist treatment, is provided below.

A 2014 two-phase study investigating the safety and efficacy of SROM compared to methadone in adults with opioid dependence who had been in methadone maintenance programs for at least 26 weeks found those on SROM reported fewer cravings, higher levels of treatment satisfaction, and lower levels of stress. In the first phase, patients were randomly assigned to receive either methadone or SROM for 11 weeks. In the second phase, the medications were switched, so each patient received both methadone and SROM for 11 weeks each. After

the second 11-week phase, patients from both groups received a 25-week extension of SROM. Those individuals who switched from methadone to SROM during the study's extension period reported zero loss of efficacy or tolerance to medication.⁵⁹ SROM's non-inferiority⁵⁹ and favourable side effect profile compared to methadone for the treatment of opioid use disorder⁶⁰ (specifically its lack of association with a prolonged QTc and subsequent risk for arrhythmia and fewer drug-drug interactions) makes it a suitable alternative to methadone.

For patients receiving iOAT and supplementary methadone, there is some research evidence that switching from supplementary methadone to slow-release oral morphine may offer advantages for patients wishing to de-intensify treatment (reduction in iOAT dose or frequency of daily injections). In a small observational study (n=12), former participants in the Randomized Injectable Opiate Treatment trial (RIOTT) maintained on injectable diacetylmorphine supplemented with oral methadone underwent a planned transition from supplemental methadone to slow-release oral morphine (SROM) with no planned decrease in their iOAT dose.⁶¹ Patients were started on a 1:6 (methadone:SROM) dose ratio with a 25-30% reduction in initial SROM dose to maintain stable peak concentrations. The transition was performed over five days, with half of the original methadone dose prescribed on day 1, 30% of the original methadone dose on day 2, 20% on day 3, and no methadone prescribed thereafter.⁶¹ Prior to the transition, all 12 patients had identified reduction of their injectable medication dose as a treatment goal. Study results indicate that, 10 weeks after the transition from supplemental methadone to SROM, patients were able to reduce the daily dose of diacetylmorphine from an average of 382mg to 315mg.⁶¹ Patients also reported fewer cravings and improved sleep and quality of life after switching from methadone to SROM. Although more research is needed, this preliminary study suggests that SROM may be a viable alternative to supplementary oral methadone, and may have advantages in patients wishing to reduce injectable opioid medications and/or those considering transition to oral opioid agonist medications. It should be highlighted that this is a small observational study and additional research is needed in area to optimize transitions from iOAT to SROM.

3. Transition from Hydromorphone to Buprenorphine/Naloxone

There is currently very limited literature on transitioning from iOAT to buprenorphine/naloxone.⁶² Several patients have been successfully transitioned using the Bernese method (i.e., starting with a very low dose of buprenorphine/naloxone overlapping with iOAT, with small daily dose increases until iOAT is stopped abruptly once a sufficient dose of buprenorphine/naloxone has been reached) in Switzerland.⁶² Additionally, two patients have been successfully transitioned in Vancouver in in-patient withdrawal management facilities, following the induction guidelines used in BCCSU's [A Guideline for the Clinical Management of Opioid Use Disorder](#). Transition to buprenorphine/naloxone should follow the same approach used for transitioning patients from any high dose short-acting opioids onto buprenorphine/naloxone, which can be found in [A Guideline for the Clinical Management of Opioid Use Disorder](#). It is recommended that patients transitioning from iOAT to buprenorphine/naloxone be seen frequently after their induction to maintain continuity of care, given the intensity of the injectable treatment they are transitioning out of.

Provider-Initiated De-Intensification of Treatment

Although this document emphasizes that patients should never be cut off from treatment, there are circumstances in which provider-initiated de-intensification of treatment from iOAT to oral OAT is indicated. These circumstances include situations where patient behaviour represents a threat to safety, including violence against staff or other patients, or attempted or successful diversion. Decisions to initiate de-intensification of treatment should be made with the recognition that this de-intensification of treatment, if initiated by the healthcare provider rather than patient, may be accompanied by deterioration of the patient's physical and mental health.

Provider-initiated de-intensification of treatment is not recommended for a first attempt at diversion. Reasons for attempted or successful diversion should be explored with the patient. The treatment team should then meet

to discuss strategies to prevent and manage further diversion attempts. Clinical judgment should be used to determine if a short term conversion to oral OAT is necessary while determining the treatment team's response to diversion.

For provider-initiated conversion to oral OAT due to behaviour such as violence or diversion, it may be done more rapidly using the conversion table in **Appendix 5**, with a reduction in oral OAT dose to account for incomplete cross-tolerance. In this case, prescribers must work closely with patients to create a treatment plan with additional supports to mitigate potential risk of involuntary de-intensification of treatment.

Appendix 7: Urine Drug Testing

Regular urine drug testing (UDT) is considered the standard of care in opioid agonist treatment programs. UDT can be used to confirm treatment adherence and any self-reported use of non-medical opioids or other substances, detect use of other substances which may affect patient safety (e.g., benzodiazepines, fentanyl), and evaluate treatment response and outcomes (e.g., abstinence from heroin or other opioids).

Point-of-care urine drug testing is useful for providing immediate feedback to patients and for making prompt treatment decisions. Physicians are compensated through MSP (fee code P15039) for performing and interpreting point-of-care UDT as part of opioid agonist treatment up to a maximum of 26 UDT per patient per year. Typically, point-of-care UDT can be used to detect amphetamines, benzodiazepines, cocaine, opioids (morphine, codeine, heroin metabolite, opium, and sometimes hydromorphone), oxycodone, buprenorphine and methadone. Specific substances tested for will vary by product and manufacturer, and prescribing physicians should ensure that hydromorphone is included in the detection panel if UDT is intended to be used to monitor treatment adherence. Given the public health emergency in British Columbia, point-of-care tests should include fentanyl when possible.

Laboratory UDT may also be used periodically to verify point-of-care UDT results, particularly if there is a discrepancy with self-reported substance use. In addition, laboratory UDT offers improved sensitivity and specificity, as well as targeted detection and quantification of specific substances such as amphetamines (amphetamine, dextro- and methamphetamine, MDMA (Ecstasy)), benzodiazepines (diazepam, oxazepam, temazepam, triazolam), cocaine (benzoylecgonine metabolite), buprenorphine, methadone (EDDP metabolite), and opioids (heroin metabolite, morphine, codeine). Urine drug testing for fentanyl and other synthetic analogues must be specifically requisitioned. Availability, cost, and general process for requesting UDT for specific substances should be confirmed with local or hospital laboratory services.

Similar to other oral agonist treatment, it is recommended that during initiation and dose escalation, urine drug testing should be performed more frequently (i.e., at least monthly or more frequently as required) to confirm self-reported abstinence from non-medical opioid use and/or to monitor patient safety. During stabilization, both scheduled and random UDTs should be employed as appropriate. Patients who refuse random or scheduled UDTs should be reassessed as this may indicate risk of relapse, misuse, or diversion. UDT can be employed as appropriate and at the discretion of the treating physician, and when indicated, for example, if there are concerns of undisclosed relapse of non-medical or illegal opioid use, use of other substances, suboptimal adherence, or diversion.

It is emphasized that UDT should not be used punitively or as the sole justification for patient removal from iOAT programs; rather, patients who are showing signs of instability, or who refuse to provide random or scheduled UDT should be scheduled for more intensive follow-up and reassessment. Following discussion with the patient about any underlying issues contributing to treatment instability, physicians can consider adjusting iOAT dose, prescribing a supplemental evening dose of oral methadone or adjusting evening methadone dose if current dose is inadequate; increasing the frequency of clinical appointments in order to provide more intensive support, monitoring and assessment; and/or providing referrals to adjunct psychosocial and community-based supports, as appropriate. If treatment intensification does not adequately address clinical or social instability, and/or if patient safety is a serious concern, physicians and patients may need to consider alternative treatment options or care settings, such as the comprehensive and dedicated supervised iOAT model of care.

Appendix 8: Sample Treatment Agreement

Injectable Opioid Agonist Treatment Agreement and Consent

PATIENT INFORMATION	
Surname: _____	Given name(s): _____
Date of birth: _____	PHN: _____

PATIENT AGREEMENT

I UNDERSTAND AND AGREE THAT:

- I am being started on:
 - Hydromorphone for the treatment of opioid use disorder.
- While I am receiving hydromorphone treatment, I will not obtain opioid prescriptions or other psychoactive medications (e.g., sleeping pills or pain medication) from other doctors, clinics, or elsewhere.
- For my safety, I give consent to my hydromorphone prescriber to communicate with my pharmacist and any other physicians currently or previously involved in my care, and to check my PharmaNet profile.
- I will work with my hydromorphone prescriber to develop a treatment plan and set goals. We will review them regularly and change as needed.
- In addition to hydromorphone, I can participate in counseling or peer-support groups and other programs as part of my treatment plan. My hydromorphone prescriber will give me information about the options and programs available in my community.
- I can expect confidentiality about my treatment from my doctor and other healthcare providers. My personal information will not be shared except with other healthcare providers as I agreed to above.
- I can decide if I want to continue, stop or change my treatment plan at any time. I agree to make this decision with my prescriber.
- Hydromorphone treatment will require multiple daily trips to the facility where I receive my medication, which may impact my work, school or other responsibilities.
- If I do not attend the facility where I receive my medication for 3 consecutive doses or 1 day (number of missed doses may change once I am clinical stable), my prescriber and I will discuss the reasons for missed doses and if changes to treatment (including transitioning to a less intensive treatment option) is appropriate.
- I understand that missing more than 6 to 9 doses (3 days) may cause a loss of tolerance and may require that, for my safety, I take a lower dose until I stabilize.
- I will not be cut off from treatment. If hydromorphone is not providing the results expected, my prescriber will work with me to adjust my dosage, increase psychosocial supports, and/or explore other treatment options. If my prescriber can no longer provide care for me, they will refer me to another prescriber who can.

I UNDERSTAND THAT I AM EXPECTED TO:

- Provide urine for drug testing on a regular basis.
- Provide urine samples at the clinic and that these samples are not to be altered. Urine samples that are cold or appear to have been altered will be treated as a serious issue and may affect my treatment plan.
- Avoid using alcohol or other drugs, such as prescription or over the counter opioid medications, sleeping pills, or tranquilizers. I understand that combining these medications with hydromorphone can lead to overdose and other serious harms and may affect my treatment plan.
- Notify any health care provider that I receive care from that I am taking hydromorphone for treatment of opioid use disorder.
- Notify my primary care provider if I become pregnant (if applicable)**
I understand that I must inform my prescriber if I am pregnant, suspect I may be pregnant, or if I am planning a pregnancy.

PATIENT IDENTIFIED GOALS

- _____
- _____
- _____
- _____

PRESCRIBER AGREEMENT

I confirm that:

- This form has been reviewed in detail with the patient and they understand its content fully. This should be reviewed again when the patient is not in withdrawal.
- The patient was given time to ask questions and seek clarification before signing this document.
- The evidence for other treatment options was reviewed, and the patient agrees to hydromorphone.
- Information and resources to support psychosocial treatment interventions and supports will be provided to the patient.
- PharmaNet was reviewed to identify other prescribed medications, and will be checked at each subsequent appointment.
- A treatment plan with clear goals was developed with the patient, and will be reviewed and documented regularly during treatment.

CONSENT

Patient's signature:	_____	Date:	_____
Prescriber's signature:	_____	Date:	_____

Appendix 9: Diacetylmorphine

The clinical recommendations presented in the main document should be followed for diacetylmorphine, with diacetylmorphine-specific recommendations and protocols outlined below (obtaining and preparing diacetylmorphine; selection of dose; dosage equivalence with methadone; titration protocol).

Obtaining and Preparing Diacetylmorphine

As with hydromorphone, diacetylmorphine may be dispensed by pharmacies in two ways – either through advanced compounding and preparation of doses in a NAPRA-compliant pharmacy³² or via delivery of single-use vials by a local pharmacy, which are drawn into a syringe prior to administration. Health authorities should be involved in providing this service and/or contracting for pharmacy services within their area. It is important to note that the procurement mechanisms for access to diacetylmorphine are evolving rapidly and this document will be updated on an as needed basis to reflect the most up to date information.

Diacetylmorphine is currently available via two federal mechanisms:

1) [Drugs for Urgent Public Health Need](#) (UPHN)⁶³: The drugs identified on this web-based list have been requested by a federal or provincial public health official to address an immediate and urgent public health need within their jurisdiction. This mechanism is to support population needs rather than individual patient needs (which are addressed via the Special Access Program). It is important to note that there are two sections of the Narcotic Control Regulations (NCR) that restrict use of diacetylmorphine to a hospital setting:

- Subsection 24(4) of the NCR does not allow a licensed dealer to sell or provide diacetylmorphine to a pharmacist unless they are a hospital^k employee or are exempted under section 56 of the CDSA with respect to its possession, and;
- Subsection 53(4) prohibits practitioners of medicine and dentistry from prescribing diacetylmorphine, and from administering it unless the person is an in-patient or out-patient of a hospital.

Drugs accessed via the UPHN regulatory pathway enable a public health official to request a quantity of drug deemed necessary for use in their jurisdiction for an urgent public health need in Canada, and allow for repeated importation of the drug as needed for a period of one year. Drugs included on this list can be renewed by the provincial public health officer on a yearly basis. Those wishing to obtain diacetylmorphine via the UPHN mechanism are encouraged to contact the Ministry of Health to provide assistance in navigating access to this medication.

2) Special Access Program (SAP): This program remains in place and is another avenue to allow access to drugs that are not authorized for sale in Canada; this regulatory mechanism is designed to address individual patient needs. The decision to authorize or deny an SAP request is discretionary and made on a case-by-case basis. This is based on availability of alternative medications and information provided by the prescriber regarding the use, safety, and efficacy of the drug. If the request is approved and access to the drug is granted, the practitioner must report on the use of the drug in the particular patient. This includes any adverse events that occur, in addition to accounting for all quantities received; the information should be provided to both the drug manufacturer and the SAP.

Regardless of the mechanism for procurement, diacetylmorphine must be stored under the security directives of Health Canada and additionally the Office of Controlled Substances (Health Canada) determines how diacetylmorphine can be distributed.

k. A 'hospital' within the meaning of the NCR must be, "licensed, approved or designed by a province..." therefore this does not cover only traditional hospital models and can be further defined by the province.

Injectable Diacetylmorphine

Diacetylmorphine can only be imported into Canada from the manufacturer in Switzerland, by a Health Canada licensed dealer. The role of the licensed dealer is outlined in the Narcotic Control Regulations, with compliance requiring highly specialized knowledge, facilities, and processes.⁶⁴ Specific eligibility criteria must be met and applications are reviewed on a case-by-case basis.

In addition to Narcotic Control regulations, compliance with Health Canada's Directive on Physical Security Requirements Controlled Substances (Licensed Dealers Security Requirements for the Storage of Controlled Substances) is required.⁶⁵ This entails meeting the minimum accepted level of security outlined in Health Canada's Directive. These standards are assessed on a case-by-case basis and relate to securing the environment in which the medication is stored.

The Licensed Dealer is also responsible for narcotic accountability at all stages including reporting on medication wastage, loss, and destruction of the drug. Expertise is required in managing the timing of import and export permits to ensure adequate supply of medication while meeting necessary storage requirements.

Prescribing Injectable Diacetylmorphine

Selection of Dose

Due to high inter-individual variability, each individual's dose must be carefully determined. There are no fixed doses for optimal stable dosing of diacetylmorphine. Various therapy centres who have offered this treatment have developed a regimen for initial titration and stabilization, as well as conversion of diacetylmorphine doses to methadone. The upward titration at the start of therapy should begin with a safe dose and follow the protocol outlined later in this appendix. Maximum diacetylmorphine dosages are based on the Swiss clinical studies and were adopted by all the other settings.⁵⁴

Maximum recommended daily doses of diacetylmorphine can be found in Table 10 below.

Table 10—Maximum Recommended Daily Diacetylmorphine Doses

Medication	Diacetylmorphine
Maximum Number Doses Per Day	3
Maximum Daily Dose	1000mg
Maximum Per Dose	400mg

Dose increases need to be tolerated in order to continue at that dose. Doses that are not tolerated, as per assessment during either the pre- or post-injection assessment periods, should be reduced.

Dosage Equivalence with Oral Methadone and Slow-Release Oral Morphine

In order to maintain an average degree of saturation of the opiate receptors by opioids to prevent withdrawal symptoms and avoid over-dosage, for those receiving an evening dose of oral methadone or slow-release oral morphine, it is critical to establish a conversion factor for switching between methadone or slow-release oral morphine and diacetylmorphine.

The opiate bioavailability of the individual pharmaceutical agents must be considered when converting dosages. A 100% bioavailability of diacetylmorphine injectable solution is assumed, irrespective of whether it is administered intravenously, subcutaneously, or intramuscularly. The calculation is always based on the intended effective opioid dose.

The conversion should be based on doses received, not prescribed. See the conversion table in **Appendix 5**.

Diacetylmorphine Titration Protocol

The following outlines the titration process recommended for patients not receiving oral OAT at the time of treatment initiation.

For patients transitioning from oral OAT to iOAT, the titration process is the same as the initial titration procedure described below, but special considerations should be made on a case-by-case basis to avoid withdrawal (e.g., target dose based on approximate conversion), while ensuring a cautious, safe, and patient-centered transition.

As with the general process for iOAT, doses are self-administered intravenously or intra-muscularly under supervision, with physicians, Registered Nurses, and Registered Psychiatric Nurses able to administer intra-muscular doses when clinically indicated (see **Appendix 2**).

At any time during the titration period, a physician or nurse may order a lower dose or a more gradual titration based on patient response and safety concerns. In order to allow flexibility, the patient can also request a lower dose or a more gradual titration process, such as only increasing the dose by 15mg, or not taking a second dose, etc.

It is recommended that the titration process be started between Monday and Wednesday to avoid dose increases on the weekend.

Day 1

Dose 1: Give 15mg, wait 15 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 2: If earlier doses were well tolerated, give 45mg. Wait 30 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 3: If earlier doses were well tolerated, give 75mg. Wait 30 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Consider co-prescription of oral OAT (see below).

Day 2

Dose 1: Administer 40% of the total daily dose at Day 1 (up to a total of 90mg if patient tolerated all possible doses on Day 1). Wait 30 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 2: Administer the maximum tolerated amount of Dose 1 (up to a total of 120mg). Wait 30 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Minimum 3 hours between injections.

Dose 3: Administer the maximum tolerated amount of Dose 2 (up to a total of 150mg). Wait 30 minutes. If no intoxication, give 30mg more based on clinical judgment and discussion with patient. Observe for 30 minutes after second dose.

Consider co-prescription of oral OAT (see below).

Day 3

Administer the maximum tolerated amount at Day 2 for each of the 3 doses on Day 3. After consulting with the physician, adjust the dosage once a week until the patient feels comfortable (i.e., reduced cravings and withdrawal symptoms) and does not show any excessive intoxication or respiratory depression or until the maximum dose is reached (400mg/dose and/or 1000mg/day). Dose increases are discouraged on weekends and holidays.

Note: For the pharmacy-based model, where titration occurs at the prescriber's office or clinic, it is recommended that initiation of treatment be scheduled such that the first pharmacy-witnessed dose does not fall on a weekend or other day in which the prescriber is unavailable.

Co-Prescription of Oral OAT

A small dose of oral OAT (i.e., slow-release oral morphine) may be taken under supervision with the last dose of the day to bridge until the first dose the following morning. Caution and safety should guide co-prescription, while working to ensure patient comfort. Nurses should assess the patient each day during the titration period to ensure the co-prescribed oral OAT is appropriately dosed.

Appendix 10: Frequently Asked Questions

Frequently Asked Questions about injectable opioid agonist treatment (iOAT).

Do patients require continually escalating doses of hydromorphone?

In each of the randomized controlled trials, the recorded average dose was approximately half of the maximum daily dose. In addition, clinical experience at Crosstown Clinic indicates that once patients reach an adequate dose to treat withdrawal and cravings, they tend to remain stable at that dose over time or gradually start to reduce their dose.

Should the public be concerned about iOAT programs causing security and public safety issues?

The findings of three randomized controlled trials investigating the impact of newly established iOAT clinics on crime in their communities in the Netherlands, UK, and Canada have indicated no negative effects on public safety and observed growing local public support.

Why should my tax dollars go towards providing free iOAT?

Injectable opioid agonist treatment has been found effective for individuals who have not benefited from other treatment options for opioid use disorder. Economic evaluations have consistently found that the effective treatment of opioid use disorder reduces costs to society due to criminal involvement and a range of healthcare costs.

Is this just giving people free drugs?

Injectable opioid agonist treatment should be understood as one part of a continuum of care for individuals with an opioid use disorder. Depending on each patient's specific needs, this full complement of services, provided either on-site or through referral, may include supportive recovery housing, psychosocial treatment interventions and supports, primary care services, trauma therapy, and specialized services for women, youth, and Indigenous peoples. By stabilizing patients and providing a point of regular contact with healthcare services, iOAT clinics facilitate the establishment of necessary therapeutic relationships and routines.

Will people accept hydromorphone or will they refuse anything but prescription heroin (diacetylmorphine)?

Hydromorphone has been shown to be as effective as diacetylmorphine (prescription heroin) in the treatment of opioid use disorder. During the SALOME trial, patients were randomly assigned to either diacetylmorphine or hydromorphone in a blinded fashion; participants did not know which medication they were receiving, nor could they, after six months of treatment, guess better than chance which treatment they were receiving. Retention remained above 75% at 6 months. At the six-month assessment, participants were asked, "if only injectable hydromorphone was available, in addition to what is available in the community, would you start this treatment?" 82.2% responded yes, 5.4% no, and 8.9% unsure.

Why do we need this? Can't people just take methadone or buprenorphine/naloxone?

Injectable opioid agonist treatment is indicated for those individuals who have not benefited from oral opioid agonist treatment (i.e., methadone, buprenorphine/naloxone, and/or slow-release oral morphine). For patients

who are not able to stop or reduce use of non-medical opioids with methadone or other oral options injectable opioid agonist treatment offers an evidence-based alternative.

Is the goal to transition people off hydromorphone as quickly as possible?

This document recommends that treatment intensity be continually matched with individual patient needs and circumstances. When appropriate, patients will be transitioned to less-intensive treatments. Ensuring appropriate movement along the continuum of care requires routine discussion of treatment progress and goals with patients and their families (when appropriate) whereby the possibility of transition to less intensive treatment modalities can be assessed.

Was oral hydromorphone studied as well as injectable hydromorphone?

Yes. SALOME was initially planned to have a second phase, a non-inferiority study of oral medication versus continuation of injectable medication (i.e., switching from the injectable to the oral form of the medication compared to continuation of injectable treatment). Due to the unblinded nature of this phase of the study, clinical observations were able to be made in patients who transitioned from injectable to oral medications, including significantly lower retention rates, significantly higher rates of missed treatment sessions, and clinical deterioration of participants who had been stabilized on and benefiting from injectable treatment, that strongly suggested that non-inferiority of the oral medication would not be demonstrated. Based on these observations and a review of Phase II data, the Data and Safety Monitoring Board recommended that the second phase of SALOME be stopped due to the low probability of a finding of non-inferiority.

Aren't you just substituting one drug for another?

Individuals with opioid use disorder are physically dependent on opioids and will experience painful withdrawal symptoms (e.g., fevers and chills, diarrhea, and other flu-like symptoms) without some form of opioid. Opioid agonist treatment, whether oral or injectable, is designed to prevent withdrawal symptoms and manage cravings in addition to replacing ongoing injection use of non-medical drugs that may be adulterated with safe, pharmaceutical-grade opioid agonists in safe and hygienic environments, thereby reducing the potential harms of IV drug use. This allows people to re-engage with the health care system and society rather than resort to drug-seeking and criminal behaviour to avoid withdrawal symptoms.

If someone has experienced multiple overdoses are they a candidate for iOAT?

The considerations for eligibility in this guidance document were developed with flexibility to ensure that individual circumstances and clinical judgment inform the decision to prescribe iOAT to individuals with opioid use disorder when deemed appropriate by the care team. History of non-fatal overdose may be helpful for informing physician discretion, but should not be understood as an eligibility requirement, as such a requirement could unintentionally promote high-risk behaviour.

Is iOAT only for people who have tried oral OAT and not benefited?

In most countries where iOAT is prescribed, it is considered a second-line treatment for people with severe opioid use disorder who have not benefited from oral OAT (buprenorphine/naloxone or methadone), due to a higher risk of side effects and higher intensity of treatment. Additionally, most of the research on iOAT has been done with people who have tried but not benefited from oral OAT in the past. However, one study that

compared diacetylmorphine to methadone included a small proportion of people who had not tried oral OAT, but had tried other non-pharmacological treatment in the past. This study found that diacetylmorphine was effective regardless of past oral OAT experience. However, more controlled trials are needed in order to reach a strong conclusion and a clear consensus on prescribing iOAT for those who have not received oral OAT before.

Is injectable naltrexone an option for severe and/or treatment-refractory opioid use disorder? Should it be tried before hydromorphone or diacetylmorphine?

Naltrexone is a different type of medication used for the treatment of opioid use disorder. Unlike opioid agonist treatments (e.g. hydromorphone, methadone), naltrexone is an opioid antagonist, meaning that it fully blocks the effect of opioids, but may not reduce cravings. Currently, only oral naltrexone is available in Canada and may be used to prevent relapse to opioid use, although studies show poor adherence to this medication. The efficacy of injectable naltrexone in those with severe and/or treatment-refractory opioid use disorder is unknown. If a patient requests injectable naltrexone, the physician should assess the suitability of this treatment on a patient-by-patient basis. This treatment should not be required before iOAT is considered. Please refer to the BCCSU's A Guideline for the Clinical Management of Opioid Use Disorder for more information on injectable naltrexone.

Is injection depot buprenorphine an option for severe and/or treatment-refractory opioid use disorder? Should it be tried before hydromorphone or diacetylmorphine?

Injection depot buprenorphine is only available in Canada through the Special Access Programme. The efficacy of injection depot buprenorphine for those with severe and/or treatment-refractory opioid use disorder is unknown. If a patient requests injectable depot buprenorphine, the physician should assess the suitability of this treatment on a patient-by-patient basis. This treatment should not be required before iOAT is considered.

What happens to patients on the program who are continuing to use fentanyl and other opioids on a regular basis?

Continued use of illegal and/or non-medical opioids while on iOAT should be considered an indication to assess the patient and consider intensifying treatment. Intensification of treatment may include adding an evening dose of slow-release oral morphine or methadone, increasing an existing evening dose of slow-release oral morphine or methadone, increasing the dose of injectable medication, transferring to a more intensive model of care (for example, moving from a community health clinic to a comprehensive and dedicated iOAT model), or increasing psychosocial treatment interventions and/or supports.

If a patient is found to be intoxicated during the pre-assessment, their dose should be postponed or withheld. Repeated findings of intoxication in the pre-assessment should be treated as an indication to assess the patient and consider intensification of treatment, as outlined above.

What if patients want to attend for hydromorphone doses more often than three times per day?

Clinical experience has shown that patients do not generally want to attend more than three times per day. Attending multiple times per day is a substantial time commitment that can be disruptive to other life activities. Additionally, once patients are stabilized, they tend to attend less frequently, working with their prescriber to decrease the number of injections per day.

In the rare case that a patient wants to attend more frequently the prescriber can work with the patient to optimize their oral OAT dose to prevent cravings and withdrawal symptoms between visits.

If hydromorphone and prescription heroin are provided by the government, does that mean all drugs will be made available by the government?

Hydromorphone and diacetylmorphine are evidence-based treatments generally considered for patients with severe and/or refractory opioid use disorder who have not benefited from oral opioid agonist treatments. Other injectable opioids have not been empirically studied in this context and are not recommended for treatment of opioid use disorder at this time. Legalization or provision in any context other than the provision of hydromorphone and diacetylmorphine for the specific purpose of treating opioid use disorder is beyond the scope of this document.

Will patients who overdose on fentanyl-laced cocaine be offered iOAT?

Injectable opioid agonist treatment is indicated for patients with opioid use disorder who have not benefited from oral OAT. Stimulant users who do not have concurrent opioid use disorder would not be considered for iOAT. Due to the increasingly contaminated drug supply, there may be individuals who have experienced an opioid overdose who do not have opioid use disorder and the other indications for iOAT.

Do patients 'get high' from the prescribed iOAT doses?

The effectiveness of iOAT is dependent on providing enough of the treatment to eliminate the patient's cravings and withdrawal symptoms, while not compromising the safety of the patient. This offers an opportunity to engage patients who may otherwise not be attracted to treatment. The stability achieved from access to iOAT allows patients and the care team to address the reasons behind the need for the euphoric effects of the medication. When these underlying reasons are addressed, patients may be prepared to move to less intense treatment options.

References

1. British Columbia Centre on Substance Use (BCCSU). A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver, BC, Canada: British Columbia Centre on Substance Use (BCCSU); 2017.
2. Government of Canada. Regulations Amending the Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need). Canada Gazette 2017; <http://www.gazette.gc.ca/rp-pr/p1/2017/2017-04-22/html/reg3-eng.php>. Accessed June 27, 2017, 2017.
3. Oviedo-Joekes E, Guh D, Brissette S, et al. Hydromorphone compared with diacetylmorphine for long-term opioid dependence: A randomized clinical trial. *JAMA Psychiatry*. 2016;73(5):447-455.
4. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database of Systematic Reviews*. 2011(12).
5. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*. 2011;106(1):32-51.
6. Haber PS, Demirkol A, Lange K, Murnion B. Management of injecting drug users admitted to hospital. *The Lancet*. 2009;374(9697):1284-1293.
7. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2007;64(5):566-576.
8. BC Coroners Service. Illicit Drug Overdose Deaths in BC: January 1, 2007-April 30, 2017. In: General MoPSaS, ed. Burnaby, BC: Office of the Chief Coroner; 2017.
9. BC Coroners Service. Illicit Drug Overdose Deaths in BC: January 1, 2007-July 31, 2017. In: General MoPSaS, ed. Burnaby, BC: Office of the Chief Coroner; 2017.
10. BC Coroners Service. Illicit Drug Overdose Deaths in BC: January 1, 2007-February 28, 2017. In: Coroner OotC, ed. Burnaby, BC: Office of the Chief Coroner; 2017.
11. BC Coroners Service. Illicit Drug Overdose Deaths in BC: January 1, 2007-March 31, 2017. In: Coroner OotC, ed. Burnaby, BC: BC Coroner's Service; 2017.
12. BC Coroners Service. Fentanyl-Detected Illicit Drug Overdose Deaths January 1, 2012 to July 31, 2017. In: Coroner OotC, ed. Burnaby, BC: BC Coroner's Service; 2017.
13. Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996-2006. *J Subst Abuse Treat*. 2010;39(1):22-31.
14. Stein BD, Gordon AJ, Sorbero M, Dick AW, Schuster J, Farmer C. The impact of buprenorphine on treatment of opioid dependence in a Medicaid population: Recent service utilization trends in the use of buprenorphine and methadone. *Drug and Alcohol Dependence*. 2012;123(1-3):72-78.
15. Rosenthal RN, Lofwall MR, Kim S, et al. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: A randomized clinical trial. *JAMA*. 2016;316(3):282-290.
16. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane database of systematic reviews*. 2009;3.
17. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane database of systematic reviews*. 2014;2:CD002207.

18. World Health Organization. WHO Model List of Essential Medicines. 19th ed: World Health Organization; 2015.
19. Reisinger HS, Schwartz RP, Mitchell SG, et al. Premature Discharge from Methadone Treatment: Patient Perspectives. *Journal of psychoactive drugs*. 2009;41(3):285-296.
20. Magura S, Nwakeze PC, Demsky S. RESEARCH REPORT Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. *Addiction*. 1998;93(1):51-60.
21. Office of the Provincial Health Officer. BC Opioid Substitution Treatment System: Performance Measures 2014/2015-2015/2016. In: Office of the Provincial Health Officer, ed: Office of the Provincial Health Officer; 2017.
22. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of addictive diseases*. 2016;35(1):22-35.
23. Proctor SL, Copeland AL, Kopak AM, Herschman PL, Polukhina N. A naturalistic comparison of the effectiveness of methadone and two sublingual formulations of buprenorphine on maintenance treatment outcomes: Findings from a retrospective multisite study. *Experimental and clinical psychopharmacology*. 2014;22(5):424-433.
24. Strang J, Groshkova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *The British Journal of Psychiatry*. 2015;207(1):5-14.
25. Oviedo-Joekes E, Brissette S, Marsh DC, et al. Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction. *New England Journal of Medicine*. 2009;361(8):777-786.
26. Strang J, Groshkova T, Metrevian, N. New Heroin-Assisted Treatment: Recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond. In: *Addiction EMCfDaD*, ed. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2012.
27. Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D. Heroin-assisted treatment for opioid dependence: Randomised controlled trial. *The British journal of psychiatry : the journal of mental science*. 2007;191:55-62.
28. van den Brink W, Hendriks VM, Blanken P, Koeter MW, van Zwieten BJ, van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. *BMJ (Clinical research ed)*. 2003;327(7410):310.
29. Proctor SL, Copeland AL, Kopak AM, Herschman PL, Polukhina N. A naturalistic comparison of the effectiveness of methadone and two sublingual formulations of buprenorphine on maintenance treatment outcomes: findings from a retrospective multisite study. *Experimental and clinical psychopharmacology*. 2014;22(5):424-433.
30. Oviedo-Joekes E, Brissette S, Marsh DC, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. *N Engl J Med*. 2009;361(8):777-786.
31. March JC, Oviedo-Joekes E, Perea-Milla E, Carrasco F. Controlled trial of prescribed heroin in the treatment of opioid addiction. *Journal of substance abuse treatment*. 2006;31(2):203-211.
32. Strang J, Metrevian N, Lintzeris N, et al. Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. *Lancet*. 2010;375(9729):1885-1895.
33. Demaret I, Quertemont E, Litran G, et al. Efficacy of Heroin-Assisted Treatment in Belgium: A Randomised Controlled Trial. *European Addiction Research*. 2015;21(4):179-187.

34. Strang J, Groshkova T, Metrebian N, Addiction EMCfDaD. New heroin-assisted treatment: recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond. Publications Office of the European Union Luxembourg; 2012.
35. Fischer B, Oviedo-Joekes E, Blanken P, et al. Heroin-assisted Treatment (HAT) a Decade Later: A Brief Update on Science and Politics. *Journal of Urban Health : Bulletin of the New York Academy of Medicine*. 2007;84(4):552-562.
36. Hallam C. Heroin Assisted Treatment: The State of play. International Drug Policy Consortium Briefing Paper. 2010:14.
37. Federal Institute for Drugs and Medical Devices. Report on the Substitution Register. 2017; http://www.bfarm.de/EN/FederalOpiumAgency/substitReg/Subst_Bericht/_node.html. Accessed June 14, 2017, 2017.
38. EMCDDA, ed New Heroin-assisted treatment. Recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2011. EMCDDA Insights; No. 11.
39. Demaret I, Quertemont E, Litran G, et al. Loss of treatment benefit when heroin-assisted treatment is stopped after 12 months. *Journal of Substance Abuse Treatment*. 2016;69:72-75.
40. Haasen C, Verthein U, Eiroa-Orosa FJ, Schafer I, Reimer J. Is Heroin-Assisted Treatment Effective for Patients with No Previous Maintenance Treatment? Results from a German Randomised Controlled Trial. *European Addiction Research*. 2010;16(3):124-130.
41. Oviedo-Joekes E, Brissette S, MacDonald S, et al. Safety profile of injectable hydromorphone and diacetylmorphine for long-term severe opioid use disorder. *Drug & Alcohol Dependence*. 176:55-62.
42. Yi P, Pryzbylowski P. Opioid Induced Hyperalgesia. *Pain Medicine*. 2015;16(suppl_1):S32-S36.
43. Substance Abuse and Mental Health Services Administration. SAMHSA's Working Definition of Recovery: 10 Guiding Principles of Recovery. In: Substance Abuse and Mental Health Services Administration, ed. Rockville, MD: SAMHSA; 2012.
44. Baumgartner GR, Rowen RC. CLONIDINE VS CHLORDIAZEPOXIDE IN THE MANAGEMENT OF ACUTE ALCOHOL-WITHDRAWAL SYNDROME. *Archives of internal medicine*. 1987;147(7):1223-1226.
45. Korthuis PT, Gregg J, Rogers WE, McCarty D, Nicolaidis C, Boverman J. Patients' Reasons for Choosing Office-Based Buprenorphine: Preference for Patient-Centered Care. *Journal of Addiction Medicine*. 2010;4(4):204-210.
46. Schwartz RP, Kelly SM, Mitchell SG, et al. Patient-centered methadone treatment: a randomized clinical trial. *Addiction*. 2017;112(3):454-464.
47. Barrio P, Gual A. Patient-centered care interventions for the management of alcohol use disorders: a systematic review of randomized controlled trials. *Patient Preference and Adherence*. 2016;10:1823-1845.
48. Mead N, Bower P. Patient-centredness: a conceptual framework and review of the empirical literature. *Soc Sci Med*. 2000;51(7):1087-1110.
49. Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*. 2016;73(1):39-47.
50. Arthur E SA, Dartnall M, Beltgens P, Poole N, Smylie D, North N, Schmidt R. Trauma-Informed Practice Guide. 2013; http://bccewh.bc.ca/wp-content/uploads/2012/05/2013_TIP-Guide.pdf.
51. BC Harm Reduction Strategies and Services. Respectful Language and Stigma: Regarding People Who Use Substances. *Toward the Heart*; 2017.

52. College of Physicians and Surgeons of British Columbia. Safe Prescribing of Drugs with Potential for Misuse/Diversion. 2016.
53. National Association of Pharmacy Regulatory Authorities. Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. Ottawa, Canada; 2015.
54. College of Pharmacists of British Columbia. Pharmacy Operations and Drug Scheduling Act-Bylaws. College of Pharmacists of British Columbia; 2017.
55. Office fédéral de la santé publique OFSP. MANUEL TRAITEMENT AVEC PRESCRIPTION DE DIACETYLMORPHINE: Directives et explications complémentaires aux dispositions légales 2015.
56. Publique OFdS. Manuel Traitement avec prescription d'héroïne. Directives, recommandations, informations. Berne. Swiss: Office Fédéral de la Santé Publique; 2004 2004.
57. Pasero C. Assessment of Sedation During Opioid Administration for Pain Management. *Journal of PeriAnesthesia Nursing*.24(3):186-190.
58. Jegu J, Gallini A, Soler P, Montastruc J-L, Lapeyre-Mestre M. Slow-release oral morphine for opioid maintenance treatment: a systematic review. *British Journal of Clinical Pharmacology*. 2011;71(6):832-843.
59. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev*. 2013(6).
60. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction (Abingdon, England)*. 2014;109(4):617-626.
61. Hammig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat*. 2014;47(4):275-281.
62. Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: Post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug and alcohol review*. 2012;31(4):492-498.
63. Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Substance Abuse and Rehabilitation*. 2016;7:99-105.
64. Government of Canada. Health Canada to propose regulatory change to enable consideration of applications under the Special Access Programme to facilitate treatment of chronic relapsing opioid dependence. 2016; <http://news.gc.ca/web/article-en.do?nid=1065009>.
65. Ministry of Justice. Narcotic Control Regulations. 2017.
66. Health Canada. DIRECTIVE ON PHYSICAL SECURITY REQUIREMENTS FOR CONTROLLED SUBSTANCES (Security Requirements for Licensed Dealers for the Storage of Controlled Substances). 2005.